（資料１）研究班独自のホームページの開設（代表者挨拶部分を抜粋）

原発性脂質異常症研究

厚生労働科学研究費補助金　難治性疾患政策研究事業

「原発性高脂血症に関する調査研究班」

TOP | 概要 | 代表者挨拶 | 患者様・ご家族の方へ | 医療関係者向け情報 | 研究成果 | リンク

代表者ご挨拶

原発性高脂血症調査研究班

厚生労働省　難治性疾患克服政策事業

原発性高脂血症とは、血漿リポタンパクの異常を示す病態の中で、
食事性や糖尿病などといった、原因が明らかではないものの総称である。
原発性高脂血症は、顕著な高LDL-C血症を示す、家族性高コレステロール血症(FH)、
高トリグリセリド血症を示す、原発性高カイロミクロン血症、
低HDL-C血症を示す、レシチンコレステロールアシルトランスフェラーゼ（LCAT）欠損症やタンジール病、
植物ステロールが増加するシトステロール血症、血清コレスタノールが上昇する脳腱黄色腫症、
低LDL-Cを示す無βリポタンパク血症などがある。
原発性高脂血症の多くは、これまでの研究により原因遺伝子まで同定され、
病態生理が明らかになってきた。

日本において、原発性高脂血症研究の基盤ができる中、「原発性高脂血症に関する調査研究班」は、
厚生省（当時）により1983年に結成された。その後35年、高脂血症に関わる多くの先生方の業績により、
スタチンの臨床研究、LDLアフェレシスの開発など、
現在においても高脂血症治療の中核をなす治療法が開発されてきたことは、
特記すべきことである。

LDLアフェレシス治療は、それまで有効な治療手段の無かったFHホモ接合体に対しても
LDL-C値を低下させることができるツールであり、動脈硬化の進展予防に大きな効果を示した。
しかしながら、LDLアフェレシス治療は、結果的には高脂血症治療に高額医療を持ち込むことにもなった。
患者側としては、小児期には小児慢性特定疾患として医療費助成を受けることができたが、
成人に達した後の医療費負担が切実な課題となっていた。
そのため、FHホモ接合体患者を中心に、「家族性高コレステロール血症・アフェレーシス患者会」が発足した。
患者会は、研究班と共に様々な活動をする中、2009年に原発性高脂血症の中では最初の疾患として、
FHホモ接合体が特定疾患に指定された。
研究班の研究が、医療から行政に移行した瞬間でもあったと言える。

2015年に、「難病の患者に対する医療等に関する法律（難病法）」が施行され、
助成対象となる疾患が56疾患から306疾患に、さらに2016年には330疾患となった。
その際、原発性高脂血症の中では、LCAT欠損症、シトステロール血症、タンジール病、
原発性高カイロミクロン血症、脳腱黄色腫症、無βリポタンパク血症が、指定難病に指定され、
FHホモ接合体も、引き続き指定難病となったため、原発性高脂血症の中で指定難病は7疾患となった。
これらの疾患の診断基準や疾患概念、診療指針が研究班により作成された。

一方、2015年には、国立研究開発法人日本医療研究開発機構（AMED）が設立され、
難病研究班の中の実験等の部分はAMEDに移行し、難病班においては調査研究を分担することとなった。
これにより、難病研究班の活動内容は、研究開発の部分が無くなり、
疫学調査、ガイドライン作成、疾患登録等に特化されることになった。
2018年4月より開始した今期の班においては、上記7疾患について、総説の作成、
HP作成、疾患登録、患者への情報発信を通じ、難病患者の予後改善を最大の目的とした活動を行っている。

「原発性高脂血症に関する調査研究班」班長
国立循環器病研究センター研究所病態代謝部
斯波真理子

TOP　概要　代表者挨拶　患者様・ご家族の方へ　医療関係者向け情報　研究成果　リンク

「原発性高脂血症に関する調査研究班」

（資料２）班会議会議次第

2－1　**平成 30 年度全体班会議**

日時：平成 31 年 1 月 5 日（土）9 時から 15 時
場所：日内会館（本郷 3 丁目）4 階会議室
参加人数：39 名（武村真治先生含む）

斯波班長挨拶
議題１．新規班員のご承認
議題２．年度タイムスケジュールの確認
議題３．次回班会議の方式・日程・場所
議題４．成果申告書と計画書の提出報告
議題５．患者会との連携の報告
議題６．班独自の HP の作成・開設
議題７．難病プラットフォーム
議題８．PROLIPID の拡充と現状・将来展望
議題９．日本語システマティックレビューのご承認
議題 10.　疾患担当責任者への過負荷に関すること
議題 11.　日本語総説の英文化について
議題 12.　極端な低 HDL-C 血症に遭遇時のフローチャート案
議題 13.　患者向け資料作成と HP へのアップロード
議題 14.　関連学会シンポジウム等での疾患啓発計画
議題 15.　現行診断基準の課題明確化と次期全面改訂への準備
議題 16.　診断・治療に必須だが未保険収載または効能追加要望項目
議題 17.　FH の新しい治療選択に関わる諸問題
議題 18.　小児 FH 健診スクリーニングについて（南野先生）
議題 19.　青年期 FH 健診スクリーニングについて（岡崎（佐）先生）
議題 20.　FH 診断基準の蓋然性について（小倉）
議題 21.　成人指定難病と小児慢性疾病の不一致について
議題 22.　小児成人移行期医療の課題の明確化と対策
議題 23.　その他のお願い事項
国立保健医療科学院・研究事業推進官　武村真治先生による総括

2-2　令和元年度第 1 回班会議

日時：令和元年 7 月 13 日（土）9 時から 15 時（日本動脈硬化学会総会・学術集会翌日）
場所：TKP 京都駅前カンファレンスセンター
参加人数：30 名

斯波班長挨拶
議題１．年度タイムスケジュールの確認
議題２．次回班会議の方式・日程・場所
議題３．交付申請書、事業実績報告書・研究報告書等の提出報告と経費使用に関する
　　お願い
議題４．平成 30 年度研究課題評価結果と交付基準額　　決定報告

議題５．患者会との連携について
議題６．班独自の HP の作成・開設状況報告
議題７．　PROLIPID の拡充と現状・将来展望
議題８．指定難病患者データベース及び小児慢性特定疾病児童等データベースの
　　第三者利用
議題９．AMED 臨床ゲノム情報　情報統合データベース整備事業（溝上班）の紹介
議題 10. 成人指定難病と小児慢性特定疾病の疾患の不一致、何が問題か？
議題 11.　英文総説の作成について
議題 12.　極端な低 HDL-C 血症に遭遇時のフローチャート案
議題 13.　患者向け資料作成と HP へのアップロード
議題 14.　関連学会シンポジウム等での疾患啓発計画
議題 15.　臨床調査個人票・診断基準改定案の学会承認
議題 16.　診断・治療に必須だが未保険収載または効能追加要望項目
議題 17.　FH の新診断基準策定に関すること
議題 18.　FH、LCATD に関する国際協調
議題 19.　FH の新しい治療選択に関わる諸問題
議題 20.　その他

2-3. 令和元年度第 2 回班会議

日時：令和 2 年 1 月 5 日（土）9 時から 15 時
場所：日内会館（本郷 3 丁目）4 階会議室
参加人数：41 名（難病対策課先生 1 名含む）

斯波班長挨拶
（＋遺伝学用語改訂について）
議題１．年度タイムスケジュールの確認
議題２．次回班会議の方式・日程・場所
議題３．成果申告書と計画書の提出報告
議題４．厚生労働科学研究費補助金経費使用について
議題５．患者会との連携についての報告
議題６．班独自の HP の現状報告
議題７．英文総説の公表スケジュールについて
議題８．患者向け資料作成と HP へのアップロード
議題９．　AMED-臨床ゲノム情報統合データベース整備事業（溝上班）の報告
議題 10. 関連学会シンポジウム等での疾患啓発計画
議題 11.　PROLIPID の拡充と現状・将来展望
議題 12.　指定難病患者データベース及び小児慢性特定疾病児童等データベースの
　　第三者利用
議題 13.　成人指定難病と小児慢性特定疾病の疾患の不一致
　　アポ A-I 欠損症・アポ E 欠損症（異常症）の診断基準作成と学会承認
議題 14.　診断基準改定案の学会承認・臨床調査個人票の班会議承認
議題 15.　診断・治療に必須だが未保険収載または効能追加要望項目の現状、進捗状況
議題 16.　FH 健診スクリーニングの進捗状況
議題 17.　FH、LCAT 欠損症に関する国際協調

議題 18.　FH の新しい治療選択に関わる諸問題
議題 19.　その他

2－4. 令和２年度第１回班会議

日時：令和 2 年９月６日（日）13 時から 15 時 30 分
場所：WEB 開催
参加人数：41 名（武村真治先生含む）

斯波班長挨拶
１．基本的戦略（本研究班の位置づけ）
２．全担当疾患のレジストリシステム構築（PROLIPID の拡充）
３．指定難病患者及び小児慢性特定疾病児童等データベースの第三者利用
４．班独自のホームページの作成・公開
５．全担当疾患の総説の執筆と公開
６．患者向けの療養上の注意点等のまとめと班 HP での公開
７．関連学会シンポジウム等での疾患啓発の実施
８．現行診断基準の妥当性評価と次期改訂への準備
９．診断・治療に必須だが未保険収載または効能追加が望ましい項目の明確化
10. 小児成人移行期医療の課題の明確化と対策
11.　FH の新しい治療をめぐる諸問題
12.　FH の新しい診断基準・診療ガイドライン作成
13.　FH ホモ接合体の臨床個人調査票に関する論点
14.　FH のスクリーニングのあり方に関する研究
総括

2－5. 令和２年度第２回班会議

日時：令和 2 年１月 11 日（月祝）9 時から 12 時 30 分
場所：WEB 開催
参加人数：39 名（武村真治先生含む）

斯波班長挨拶
１．基本的戦略（本研究班の位置づけ）
２．全担当疾患のレジストリシステム構築（PROLIPID の拡充）
３．指定難病患者及び小児慢性特定疾病児童等データベースの第三者利用
４．班独自のホームページの作成・公開
５．全担当疾患の総説の執筆と公開
６．患者向けの療養上の注意点等のまとめと班 HP での公開
７．関連学会シンポジウム等での疾患啓発の実施
８．現行診断基準の妥当性評価と次期改訂への準備
９．診断・治療に必須だが未保険収載または効能追加が望ましい項目の明確化
10. 小児成人移行期医療の課題の明確化と対策
11.　FH の新しい治療をめぐる諸問題

12.　FH の新しい診断基準・診療ガイドライン作成
13.　FH ホモ接合体の臨床個人調査票に関する論点
14.　FH のスクリーニングのあり方に関する研究
15.　FH ホモ接合体の全例登録
16. AMED との連携、国際協調など
17. 難病患者の就労支援
総括

家族性高コレステロール血症ホモ接合体

① 要約

家族性高コレステロール血症(FH)ホモ接合体は，常染色体優性遺伝である FH ヘテロ接合体の原因遺伝子変異を 2 つ有する重症例であり，LDL コレステロールはヘテロ接合体の 2 倍以上となりうる．かつて FH ホモ接合体は 100 万人に 1 人程度とされてきたが，近年は 17-30 万人に 1 人程度であることがわかっている．FH ホモ接合体では LDL 受容体機能が概ね失われているため，FH ヘテロ接合体に比べ LDL コレステロールが高値であるたけでなく，スタチンなどの治療に抵抗性であり，生命予後も不良であることから，ヘテロ接合体とは明確に区別することが重要である．ホモ接合体が疑わしい場合は，家族調査など臨床情報収集に加え，積極的な遺伝子診断も考慮すべきである．治療では可能な限り早期から強力に LDL 低下療法を開始すべきであり，LDL アフェレシスが治療の中核を成す．しかし LDL アフェレシスだけで十分に LDL コレステロールを低下させることは困難であり，患者個別に効果がある薬剤は複数併用する必要がある．LDL 受容体活性が残存する場合には、スタチン，エゼチミブ，PCSK9 阻害薬の効果も期待できる．MTP 阻害薬は LDL 受容体機能に依存しない薬剤であるため，本疾患でも多くの場合に有効である．

② はじめに

家族性高コレステロール血症(familial hypercholesterolemia：FH)は，出生時より高 LDL コレステロール血症が持続することで冠動脈硬化症を通常より早期に発症する常染色体優性遺伝性疾患である[1]．疾患発症の原因となる遺伝子変異を 1 つ有する FH ヘテロ接合体では，無治療では若年死のリスクがある疾患であるが，早期発見・早期治療が予後改善に非常に有効である．遺伝子変異を 2 つ有する FH ホモ接合体では LDL コレステロールがさらに高値である上に，スタチンなど既存治療薬の有効性も低く，生命予後がさらに不良であるため，より一層の早期発見と LDL アフェレシスを含む強力な治療開始が必要である．

③ 疾患の概要(特徴・合併症・自然予後等)

FH の三徴は，高 LDL コレステロール血症，早発性冠動脈硬化症，皮膚と腱の黄色腫である．遺伝子異常による LDL 受容体機能低下が原因であり，ホモ接合体では LDL 受容体機能が完全にもしくは完全近く失われている．常染色体優性遺伝疾患のホモ接合体であり，稀な症例を除けば原則としてヘテロ接合体である両親もホモ接合体の半分程度の高 LDL

コレステロール血症を呈する.

1）高 LDL コレステロール血症

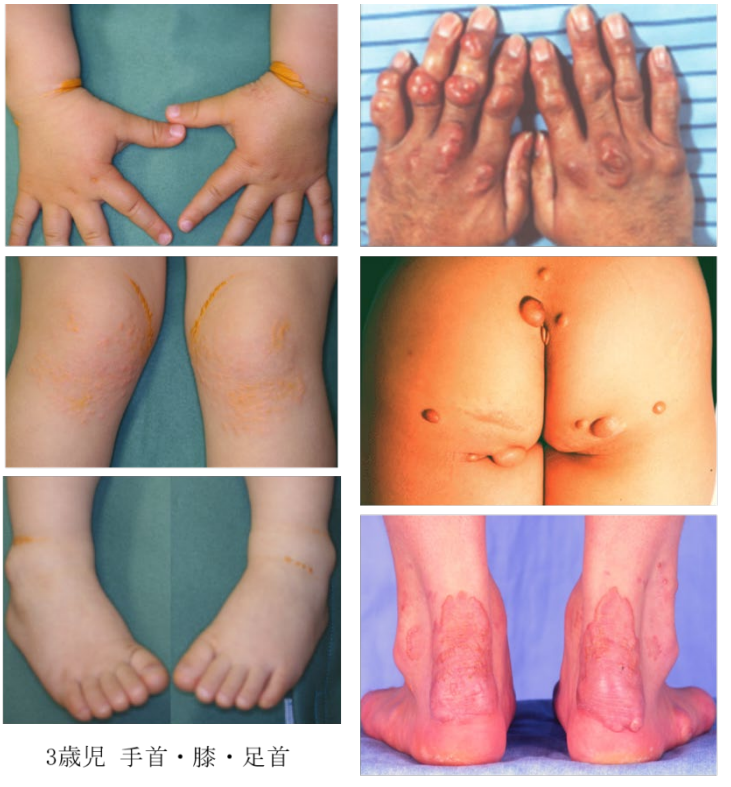
FH ホモ接合体では LDL コレステロール値は 500mg/dL を超えることが多いが，370mg/dL 程度の症例もある．出生時より高 LDL コレステロール血症が持続するため，動脈硬化性疾患のリスクが非常に高くなる．LDL コレステロール値×時間（年）の積算値にイベント発症の閾値があるとする LDL コレステロール蓄積仮説が，本疾患での冠動脈疾患リスク上昇をよく説明しているとされ，低めに見積もっても 11 歳程度で閾値に達する[2].

2）早発性冠動脈硬化症

小児期から狭心症や心筋梗塞を発症することに加え，しばしば認められる大動脈弁上狭窄（図 2）も心血管死の重要な原因となるため、未治療の場合，30 歳以上の存命は困難とされる．また治療を行っていても，加齢に伴い大動脈瘤や末梢性動脈疾患，脳血管疾患など全身の血管に動脈硬化性病変を生じうる．可能な限り早期から強力な LDL コレステロール低下療法を行うことが有効であると考えられる．

3）皮膚黄色腫および腱黄色腫（図 1）

ヘテロ接合体では思春期～成人期に出現する腱黄色腫が特異的身体所見であるが，ホモ接合体では乳幼児期に皮膚黄色腫が出現することが多く，これが医療機関受診のきっかけとなりうる[3]. なおホモ接合体であっても乳幼児期には腱黄色腫は通常認めない.



3歳児 手首・膝・足首　　成人 手指・殿部・アキレス腱周囲

図1. FHホモ接合体で認める皮膚黄色腫
成人例では手指伸筋腱およびアキレス腱に腱黄色腫も認める

④ **疾患頻度**

1970 年代には FH ヘテロ接合体は 500 人に 1 人，ホモ接合体は 100 万人に 1 人とされてきた [4]．しかし近年分子遺伝学的研究などから，日本を含む多くの国々でヘテロ接合体が 200-300 人に 1 人程度，地域差はあると思われるがホモ接合体は 17-30 万人に 1 人程度と，以前の想定より高頻度であることがわかってきた [5]．

⑤ **遺伝学(病因遺伝子、遺伝形式等)**

臨床診断された FH の 6-8 割程度で疾患原性変異(pathogenic mutation)が同定され，そのほとんどは LDL 受容体遺伝子(*LDLR*)である [6,7]．LDL 受容体に対するリガンドであるアポリポ蛋白 B100 遺伝子(*APOB*)でも FH の原因になる変異が主に白人で報告されている．2003 年に 3 番目の原因遺伝子として，LDL 受容体分解を制御する proprotein convertase, subtilistin/kexin-type 9 (PCSK9) をコードする遺伝子 *PCSK9* が報告され，本邦では臨床診断された FH の 5%前後が PCSK9 遺伝子変異によると報告されている [8]．*LDLR, APOB, PSCK9* による FH は常染色体優性遺伝形式を示し，FH ホモ接合体は遺伝子診断で２つの病原性変異を有する．多くは *LDLR* 遺伝子の両アリルに変異を有する（真性ホモ接合体・複合ヘテロ接合体）が，一部は二種の遺伝子(例えば *LDLR* 変異と *PSCK9* 変異)の組合せによる（ダブルヘテロ接合体）と報告されている [9]．真性ホモ接合体・複合ヘテロ接合体では両親は FH ヘテロ接合体であるが，ダブルヘテロ接合体の場合は片親から 2 つの変異が遺伝する可能性があり，単純なメンデル遺伝形式に従わない．

非常に稀な劣性遺伝性形式の FH ホモ接合体として，常染色体劣性遺伝性高コレステロール血症 (Autosomal Recessive Hypercholesterolemia：ARH) が本邦でも数家系報告されている [10,11]．*LDLRAP1* 遺伝子変異が原因として同定され，この場合ヘテロ接合体は高 LDL コレステロール血症を呈さない．従って、両親が正脂血症の場合は ARH も疑う必要がある．

逆に臨床診断された FH ヘテロ接合体の 2-4 割において遺伝子診断では原因遺伝子変異が確認されない．まだ知られていない原因遺伝子の可能性や，解析技術の限界などが理由と考えられる．したがって遺伝子変異が 2 つ確認できなくても FH ホモ接合体を否定できないことに留意する．また原因遺伝子が同定されない FH ヘテロ接合体の一部は polygenic hypercholesterolemia との報告があるが [12]，ホモ接合体診断での位置づけは定まっていない．したがって身体所見および家族調査などによる臨床診断を十分に行ったうえで遺伝子解析を併用することが望ましい．なお 2018 年 11 月時点で FH の遺伝子

診断は保険収載されていない.

⑥ 病態

遺伝的にLDL受容体機能が完全もしくは完全近く失われているため，出生時から（正確には胎児期から）重度の高LDLコレステロール血症が持続する。その結果、乳幼児期から始まる心血管疾患が生命予後を規定する.またコレステロールの組織沈着である皮膚黄色腫が乳幼児期から出現し，腱黄色腫もヘテロ接合体に比べ著明となる.

なお細胞内に血中のLDLコレステロールを取りこむ能力が低下しているが，コレステロールを前駆体として合成される性ホルモンや副腎皮質ホルモンの欠乏症などが臨床的に問題となることはない.

⑦ 我が国の診断基準と診断方法の実際

1) 臨床診断：典型例は血清総コレステロール600mg/dL以上だが[13]，総コレステロール値450 mg/dL以上（LDLコレステロール値 370mg/dL以上）あればFHホモ接合体の可能性があり、小児期から重症の高コレステロール血症を反映する黄色腫などのの症候から臨床的に診断される。小児期から動脈硬化性疾患が進行するため早期より本疾患を疑うことが重要である.

   小児期には皮膚黄色腫が特徴的で，皮膚科を最初に受診することがある[9]（図1)。FH ホモ接合体の黄色腫は手指関節、肘関節、膝関節など、機械的刺激を受ける部位に多発する。

   PCSK9阻害薬の効果が乏しいことが診断のきっかけとなる場合があるが，FH ヘテロ接合体の重症例と区別が困難な場合があり、疑わしい症例の診断には遺伝子解析が必要である。原則として両親がFHヘテロ接合体であるが，後述するダブルヘテロ接合体などでは当てはまらない場合もある.

   なお線維芽細胞LDL受容体活性は診断の参考になるが，現在国内で受託している検査会社はない.リンパ球LDL受容体活性測定の受託は行われているが(保険未収載)，診断閾値の設定が困難であり，FHホモ接合体の診断根拠とすることは難しい.

2) 遺伝子診断：FHの原因となる遺伝子変異を2つ有する場合にFHヘテロ接合体と診断する．遺伝子診断の上では同一変異が2つの場合を真性ホモ接合体，同じ遺伝子の異なる変異の組合せを複合ヘテロ接合体，異なる遺伝子の変異の組合せをダブルヘテロ接合体と呼称する[9]．常染色体優性遺伝形式となるのが*LDLR*遺伝子，*APOB*遺

伝子，*PCSK9* 遺伝子，常染色体劣性遺伝性形式となるのが *LDLRAP1* 遺伝子である．なおヘテロ接合体の検討から FH における原因遺伝子変異の検出率は 6–8 割程度である．2 つの変異が確認出来ない場合は臨床情報と合わせて判断する．

遺伝子診断の結果から薬剤への反応性などが予測可能であり，治療計画を立てる上でも非常に有用な情報であるため，ホモ接合体が疑われる症例では遺伝子診断が強く勧められる（保険未収載）．疾患原性の判断が難しい変異もあるため，遺伝子診断には経験のある専門医に相談が必要である．

⑧ 動脈硬化症の診断

無治療例の多くは 30 歳までに心血管死するとされる．FH ホモ接合体と診断された場合，現時点での動脈硬化症を十分に評価する必要がある．小児期でも狭心症，心筋梗塞，大動脈弁上狭窄（図 2）など生命予後を左右する疾患を有している可能性があり，無治療年齢が成人に近くなれば極めて危険である．小児期では一般に心血管病変が先行するが，年齢が高くなれば全身の動脈硬化症が進行する．

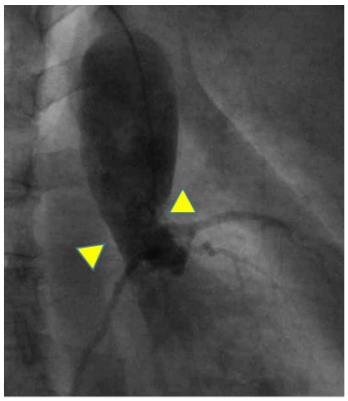


図2. FHホモ接合体で認めた大動脈弁上狭窄
大動脈弁狭窄症同様に心不全や突然死の原因となる

心エコー，頚動脈エコー，心電図などの非侵襲的検査，必要に応じて大動脈 CT 検査や，冠動脈 CT，冠動脈造影など造影検査も考慮する必要がある．運動負荷検査は心機能など安全性を慎重に評価したうえで検討する．

⑨ 鑑別疾患

高 LDL コレステロール血症および著明な黄色腫が出現する疾患を鑑別する必要がある．続発性高脂血症でもホモ接合体並みの高 LDL コレステロール血症を呈し得る。原発性胆汁性胆管炎では黄色腫すら生じることがある．

乳幼児期にホモ接合体並みの高 LDL コレステロール値と皮膚黄色腫を呈する疾患に，シトステロール血症がある（シトステロール血症の項参照）。*ABCG5/ABCG8* 遺伝子変異が原

因の劣性遺伝形式を呈する[14]．LDL コレステロールは離乳後に低下するが，血中植物ステロール(シトステロール，カンペステロールなど)高値は持続する．

脳腱黄色腫症は脳および腱に黄色腫が出現する常染色体劣性遺伝疾患で，*CYP27A* 遺伝子変異による胆汁酸合成障害である．コレステロールではなく血中コレスタノール高値で診断される．しばしば中枢神経症状（精神発育遅滞，認知症，運動失調など）を伴う．

⑩ 現在の治療法

小児期から致死的心血管疾患に罹患する可能性があるため，可能な限り速やかかつ強力な LDL コレステロールの継続的低下が重要である[9,13]（図 3，4）．小児期であっても心血管疾患合併の可能性が高く，冠動脈疾患，弁疾患（特に大動脈弁上狭窄），大動脈瘤などの評価を行い病状に応じた治療を行う．

１）成人 FH ホモ接合体（図 3）

LDL コレステロールの管理目標値は、一次予防では 100mg/dL 未満，二次予防では 70mg/dL 未満であるが[15]，その達成は容易ではない．まずスタチンを速やかに最大耐用量まで増量する．LDL 受容体の残存活性があれば、スタチン，エゼチミブ，レジン，PCSK9 阻害薬の効果も期待できる．MTP 阻害薬(lomitapide)は，LDL 受容体機能に依存しない薬剤であり，FH ホモ接合体に有効な内服薬である[16,17]．十分な栄養指導，節酒指導の上，ごく少量から開始し，消化器症状，肝障害などの副作用に注意して徐々に増量する．

最大耐用量のスタチンの効果は一ヶ月程度で判定し，更に、エゼチミブ，レジン，プロブコール，PCSK9 阻害薬などの薬剤も併用する。効果が十分でなければ LDL アフェレシス開始を考慮する[13]．

FH ホモ接合体では薬物療法で LDL コレステロールを管理目標値まで低下させることは

多くの場合困難であり，LDL アフェレシスが治療の中核をなす。治療前後の LDL コレステロール値を確認しながら 1-2 週に１回施行する．静脈のブラッドアクセスで十分な場

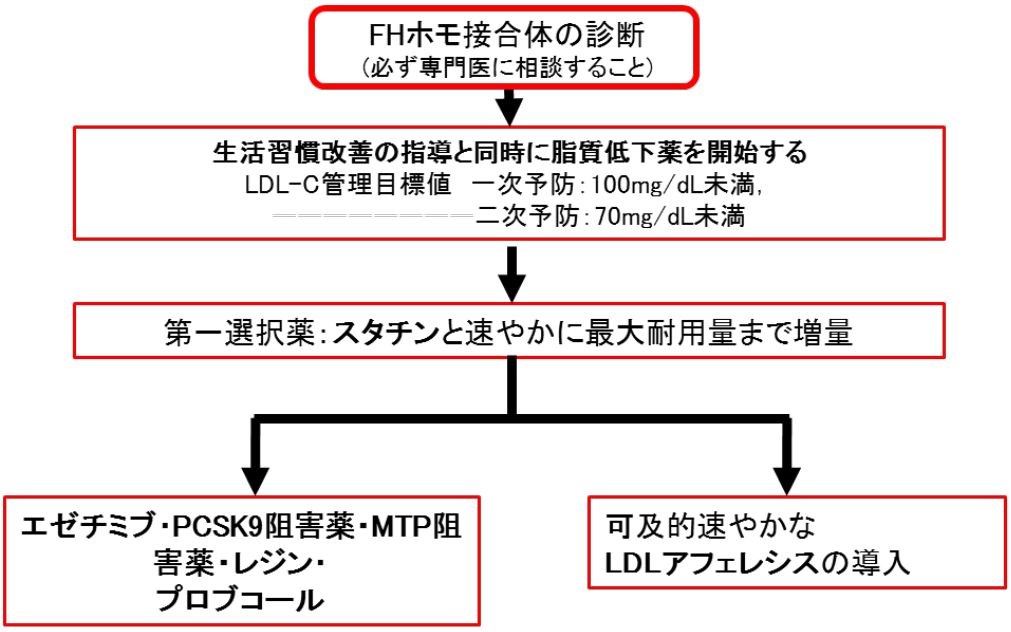


図3．成人（15歳以上）FHホモ接合体に対する治療

合が多いが，必要であればシャント作製を行う．

２）小児 FH ホモ接合体（図 4）

LDL コレステロール低下療法が生命予後を大きく左右するため，乳幼児期でも専門医に相談し治療を開始する．小児においてもまずスタチンを最大耐用量まで増量するが，効果が十分なければ LDL アフェレシス開始を考慮する．スタチンで効果がある場合はエゼチミブ，レジン，PCSK9 阻害薬など他の薬剤も有効である可能性が高く，スタチンと併用する．この場合も十分 LDL コレステロールを低下できなければ LDL アフェレシスを検討する．

体外循環が可能となるのは 4-6 歳頃であるが，3.5 歳から開始した報告もある[9]．FH ホモ接合体は乳児期で既に心血管疾患に罹患することもあり，薬物療法の反応が十分でなければ LDL アフェレシスは可能な限り早期の導入が望ましい．硫酸デキストランによる LDL 吸着療法を中心になるが，体重 30kg 未満の小児では体外循環量を抑えるため，単純血漿交換法が選択されることがある．

LDL アフェレシスが不可能な場合には，エゼチミブ・レジン・プロブコール・PCSK9 阻害薬などの薬剤による治療を検討するが，可能となれば早急にアフェレシス導入をはか

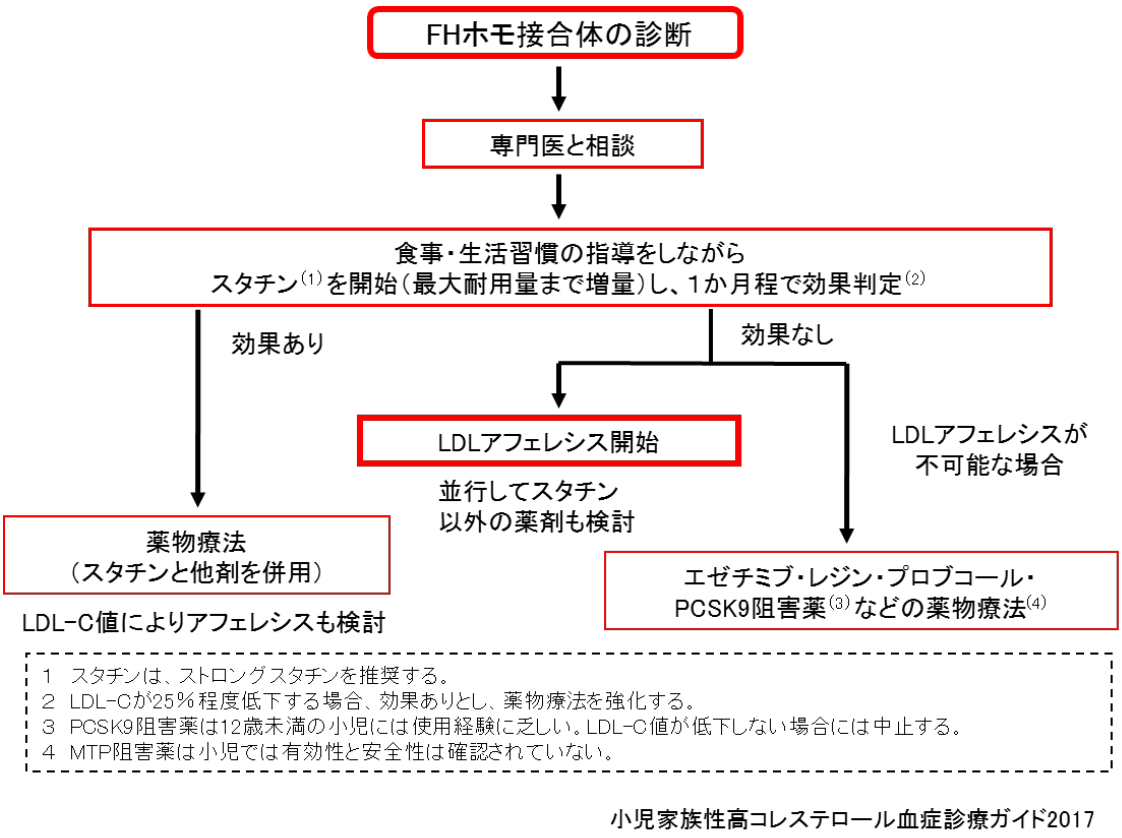


図4. 小児 FHホモ接合体に対する治療

る．

３）妊娠中の LDL 低下療法

FH ホモ接合体では妊娠可能年齢には既に冠動脈疾患を合併していることも多く，妊娠中は更に一層 LDL, VLDL が増加することもあり，LDL 低下療法継続が重要である．スタチンなど多くの薬剤は妊娠中および授乳中は禁忌であり，レジンのみが投与可能であるが効果は限定的である．妊娠中の FH ホモ接合体には LDL アフェレシスが唯一有効な治療法であると報告がされており [18]，経験のある専門医に相談する．

⑪ 将来の展望

単独で十分に有効な FH ホモ接合体の治療はいまだ存在せず，複数の治療法を併用する必要があるため，さらなる新しい治療の登場が望まれている．現在、開発中または治験実施中の治療法として以下の方法がある。

低分子干渉 RNA（siRNA）を利用して PCSK9 を阻害する inclisiran が開発されており，１回の投与で半年から 1 年持続する LDL コレステロール低下効果が示されていることから，PCSK9 阻害薬で効果がある FH ホモ接合体症例での選択枝となりうると考えられる．

ANGPTL3 抗体(evinacumab)は FH ホモ接合体でも LDL コレステロール低下効果が報告されており期待される．現在国内外で治験中である。

なお APOB アンチセンス医薬(mipomersen)が FH ホモ接合体の治療に米国では承認されているが，副作用の問題と LDL コレステロール低下効果が中等度であるため、欧州および本邦では認められていない．

LDLR 遺伝子治療が試みられているが，克服すべき課題はまだ多い．国内ではヒト幹細胞臨床研究として同種脂肪組織由来多系統前駆細胞移植療法が試みられているが，現在は安全性の確認を行っている段階にある．

おわりに

FH ホモ接合体の診断および治療においては，FH ヘテロ接合体とされていた重症例が遺伝子診断でホモ接合体と診断される事例が増え，また薬物療法でも PCSK9 阻害薬や MTP 阻害薬が使用可能となるなど，この 10 年で明らかな進歩が見られている．一方でもっと早期に診断し治療が開始できたはずの症例もいまだに少なくない．

本疾患は早期診断・早期治療が患者の生命予後改善に必須であり，治療の進歩を活かすためにも本疾患のさらなる啓蒙が喫緊の課題である．

<<PROLIPID研究について>>

＊家族性高コレステロール血症ホモ接合体は難病指定されている。病態のさらなる解明、新たな治療薬の開発、動脈硬化ハイリスク群を見分けるための診断指標同定などが喫緊の課題である。全国規模のシステマティックな症例蓄積が必須であり、厚労省の「原発性高脂血症に関する調査研究班」では、PROLIPID研究を開始し家族性高コレステロール血症ヘテロ接合体およびホモ接合体のコホート研究を開始している。

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レシチンコレステロールアシルトランスフェラーゼ（LCAT）欠損症

１．要約

レシチンコレステロールアシルトランスフェラーゼ（LCAT）は、血中でレシチンと遊離コレステロールからコレステリルエステルとリゾレシチンを生成する反応を触媒する（脂質修飾）酵素である。LCAT 欠損症は、LCAT 酵素の先天的機能異常によって引き起こされる難治性の常染色体劣性遺伝性疾患である。

HDL のエステル化活性と LDL のエステル化活性の両方を欠損する家族性 LCAT 欠損症(FLD、OMIM 245900)と HDL のエステル化活性のみ欠損する魚眼病(FED、OMIM 136120)という２つの病型に大別される。LCAT の機能に異常が生じると、LCAT の基質である体内の遊離コレステロールやリン脂質の代謝が障害され、血中リポ蛋白の濃度、組成や形態に異常が生じる。このようなリポ蛋白代謝異常により標的臓器に通常では見られない脂質蓄積が生じることで、重篤な臓器障害や合併症が引き起こされる

著明な低 HDL コレステロール血症と角膜混濁とが FLD と FED に共通する臨床症状で、FLD には更に貧血や腎機能障害を伴い、予後不良の症例では腎不全にまで進展する。

LCAT 酵素の補充療法が有効であると考えられ、現在組換え型製剤並びに遺伝子細胞治療の研究が進められている。

２．はじめに

角膜混濁、貧血、タンパク尿を呈し、慢性腎炎が疑われた 33 歳の女性が 1966 年にノルウェー・オスロの病院から報告された。腎機能は正常ではあるが、血清アルブミンはやや低く、血漿総コレステロール、トリグリセライドが高値で、ほとんどのコレステロールはエステル化されていなかった。腎生検では糸球体係蹄に泡沫細胞が認められた。患者の姉妹に同様の所見を認め遺伝性疾患であることが疑われた。その後、ノルウェーで別の 3 家系が見つかり、これらの患者は同一の遺伝子変異を有していた。患者は血中 LCAT 活性を欠損しており、Norum と Gjone により家族性 LCAT 欠損症（Familial LCAT deficiency、FLD）と名付けられた[1)]。LCAT 活性欠損の程度により、古典型(LCAT 活性 10%未満)に加えて、部分欠損型(LCAT 活性 15～40%)も存在する。また、LCAT の障害された基質特異性から、HDL のエステル化活性と LDL のエステル化活性の両方を欠損する家族性 LCAT 欠損症（FLD、OMIM 245900）と HDL のエステル化

活性のみ欠損する魚眼病（FED、OMIM 136120）という２つの病態にも大別され、その障害の状態などにより出現する症状や合併症の進展程度は多様である。

３．疾患の概要（特徴・合併症・自然予後等）

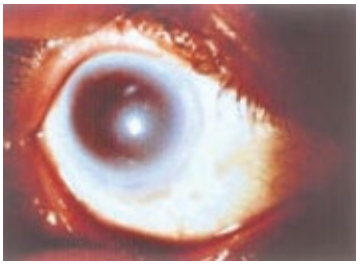
LCAT の機能異常は、LCAT の基質である体内の遊離コレステロールやリン脂質の代謝障害、血中リポ蛋白の濃度、組成や形態の異常、特殊な脂質の臓器蓄積をきたし、重篤な臓器障害を呈し得る。低 HDL コレステロール血症、角膜混濁を FLD と FED に共通に、さらに FLD は貧血や腎機能障害も伴い、予後不良の症例では腎不全に至る[1,2]。

1） 脂質異常症

多くの症例で HDL コレステロール濃度は 10 mg/dL 未満となる（20 mg/dL ほどの症例も報告されている)。血清コレステロールエステル比（CE/TC）も低下する。

2） 角膜混濁

遊離コレステロールとリン脂質が角膜に過剰に蓄積し、比較的幼少期から角膜混濁が認められる（下図参照)。FLD よりも FED においてより顕著である。角膜移植の必要となる重度の視力障害を呈する症例も報告されている。同様の角膜混濁を伴うアポリポタンパク A-I や ABCA1 の欠損（タンジール病）による低 HDL コレステロール血症との鑑別が必要である[3]。



3） 貧血

赤血球膜の脂質組成異常により標的赤血球が出現し、溶血による貧血が認められる。赤血球の半減期は健常人の半分程度である。遊離コレステロールの増加するため、二次性の sea-blue histiocytosis が骨髄、脾臓に認められる症例（シーブルー組織球症候群）が報告されている[4]。しかしながら、骨髄、脾臓の所見まで検討されている報告は少なく詳細は不明である。また溶血のため血糖値と比較して HbA1c が相対的に低値となる。

4） 蛋白尿、腎機能障害

幼少期から重篤になる症例報告はないが、FLD では蛋白尿を早期に認め、進行性の

腎不全を 40～50 歳で発症する。FED は一般に腎障害を伴わない。FLD が疑われる症例では腎生検が診断に有用である[5]。3 歳で蛋白尿が出現した FLD 症例が報告されている[6]。

４．疾患頻度および遺伝学（病因遺伝子、遺伝形式等）

第 16 番染色体短腕に存在する LCAT 遺伝子の変異が原因である。単一遺伝子（*LCAT* 遺伝子）の変異による先天性疾患であり、常染色体劣性遺伝であることから、100 万人に 1 人程度の頻度であると考えられるが、本邦での患者数は不明である。1990 年代に厚生労働省研究班がまとめた報告によると、本邦では 13 種類の変異が同定されている[7]。その後、海外で既報の変異が 2 種類、新規変異が 4 種類報告されている[8,9,10]。

５．病態

1) 脂質異常症

LCAT の α 活性の欠損により HDL 粒子の成熟が障害され、患者 HDL 分画に認められる粒子の多くはプレ β-HDL と類似の形態を示し（discoidal HDL）、連銭形成が認められる。HDL の障害に伴い、アポリポタンパク A-I、A-II も低下する。古典的 FLD は、アポリポタンパク B 含有リポ蛋白に含まれる遊離コレステロールをエステル化する活性（β 活性）も欠損するため、血漿中にコレステロールエステルはほとんど消失する。遊離コレステロールがすべての血漿リポ蛋白質画分に蓄積し、とりわけ遊離コレステロールリッチな VLDL が増加する。LDL 分画中に検出される LpX、また近年リポ蛋白の HPLC ゲルろ過解析により同定された大型 TG rich LDL（Lp8）[11]は、腎機能障害の程度と関連する。

2) 腎機能障害

糸球体基底膜、血管内皮下への遊離コレステロールとリン脂質の沈着が認められる。超遠心分離法により分離された患者 LDL 分画には複数の異なる組成の粒子が存在していることが報告されており、LpX や大型 TG rich LDL（Lp8）[11]は腎機能障害の程度と関連する。患者 LDL 中の酸化型レシチンが腎機能障害の原因とする報告がある[12]。アポリポタンパク E を含むリポ蛋白が取り込まれ、腎臓糸球体メサンギウム細胞に過剰に脂質の沈着が腎機能障害の原因とする報告もあることから、腎機能障害とアポリポタンパク E 遺伝子型との関連が注目されている[13,14]。アポリポタンパク

E は LDL 粒子における β 活性の共役分子であり、異常リポ蛋白の生成に影響を及ぼす可能性がある。また、糸球体内皮細胞、ポドサイト、メサンギウム細胞に LpX が取り込まれ、糸球体内皮細胞の機能障害および炎症性サイトカインの分泌亢進を介して、腎機能障害を惹起することが示唆するモデルマウスを用いた報告もある [15]。

3) 動脈硬化症

心血管イベントと HDL コレステロールとは逆相関が疫学調査において示されているため、HDL コレステロールの著しく低い患者の心血管イベントのリスクは増加すると予測される。しかし、この予想は LCAT 欠損症には必ずしも当てはまらない。最近、イタリアとオランダのグループは、74 名のヘテロ接合体患者を対象にした解析から、動脈硬化は FLD を生ずる変異で改善し、FED を生ずる変異で悪化すると報告している [16]。

６．我が国の診断基準と診断方法の実際

1) 現状の診断基準（厚生局長通知、難病申請で求められる基準）

必須項目

血中 HDL コレステロール値　10 mg/dL　未満、

A 症状

１．蛋白尿、腎機能障害

２．角膜混濁

B 検査所見

血液・生化学的検査所見（Cut Off 値を設定）

(1) 貧血（ヘモグロビン値＜11g/dL）

(2) 赤血球形態の異常（いわゆる「標的赤血球」「大小不同症」「奇形赤血球症」「口状赤血球」）

(3) コレステロールエステル比の低下　（正常　70%）

C 鑑別診断

以下の疾患を鑑別する。

遺伝性低 HDL コレステロール血症（タンジール病、アポリポタンパク A-Ⅰ異常症）

肝疾患（肝硬変・劇症肝炎）、胆道閉塞、低栄養、悪液質など蛋白合成低下を呈する

病態

D 遺伝学的検査

LCAT 遺伝子の変異　または、LCAT 活性・LCAT 蛋白の欠如

＜診断のカテゴリー＞

必須項目を満たした例において、以下のように判定する。

Definite：A・B のうち 1 項目以上を満たし C の鑑別すべき疾患を除外し、D を満たすもの

Probable：A・B のうち 1 項目以上を満たし C の鑑別すべき疾患を除外したもの

2)　「原発性高脂血症に関する調査研究班」が現在提案している診断基準

必須項目

１．血中 HDL コレステロール値　25 mg/dL 未満

２．LCAT 活性（外注検査可能）の極度の低下

３．コレステロールエステル比（CE/TC）の低下（65%以下）

A 症状

１．蛋白尿、腎機能障害

２．角膜混濁（視野検査またはコントラスト感度検査における機能障害）

B 検査所見

血液・生化学的検査所見

(1) 貧血（ヘモグロビン値、成人男性　13.0g/dl 以下、成人女性　12.0g/dl 以下）

(2) 赤血球形態の異常（いわゆる「標的赤血球」「大小不同症」「奇形赤血球症」「口状赤血球」）

(3) 異常リポ蛋白の出現（Lp-X、大型 TG rich LDL）

C 鑑別診断

以下の疾患を鑑別する。

他の遺伝性低 HDL コレステロール血症（タンジール病、アポリポタンパク A-Ⅰ異常症）

続発性 LCAT 欠損症（肝疾患（肝硬変・劇症肝炎）、胆道閉塞、低栄養、悪液質など蛋白合成低下を呈する病態、自己免疫性 LCAT 欠損症）

D 遺伝学的検査

１．*LCAT* 遺伝子の変異

＜診断のカテゴリー＞

必須項目 3 項目のうち 2 項目以上を満たした例において、以下のように判定する。

Definite：A・B のうち 1 項目以上を満たし C の鑑別すべき疾患を除外し、D を満たすもの

Probable：A・B のうち 1 項目以上を満たし C の鑑別すべき疾患を除外したもの

Definite、Probable を対象とする。

3) 診断方法の実際

角膜混濁と低 HDL-C 血症とが本症を疑うべき主な臨床所見であり、さらに FLD の場合は病態の進行に伴い 20 歳代で蛋白尿が出現する。HDL-C は多くの症例で 10 mg/dL 未満であるが、10 mg/dL 以上を示す症例も最近報告され、20 mg/dL 未満の場合は遺伝子や蛋白・活性解析を行うべきである。CE/TC は古典型 FLD で減少し診断に有用であるのに対し、部分欠損型や FED は大きく低下することはない。FLD の多数の症例で貧血が認められる。

（１）脂質検査

アポリポタンパク A-I、A-II が著しく減少する。リポ蛋白の電気泳動解析（アガロース、ポリアクリルアミド）で、LDL 分画を中心とした異常リポ蛋白（LpX, 大型 TG rich LDL）が出現している場合は LCAT 異常を疑い、血清または血中 LCAT 活性を測定する（外注検査可能）。LCAT は肝臓で産生される酵素であり、LCAT 活性が低下するような重篤な肝障害との鑑別が必要である。

（２）眼科検査

slit-lamp examination（細隙灯検査）により上皮を除く角膜層に灰白色の粒状斑が観察される。

（３）腎生検

FLD が疑われる場合は腎生検が有用である。糸球体基底膜、血管内皮下への遊離コレステロールとリン脂質の沈着が認められる。泡沫細胞の蓄積、ボーマン嚢や糸球体基底膜の肥厚が観察される。電子顕微鏡観察では毛細管腔、基底膜、メサンギウム領域に高電子密度の膜構造の蓄積が認められる。

（４）遺伝子解析

上記の検査に加えて遺伝子解析を考慮する。末梢単核球より DNA を抽出し、*LCAT* 遺伝子領域の塩基配列を検索する。劣性遺伝形式をとることから両親と患者に同一の変異が同定される。

７．鑑別疾患

1) 遺伝性低 HDL コレステロール血症（タンジール病、アポリポタンパク A-Ⅰ異常症）

これらの疾患は、LCAT 欠損症と同様に HDL コレステロールの著減が認められる。角膜混濁と低 HDL-C 血症はアポリポタンパク A-I 欠損症や ABCA1 欠損症（タンジール病）でも認められることから鑑別が必要である[3)]。鑑別には遺伝子検査が重要である。

2) 後発性 LCAT 欠損症

抗 LCAT 抗体の出現により LCAT 欠損症と同様に HDL コレステロールの著減や腎機能障害を合併する症例が報告されている[17,18)]。鑑別するには遺伝子検査や抗 LCAT 抗体の検索が必要である。

3) 肝疾患（肝硬変・劇症肝炎）、胆道閉塞、低栄養、悪液質など蛋白合成低下を呈する病態

LCAT は肝臓で合成される酵素であるため、肝機能の障害・低下により、LCAT の低下を生ずることがある[19,20)]。

4) 薬剤性低 HDL コレステロール血症（プロブコール服用、さらにフィブラートの併用など）

プロブコール服用時、とりわけフィブラート併用やプロブコール中断後まもない服用により、著しい低 HDL コレステロールを呈する事例が報告されており、これら薬剤の影響についても確認が必要である[21,22,23)]。

８．現在の治療法

現在承認されている効果的な治療法はない。LCAT 欠損症に有効な治療法は正常な LCAT 酵素の補充であると考えられ、組換え型酵素及び遺伝子治療法が開発されている。その他、主に合併症の進行を遅らせるために食事療法（低脂肪食）や腎機能保護を目的とした薬剤治療が試みられている。

1） 食事療法

低脂肪食により腎機能障害の進展が遅延した症例がある[10,24,25]。

2） 輸血療法

LCAT 補充を目的とし新た鮮血 （全血または血漿） 輸血療法の有効性が報告されている。LCAT 活性の上昇は認められるものの、LCAT の半減期が短いため、1 週間程度で輸血前値に戻り補充効果の持続は困難である。また、輸血に随伴する感染性リスクは避けられない。

3） 薬剤治療

根治的薬物療法は存在しない。食事療法との組み合わせで腎機能の増悪の予防や改善を目的とした薬物療法（ARB など）が試みられている[6,26,27]。

4） 遺伝子組換え型 hLCAT 蛋白質（rhLCAT）補充療法

米国で rhLCAT の臨床試験が 1 例実施されている[28]。高用量の rhLCAT の投与(9.0 mg/kg)で、HDL コレステロールの上昇等の脂質パラメーターの改善とともに貧血、腎機能の改善が認められたが、投与 2 週間後までにこれらの異常値は元に戻ることから、他の酵素補充療法と同様、繰り返し投与が必要と考えられる。

5） 遺伝子治療

遺伝子治療とは治療目的遺伝子を標的細胞に導入することにより持続的な hLCAT 蛋白質を目指すもので、通院頻度及び投与回数を抑え、患者 QOL の改善が期待できる。国内外において薬事承認に至った遺伝子治療はない。本邦では LCAT 欠損症に対して、再生医療等安全性確保法下、LCAT 遺伝子導入前脂肪細胞移植による遺伝子治療/再生医療臨床研究が厚労省より認定されている[29]。

6） 臓器移植

腎不全への腎移植治療、視力障害への角膜移植が行なわれているが再発リスクは避けられない。近年 1 例の患者について同一ドナーから腎・肝の連続移植が行われた[30]。移植後 5 年間の観察において、移植臓器の機能は維持されていたが、肝

移植後１年以内に脂質異常症が再発している。

９．将来の展望

これまで、100 種類以上の LCAT 変異が同定され、個々の症例報告がなされてきているが、その後の合併症の進展に関する報告はほとんどなく、きめ細やかな臨床的観察が患者予後の理解と新たな治療法の開発に貴重な情報となることが期待される。

現在組換え型製剤の輸注または遺伝子細胞治療による LCAT 酵素の補充療法の開発が行われている。これらの治療法が近い将来実用化され、患者の生命予後や QOL が改善されることが期待される。治療法の進展とともに本症の病態解明がさらに進むことが期待される。

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シトステロール血症

①要約

シトステロール血症とは、肝臓・小腸から腸管へのステロール排泄に関わるATP-binding cassette sub-family G member 5 (*ABCG5*)ないしはATP-binding cassette sub-family G member 8 (*ABCG8*)遺伝子の機能低下型遺伝子変異に伴い発症する劣性遺伝性形式をとる希少疾患である（文献 1)（図１)。若年性皮膚黄色腫（図２、文献 2）や冠動脈硬化症を呈することから家族性高コレステロール血症との鑑別が重要であるが、食事療法が著効することや家族歴の聴取などから鑑別可能であることも多い（文献 3)。現在は本邦で 10 数家系と推定されているが、遺伝子解析公開データベースから推定すると未診断例が多数存在することが示唆される（文献 4)。エゼチミブや陰イオン交換樹脂製剤が使用されることが多いが（文献 5)、高 LDL コレステロール血症に対してはスタチン製剤やproprotein convertase subtilisin/kexin type 9 (PCSK9)抗体製剤も有効である。また、難治例に対してはLDL アフェレシスが有効であったとの報告もある（文献 6)。今後、血中シトステロール濃度測定が保険収載されることで、本邦における本症診断が容易となりさらなる情報蓄積により本症の病態解明に繋がることが期待される。また、厚労省の「原発性高脂血症に関する調査研究班」では、PROLIPID 研究を開始している。本症が疑われる場合には専門医に紹介して、専門的な検査をすすめることが望ましい。

②はじめに

シトステロール血症は常染色体劣性遺伝形式をとる希少遺伝性脂質代謝異常症である。コレステロールと側鎖の構造が異なるシトステロールなどの植物ステロールが著明に上昇する疾患である。シトステロールなどの植物ステロールに加えてコレステロールの上昇も伴うことが多い他、幼少期からの皮膚黄色腫や早発性冠動脈硬化症などを呈するため、偽性家族性高コレステロール血症と称されることがある。

③疾患の概要（特徴・合併症・自然予後等）

乳児期に特に母乳保育に伴い、著明な高 LDL コレステロール血症(300mg/dl～900mg/dl)を呈し、ホモ接合体性家族性高コレステロール血症類似の若年性皮膚黄色腫を呈する例がある（文献 7)。また、若年性の心筋梗塞を発症し精査の結果診断される例も存在する（文献 8)。その他、関節痛、関節炎、溶血発作を呈する症例も報告されている（文献

9)。自然予後は現時点では不明確であるが、早発性冠動脈硬化症が重要な予後規定因子である。また、血族婚姻を伴うホモ接合体の場合には、その他の希少劣性疾患の併発例も報告されており（文献 10)、症状がシトステロール血症に伴うものかどうか鑑別に苦慮する場合がある。

④疾患頻度

常染色体劣性遺伝形式を呈する希少疾患とされ、これまで世界的に 100 家系、本邦では 10 数家系程度であると考えられてきたが、本邦においても多数の家系が報告されていること、さらには The Exome Aggregation Consortium (ExAC)コンソーシアムデータにおける原因遺伝子とされる *ABCG5* ないしは *ABCG8* 遺伝子の機能喪失型遺伝子変異の頻度などから推定すると、少なくとも一般人口の 20 万人に 1 人程度存在することが推定され、本邦においても 600 例程度存在する可能性がある（文献 2)。

⑤遺伝学（病因遺伝子、遺伝形式等）

腸管でのステロール排泄に関わる *ABCG5* ないしは *ABCG8* 遺伝子の機能低下型遺伝子変異に伴い発症することが知られている。常染色体劣性遺伝性形式をとることが知られているが、ヘテロ接合体のキャリアにおいても軽度～中等度の高ステロール血症（シトステロール、コレステロールなど）を呈することが知られている。また、*ABCG5* 遺伝子、*ABCG8* 遺伝子それぞれのホモないしは複合型ヘテロ接合体のみならず、*ABCG5* 遺伝子および *ABCG8* 遺伝子両者の複合型ヘテロ接合体遺伝子変異に伴う症例も報告されている（文献 11)。

⑥病態

上述の遺伝子異常･機能低下に伴いステロール(シトステロール､コレステロールなど)の胆汁中・腸管への排泄が低下し、血中濃度が上昇することが病態の本態である。シトステロールなどの植物ステロール、コレステロールのいずれかが、ないしはいずれも本症症状（若年性皮膚黄色腫、早発性冠動脈硬化症、関節痛、関節炎、溶血発作）の進展に関与するかどうかについては現時点で明確なデータは無い。

⑦我が国の診断基準と診断方法の実際

＜診断基準＞

シトステロール血症の診断基準

Definite、Probable を対象とする。

Ａ．症状

１．　皮膚黄色腫又は腱黄色腫の存在

２．　早発性冠動脈疾患（男性 45 歳未満、女性 55 歳未満）

Ｂ．検査所見

１．血液・生化学的検査所見

血清シトステロール濃度１mg/dL（10μg/ml）以上

Ｃ．鑑別診断

以下の疾患を鑑別する。

家族性高コレステロール血症、脳腱黄色腫症

Ｄ．遺伝学的検査

ABCG5/8 遺伝子の変異

＜診断のカテゴリー＞

Definite：Ａ-１及びＢ-１を満たし、Ｃの鑑別すべき疾患を除外し、Ｄを満たすもの

Probable：Ａ-１及びＢ-１を満たし、Ｃの鑑別すべき疾患を除外したもの

Possible：Ａ-１、２及びＢ-１を満たすもの

Definite、Probable を対象とする。

補足事項：

高 LDL コレステロール血症を呈したシトステロール血症では、コレステロール吸収阻害薬(エゼチミブ、コレスチミド)が著効する点が家族性高コレステロール血症と異なる。

■診断の実際

乳児期に特に母乳保育に伴い、著明な高 LDL コレステロール血症(300mg/dl～900mg/dl)を呈し、ホモ接合体性家族性高コレステロール血症類似の若年性皮膚黄色腫を呈することを契機に診断される例がある他、成人例では、早発性冠動脈硬化症を契機に診断される例、また家族性高コレステロール血症が疑われるが、食事療法が著効することから診断に至るケースがある。診断に必須である血清シトステロール濃度測定は、複数の検査会社により測定可能であるが、現在保険収載されておらず、正確な診断に至る例が極めて少ない。また、鑑別診断としての家族性高コレステロール血症や脳腱黄色腫症についても除外診断のためには遺伝子解析が必要な場合が多いことが問題であり、現状での診断率が極めて低い事の要因の一つであると考えられる。一方で、血清シトステロール濃度１mg/dL（10μg/ml）以上の基準は本症診断の感度・特異度は極めて高く、保険収載されることで診断率の上昇が期待される。

⑧鑑別疾患

家族性高コレステロール血症

脳腱黄色腫症

⑨現在の治療法

植物ステロール制限食（植物油、ナッツ類、シリアルなどを避ける）及びコレステロール制限食（200mg/日未満）が基本であり、極めて有効である。エゼチミブや陰イオン交換樹脂製剤が使用されることが多いが、高 LDL コレステロール血症に対してはスタチン製剤や PCSK9 抗体製剤も有効である。また、難治例に対しては LDL アフェレシスが導入され有効であったとの報告もある。

⑩将来の展望

血中シトステロール濃度測定が保険収載されることで、特に LDL コレステロール血症や若年性冠動脈硬化症を呈する症例の中で診断が進み、症例が集積されることで本症の自然予後を明確とすることが期待される。

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図1．肝臓および腸管におけるABCG5/ABCG8の働き

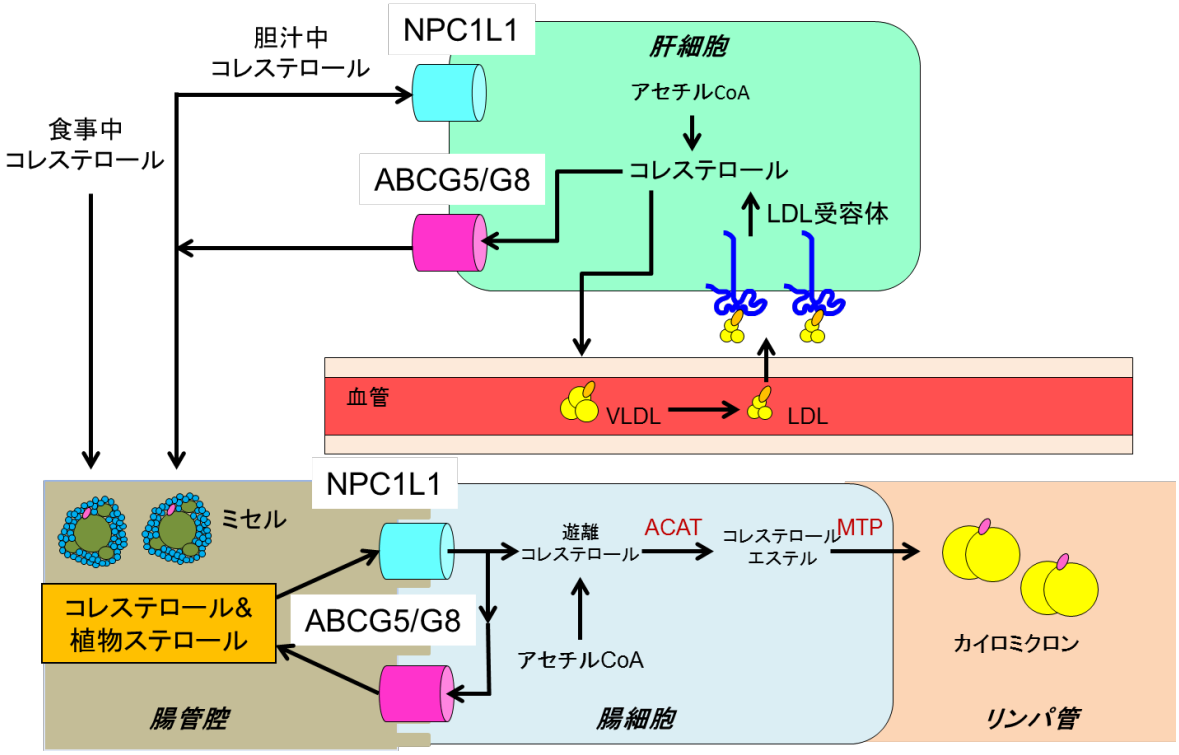
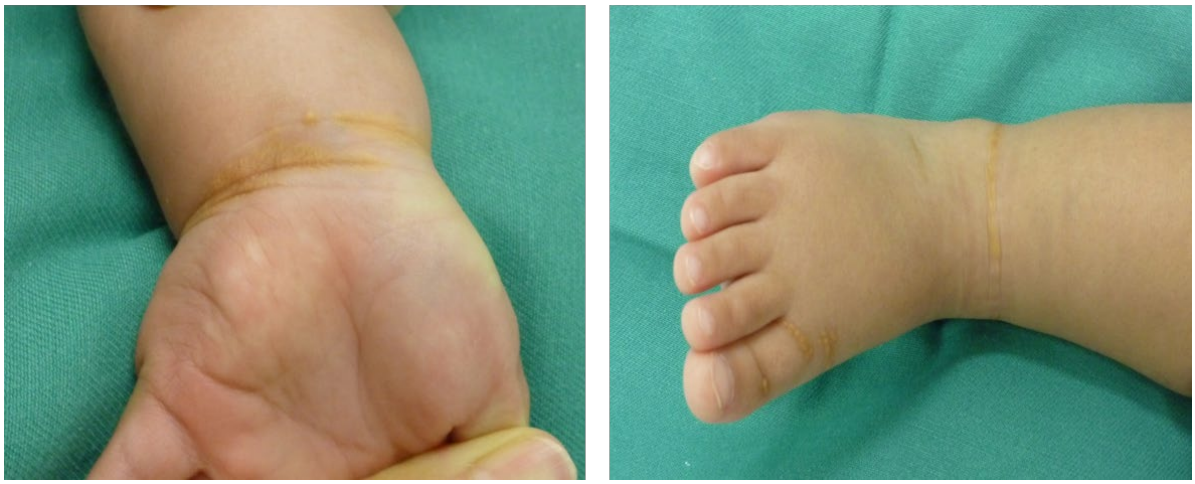


図2．シトステロール血症における皮膚黄色腫



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タンジール病

概要

タンジール病（OMIM205400）は家族性低～無 HDL コレステロール（HDL-C）血症の１つで、細胞の脂質から HDL 粒子の形成に必要な膜蛋白質 ATP 結合カセットトランスポーターA1（*ATP-binding cassette transporter A1：ABCA1*）の遺伝子の機能障害型変異に基づく疾患である。常染色体潜性（劣性）遺伝疾患で、顕在疾患であるホモ型の HDL-C は通常 5 mg/dL 未満（3±3 mg/dL)、アポリポ蛋白質 A-Ⅰも 10 mg/dL 以下の表現型を示す。文献上、本邦ではこれまでに 35 例、世界的には 109 例の症例報告があり、稀な疾患とも考えられるが、未診断例が多い可能性もある。臨床身体所見として、オレンジ色の咽頭扁桃腫大、肝脾腫、角膜混濁，リンパ節腫脹、末梢神経障害を認める。LDL-コレステロール（LDL-C）が低下する（約 37%）にもかかわらず，早発性冠動脈疾患の頻度が高い。現在のところ根治的治療法はなく、早期発見による動脈硬化性疾患の発症防止が主要な対策である。LDL-C、高血圧や喫煙などの危険因子の管理が重要であり、膵β細胞からの ABCA1 を介したインスリン分泌不全による耐糖能異常の合併も多いことが報告されているので、その治療も必要である。

はじめに

タンジール病（OMIM205400）は家族性低～無 HDL-コレステロール（HDL-C）に属する常染色体潜性（劣性）遺伝を示す疾患であり、HDL-C やアポリポ蛋白 A-I 濃度の著しい低下が主要な表現型となる[1)]。タンジール病の名前は、1959 年に最初の患者が発見・報告され、疾患の集積が見いだされたアメリカ合衆国バージニア州のチェサピーク湾にある島の名前に由来する[2)]。その後 NIH の研究者により病態生理の解析がなされてきた。1991 年に、細胞とαヘリックス型 HDL アポ蛋白質との直接作用によって、細胞のコレステロールやリン脂質がアポ蛋白質（アポ）A-I に引き抜かれ、HDL 粒子が新生されることが発見され[3)]、1995 年に本疾患由来の細胞において、この HDL 粒子新生反応が欠損することが発見された[4)]。1999 年には、その原因となる遺伝子異常が *ATP binding cassette transporter A1 (ABCA1)*の機能障害型変異であることが同定された[5-7)]。これにより、このアポ A-I と ABCA1 の相互作用を介した細胞からのコレステロール・リン脂質引き抜き反応が、HDL の主要な起源であることが証明された。この *ABCA1* 遺伝子変異のホモ接合体あるいは複合ヘテロ接合体がタンジール病の疾患表現型を示す。ヘテロ接合体においても HDL-C の低下は認められが、その程度は一定しない。

１．疾患の頻度

タンジール病の症例は、2020 年までに本邦では 35 例[8, 9)]、国外では 109 例の症例報告[8)]があり、重複を含む可能性があるが、稀な疾患とも考えられる。しかしながら、疾患を起こす *ABCA1* 遺伝子の機能障害型変異の一般人口における頻度は明らかではない。Exome Aggregation Consortium のデータベースを用いた最近の論文[10)]では、機能障害型変異（フレームシフト変異、ナンセンス変異、スプライシング変異のみで、ミスセンス変異を除く）の allele 頻度に基づくと、一般人口の 400 人に 1 人が *ABCA1* 遺伝子の機能欠失型変異のヘテロ接合体であり、世界的に見て少なくとも 640,000 人に 1 人は本疾患であると考えられる。従って、かなりの数の症例が未診断であると思われる。

２．遺伝的背景と病態生理

ABCA1 は ATP 結合カセットトランスポーターファミリーに属する膜タンパクの 1 つで、ABCA1 は細胞外のαヘリックス型アポ蛋白質による、細胞内のリン脂質やコレステロールの細胞外への搬出により、原始 HDL 粒子の形成に必須の因子である（**図 1**）。この反応は血漿 HDL 粒子の主たる産生源であり、コレステロール分子を異化できないほ乳類の体細胞において、その最終処理の経路である細胞からのコレステロール搬出の主要な機構の一つである。末梢細胞では、細胞内コレステロールレベルを感知して ABCA1 発現が増強し、コレステロールを搬出させる[11)]。一方、肝細胞では末梢から回収したコレステロールの血流中

への逆流を防ぐため、ABCA1 は双方向性の制御を受ける[12, 13]。ABCA1 の機能欠損により球状の HDL が産生されず、血漿 HDL-C の濃度は極端に低下する。また、タンジール病の患者では血漿 LDL-C 濃度も正常の 1/3 程度にまで低下が見られる。その詳細な機序は不明であるが、ヒトでは HDL 中のコレステロールがアシルエステル化され、VLDL/LDL に転送されることにより、LDL 中のコレステロールのかなりの部分は HDL 由来と考えられることから、HDL-C の顕著な減少が LDL-C レベルの減少につながる可能性が想定されている。

タンジール病の患者では、末梢組織細胞での ABCA1 欠損により、細胞内コレステロールが搬出されないため、マクロファージやシュワン細胞などにコレステロールが滞留し、エステル型コレステロールとなって蓄積し、オレンジ色の咽頭扁桃腫大、角膜混濁、肝脾腫、リンパ節腫脹、末梢神経障害をきたす。タンジール病の患者では、このコレステロール逆転送系の最初のステップの障害により、血漿 LDL-C 濃度の低下にもかかわらず、粥状動脈硬化性疾患を発症させるリスクとなっていると考えられる。

一方、ABCA1 は細胞形質膜のコレステロールに富んだドメインであるラフト構造を不安定化させるようであり[14, 15]、その機能欠損は“脂質ラフト”の増加をもたらして、これが炎症性サイトカインの分泌が亢進することも示唆されている[16]。さらに、タンジール病患者では、膵β細胞の ABCA1 欠損によるコレステロール蓄積に起因して、インスリン分泌指数（insulinogenic index）が低下することも報告されており糖尿病（耐糖能異常）を合併することが多い[17, 18]。これらの代謝異常も、本症における早発性冠動脈疾患の発症増加に関わっている可能性が考えられる[8]。

タンジール病の早期の研究で、Schaefer らは放射標識した HDL の静注によって、血漿リポ蛋白の代謝動態を解析し、患者ではアポ A-I の異化が著しく増加していることを報告した[19]。しかしながら、このアポ A-I の異化過剰のデータは、ABCA1 欠損に基づいて、細胞外 HDL の異化の観点から再解釈されるべきであろう。ヒトの多機能幹細胞由来の肝細胞を用いた最近の研究では、ABCA1 欠損が angiopoietin-like protein 3 (Angptl3)の分泌を増加させることが報告されており、このことはタンジール病患者の血漿トリグリセライド（TG）の増加と合致している[20]。

３．臨床的所見

１）血漿リポ蛋白質の異常

タンジール病患者では、血漿 HDL-C は通常 5mg/dL 以下（同定された症例の平均 3 ± 3 mg/dL）、アポ A-Ⅰは 10 mg/dL 以下の著明な低値を示す[21]。血漿

LDL-C も平均正常値の 37 % 程度に低下している。TG に富んだいわゆるレムナントリポ蛋白質粒子（VLDL から LDL への代謝の中間産物）の出現を認めることも報告されている[8]。ABCA1 遺伝子変異のヘテロ接合体では、血中 HDL-C 及びアポ A-Ⅰ値は正常者の約 50%に低下することが多いが、HDL-C レベル低下の程度は一定していない。

２）理学的所見

タンジール病患者では、HDL 生合成の障害による臓器細胞からのコレステロール搬出の低下により、種々の細胞において脂質の蓄積が認められる。本症の代表的かつ典型的所見はいわゆるオレンジ扁桃である（**図２**）[8]。扁桃は分葉・腫大し、明るいオレンジ又は黄～灰色の表面を呈する[8]。再発性扁桃炎や扁桃摘出の病歴がしばしば認められる。さらに、脾腫（**図３**）とそれに伴う血小板減少症と網状赤血球増加を認めることがある。約３分の１の症例に肝腫大も認められるが、肝機能障害は通常は認めない[22]。その他の臓器へのコレステロール蓄積は、リンパ節、胸腺、腸管粘膜、皮膚などにもみられ、角膜へのコレステロール蓄積により角膜混濁を来す。

３）末梢神経障害

タンジール病患者では、軽度から重症まで様々な末梢神経障害が報告されている。知覚障害、運動障害あるいは混合障害が、一過性にあるいは持続性に出現する。深部知覚や腱反射の低下はまれで、脳神経を含む末梢神経の再発性非対称性障害や、下肢に強い対称性の末梢神経障害や脊髄空洞症様の末梢神経障害として出現する[23, 24]。

４）心血管疾患

これまでの文献上の症例報告によれば、本邦のタンジール病患者 35 例中 12 例（34.3%）、海外での 109 例中 34 例（31.2%）が、何らかの心血管疾患（**図４**）を合併していると報告されており、本症における粥状動脈硬化の進行が示唆されている[8]。血管内超音波法（IVUS: intravascular ultrasound）による観察では、びまん性の石灰化の強い冠動脈病変が報告[25]されており、これは HDL 欠損症と耐糖能異常[17]に起因すると推定される。

４．診断基準と鑑別診断

１）診断基準

厚生労働科学研究費補助金（難治性疾患政策研究事業）原発性高脂血症調査研究班において検討されたタンジール病の診断基準を**表１**に示す。

２）鑑別診断

低 HDL-C 血症の鑑別診断におけるタンジール病診断のためのフローチャートを**図５**に示した。低 HDL-C 血症（Familial hypoalphalipoproteinemia）をきたす遺伝性疾患として、古典的レシチンコレステロールアシルトランスフェラーゼ（LCAT）欠損症、魚眼病、家族性アポリポ蛋白質 A-I 欠損症が挙げられる。

角膜混濁はこれらに共通して見られるが、扁桃腫大、末梢神経障害は本疾患に特異的で、黄色腫はアポリポタンパク A-I 欠損症にだけ認められる[24, 26]。

鑑別すべき二次性低 HDL-C 血症としては、重度の肝疾患（肝硬変症など）、薬剤起因性低 HDL-C 血症の鑑別を行う。薬剤起因性低 HDL-C 血症としては、プロブコールによる低 HDL 血症があるが、特にプロブコールとフィブラート系薬剤との併用時に顕著な低 HDL-C 血症が起こることがあるので、留意する。プロブコールは中止後も影響が数ヶ月残ることがあり、プロブコールからフィブラート系薬や選択的 PPARαモジュレーターへの切り替え使用例で HDL-C が著しく低下する例があることに注意する。

５．タンジール病に対する現在の治療法

本邦においてこれまでに報告されている患者の報告[8, 9]によれば、諸外国における患者と臨床像や遺伝的プロフィールに大きな差は認められていない。現在のところ、遺伝子治療による *ABCA1* の補充などの根治的治療法は未確立である。粥状動脈硬化性疾患の著しい増加が主たる問題であるので、合併症としての動脈硬化性疾患の有無を慎重に評価することが重要である。そのために、運動負荷心電図、経胸壁心臓超音波検査、冠動脈 CT スキャン[8]などを含めた評価を行い、動脈硬化性疾患の発症防止と早期発見に努める。糖尿病（耐糖能異常）を合併することが多いことからその治療や、高血圧、喫煙などの危険因子の管理が重要である[27]。本症の血漿 LDL-C レベルは一般に低いが、もしそうでない場合はスタチンあるいはその他の薬剤で LDL-C レベルを低下させるべきである。本症でしばしば認められる耐糖能異常は 75 g 経口ブドウ糖負荷試験を行うことにより、insulinogenic index を評価すべきであろう[17]。

６．結論と将来展望

ABCA1 遺伝子に対する遺伝子治療は将来的に可能性がある。肝臓における ABCA1 遺伝子発現の補充は血漿 HDL-C レベルを増加させるであろうが、細胞からのコレステロール搬出促進や、粥状動脈硬化巣のマクロファージ、平滑筋細胞や内皮細胞などの細胞における過剰な脂質蓄積の抑制には十分ではないと思われる。従って、本症に対する根治的治療法を開発することは容易ではないであろう。

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図１．コレステロール逆転送系における ABCA1 の役割とタンジール病の病態

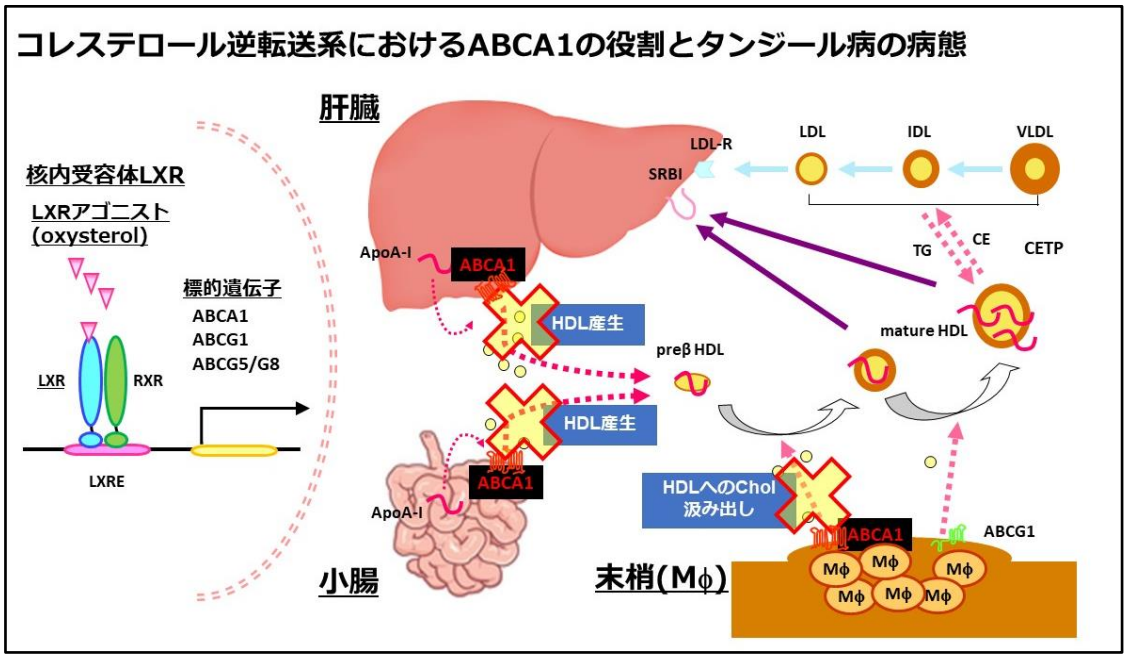


図２．タンジール病患者に認められたオレンジ扁桃（文献８より引用）

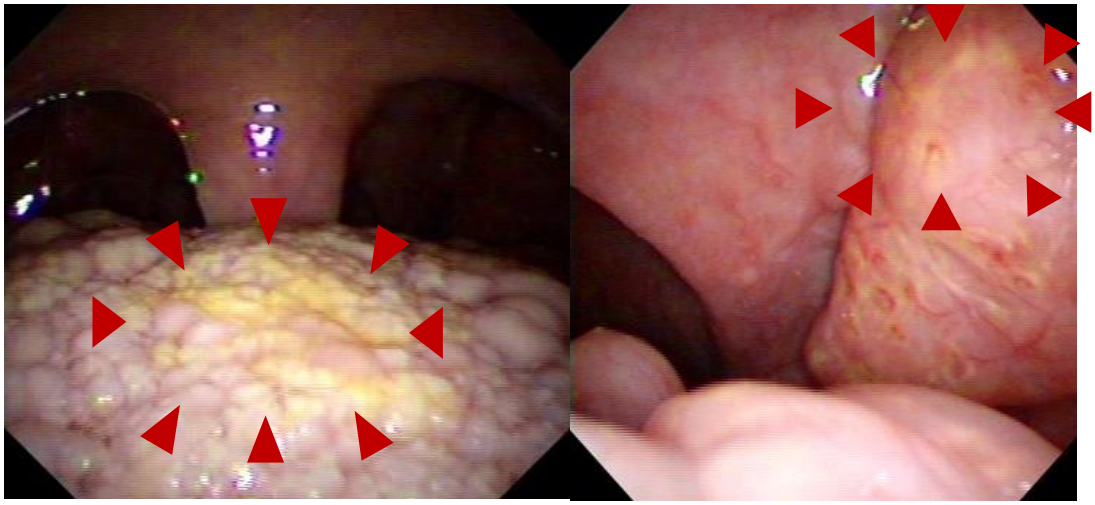


図３．40 才台の女性タンジール病患者に認められた脾腫の腹部 CT 像

（岩手医科大学、石垣　泰先生よりご提供）

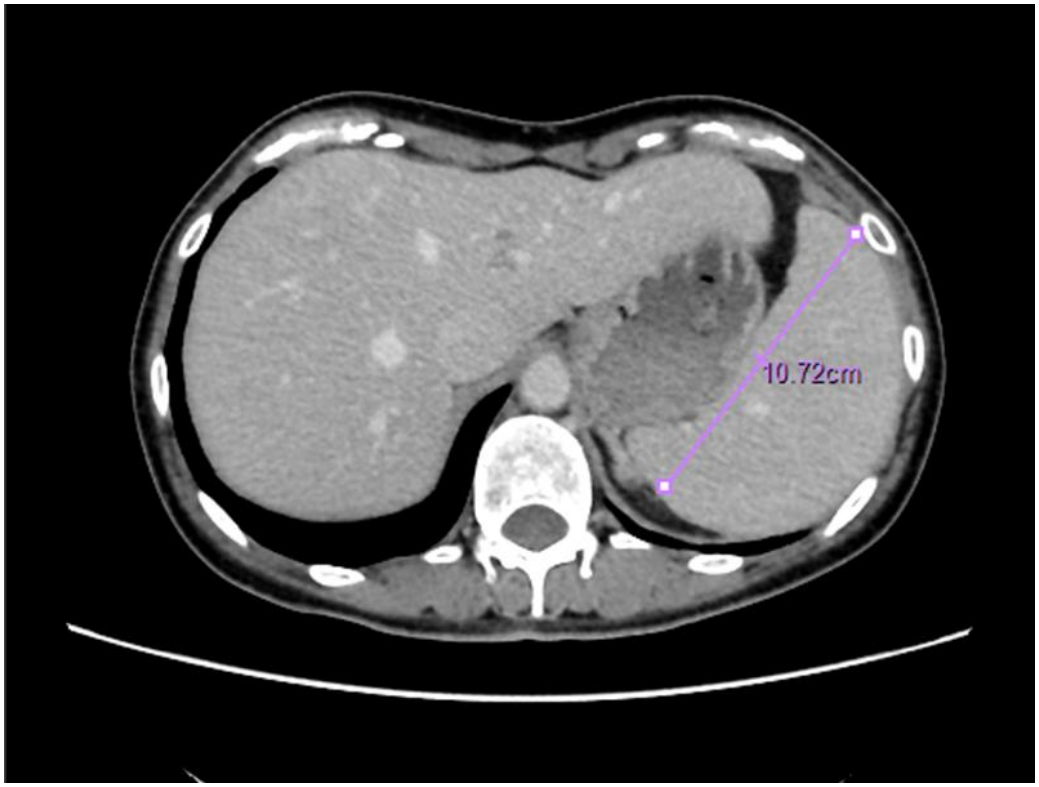


図４．50 歳台の男性タンジール病患者に認められた全身性の著しい動脈硬化性病変

矢印は動脈の狭窄や閉塞部位を示す。
（A：左冠動脈，B：右冠動脈，C：腕頭動脈，D：左腸骨動脈，E：右外腸骨動脈）

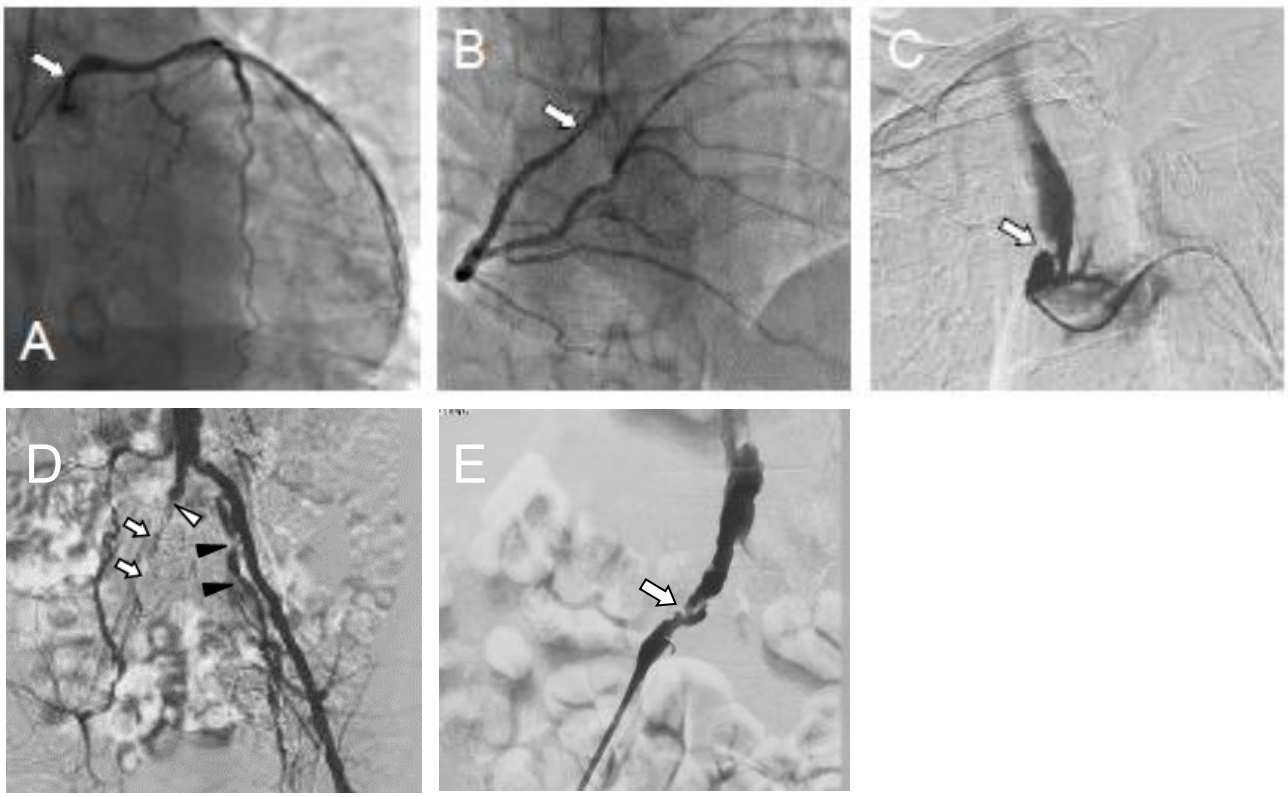
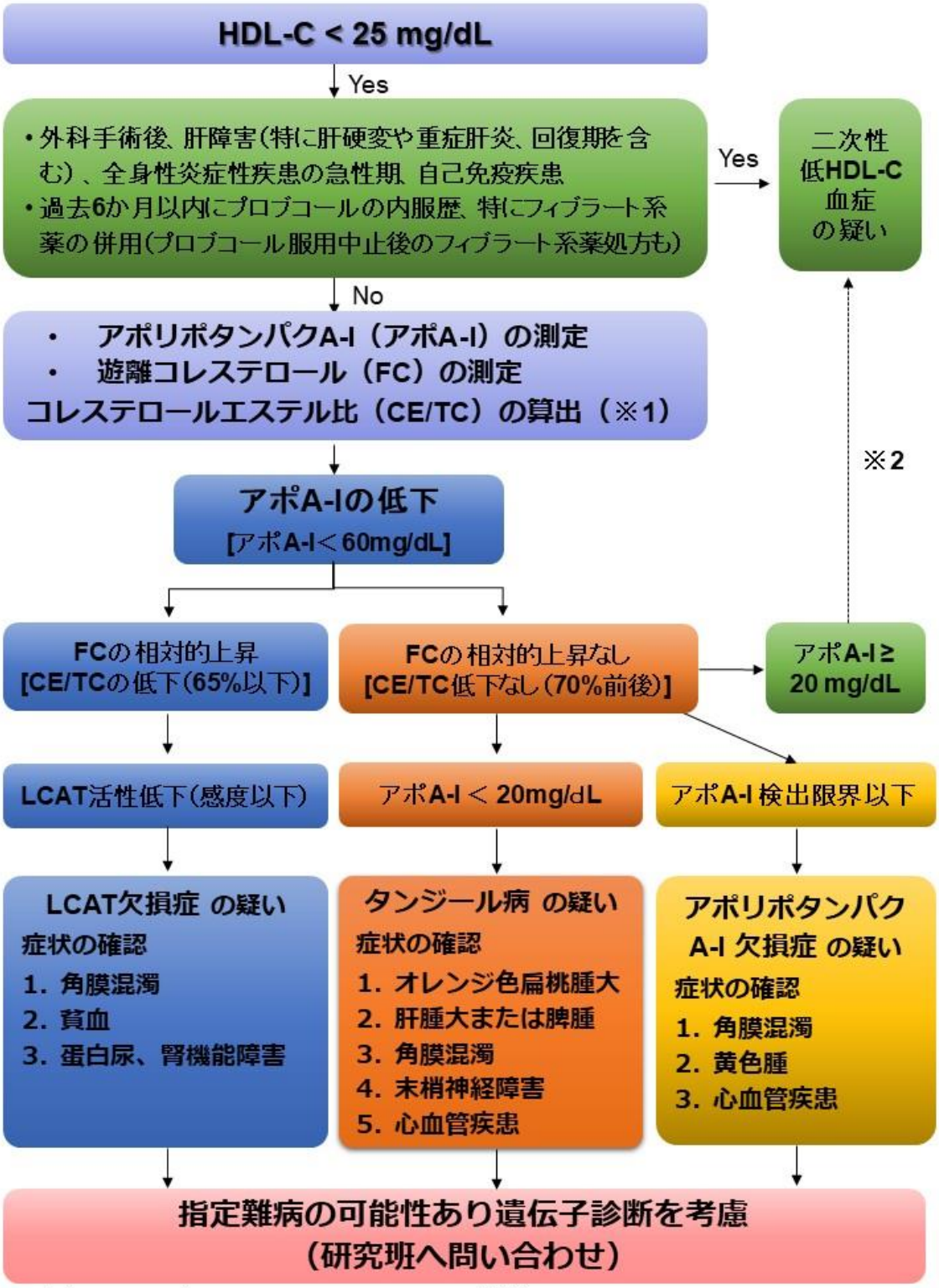


図５．低 HDL-C 血症を認めた場合の診断フローチャート



※1 CE/TC =（TC-FC）/ TC x 100 (%) による計算値
※2 タンジール病やアポリポタンパクA-I欠損症のヘテロ接合体の可能性あり

表 1. タンジール病の診断基準

Ａ．必須検査項目

１．血漿（血清）HDL コレステロール 25 mg/dL 未満

２．血漿（血清）アポ A-Ⅰ濃度 20 mg/dL 未満

Ｂ．臨床症状

１．オレンジ色の特徴的な扁桃腫大

２．肝腫大かつ/または脾腫

３．角膜混濁

４．末梢神経障害

５．心血管疾患

Ｃ．鑑別診断

以下の疾患を鑑別する。

LCAT 欠損症、アポリポタンパク A-I 欠損症、二次性低 HDL コレステロール血症*

Ｄ．遺伝子検査**

ABCA1 の遺伝子の病原性変異の同定

＜診断のカテゴリー＞

Definite: 必須項目の２項目を全て満たす例のうち、Ｂの１項目以上を満たし、Ｃの鑑別すべき疾患を除外し、D を満たすもの

Probable: 必須項目の２項目を全て満たす例のうち、Ｂの２項目以上を満たし、Ｃの鑑別すべき疾患を除外したもの

Definite、Probable を対象とする。

*外科手術後、肝障害（特に肝硬変や重症肝炎、回復期を含む） 、全身性炎症性疾患の急性期、がん等の消耗性疾患など、過去 6 か月以内のプロブコールの内服歴、プロブコールとフィブラート系薬の併用（プロブコール服用中止後のフィブラート系薬の処方も含む）

**鑑別診断が困難な場合は *ABCA1* 遺伝子検査を実施する。*ABCA1* 遺伝子の病原性変異が確認された場合は診断が可能である。遺伝子診断の方法については

（執筆責任者：小関正博、山下静也）

原発性高カイロミクロン血症

① 要約

原発性高カイロミクロン（CM）血症は、急性膵炎の発症リスクの高い難病である。CMが蓄積し始めるのは、血中トリグリセライド（TG）値が 500 mg/dl以上、特に 1,000～1,500 mg/dl程度からであるため、一般にはTG 1,000 mg/dl以上の場合を高CM血症と考える。

高CM血症は、高リポ蛋白血症のWHO分類ではI型（CMのみが増加）とV型（CMとVLDLが増加）に相当する（図１）。I型は、典型的には、CMを代謝する酵素であるリポ蛋白リパーゼ（LPL）やその関連蛋白（APOC2、GPIHBP1、LMF1、APOA5）の異常・欠損によって生じる単一遺伝子疾患が中心であり、それらは基本的に常染色体劣性遺伝を呈する稀な疾患である（図２）。遺伝子異常によるものの他、LPL、APOC2、GPIHBP1 に対する自己抗体による高CM血症も報告されている。重症例は幼小児期から発症し、膵炎に伴う腹痛などの症状の他、発疹性黄色腫（図３）、網膜脂血症、肝脾腫などを呈する。V型は、典型的には、LPL経路の遺伝子異常（*APOA5* など）によるCMやVLDLの異化障害に加えて、CMやVLDLの産生増加をきたすような環境要因（アルコール、糖尿病、薬剤など）が加わることによって生ずる。I型よりも発症が遅いことが多く、成人期から発症、後天的に増悪するケースが多い。I型同様、急性膵炎のハイリスク病態である。

原発性高CM血症の診断は、二次性の原因を除外した上で、上記LPL経路の異常を検索し、可能であれば、原因となる遺伝子変異を検索する。二次性と思われる中にも原発性が隠れていることがあり注意を要する（図４）。

原発性高CM血症の治療は、急性膵炎の予防のために、血清TG 1,000 mg/dl以下を目指し(1)、食後でもTG値が 1,500 mg/dlを超えないように(2)少しでもTG値を下げることが大切である。現時点では、原発性高CM血症の原因となるLPL経路の異常を回復しうるような根治的治療法はない。環境要因の改善（食事（低脂肪、低炭水化物）、運動、節酒など）と、限定的ではあるが高TG血症治療薬（フィブラート、選択的PPARαモジュレーターなど）が主な治療の選択肢となるが、治療抵抗性なことが多い。最近、ゲノム研究から明らかとなった高TG血症関連遺伝子（*APOC3*、*ANGPTL4* など）を標的とした新たな治療薬が開発され、原発性高CM血症への臨床応用が期待されている。

原発性高CM血症は難病指定されているが、有効な治療薬に乏しい現状を克服するために原因遺伝子のさらなる解明、新たな治療薬の開発、膵炎や動脈硬化ハイリスク群を見分けるための診断指標同定などが喫緊の課題である。希少疾患の疫学的知見を得るには、全国規模のシステマティックな症例蓄積が必須であり、厚労省の「原発性高脂血症に関する調査研究班」では、PROLIPID研究を開始している。原発性が疑われる場合には専門医に紹介して、専門的な検査をすすめることが望ましい。

② はじめに：CM代謝概説

カイロミクロン（CM）は食事由来の脂質を格納したリポ蛋白である。アポリポ蛋白B-48（apoB-48）（CM１粒子あたり 1～2 分子）(3,4)を核として小腸で合成される。その主要な生理的役割は、全身の各組織へのエネルギー源としてのTGの運搬と、小腸で吸収された脂溶性ビタミンの運搬である。CMは、その中に含まれるTGがLPLによって加水分解されることにより代謝され、CMレムナントとなり、肝臓に取り込まれる。LPL経路に異常があると、CMの代謝が停滞し、異常に蓄積し、高CM血症となる。

CMの半減期は数分程度と非常に短く、健常者の空腹時（12 時間以上絶食）の血中には通常存在しない。CMが蓄積を始めるのは、血中TG値が 500 mg/dl以上、特に 1,000～1,500 mg/dl程度からである(5)。随時採血TG値 1,000 mg/dl以上で急性膵炎を引き起こす可能性があることから(6)、TG1,000 mg/dl以上を高CM血症のスクリーニングの基準とするのが妥当であるが(2)、TG 500mg/dl以上から注意が必要である。

③ 疾患の概要（特徴・合併症・自然予後等）

I型は典型的には、単一遺伝子疾患であり、LPL経路の異常（遺伝子異常、自己抗体による阻害など）に由来する(7)。LPLはVLDLも代謝するが、VLDLは蓄積しないことが多い（おそらく肝性トリグリセリドリパーゼ（HTGL）などによりLPL非依存的にも代謝されるため）。

V型は典型的には、遺伝-環境連関により発症・増悪する(7)。LPL経路の遺伝子異常（*APOA5* など）に加えて、VLDLやCMの産生亢進をきたすような環境要因（食事過多、運動不足、アルコール多飲、糖尿病、妊娠など）が加わることにより悪化する。特に主要なものは糖尿病とアルコールであり、V型高脂血症のうち、1/3 に糖尿病が合併、1/3 にアルコール多飲があると報告されている(6)。重度のインスリン依存状態の糖尿病患者がインスリン注射を行えなかった場合などにみられる糖尿病脂血症（diabetic lipemia）では、V型だけではなくI型を呈する場合もある(6)。

I型（CMが増加）、V型（CMとVLDLが増加）は、TG、総コレステロール（TC）値によりおおまかに分類可能である。TGが 1,000 mg/dl以上ではCMが蓄積し始めるため(5)、TG > 1,000 mg/dlの場合に、I型かV型となる。このうち、V型ではVLDLも増加しているため、TC値も増加する（典型的には TC > 300 mg/dl）。一方、I型ではTCの増加は軽度にとどまる（典型的には TC < 260 mg/dl）。これはCM（TG:TC比がおよそ 10:1）よりも、VLDL（TG:TC比がおよそ 5:1）の方がコレステロール含有率が高いためである。典型的なI型では、血清TC値は血清TG値の 1/10 前後もしくはそれ以下となる。ただし、CMとVLDLはともにLPLによって代謝されるため、I型とV型は厳密には区別し難く、原因遺伝子もオーバーラップする(8)。病型分類は、厳密にどちらかに分けることに意義があるというよりは、どのリポ蛋白が増えているかの目安として重要であり、病型に典型的な合併症や二次的要因を鑑別し、治療法を選択する上で役に立つ。

I型、V型いずれにおいても、高CM血症は急性膵炎や動脈硬化のリスクとなりうる。代謝異常は生涯にわたって持続するにもかかわらず、根本的な治療薬はなく、厳重な食事制限は

ある程度有効ではあるものの遵守困難なことが多く、急性膵炎を繰り返してしまうケースも多い。

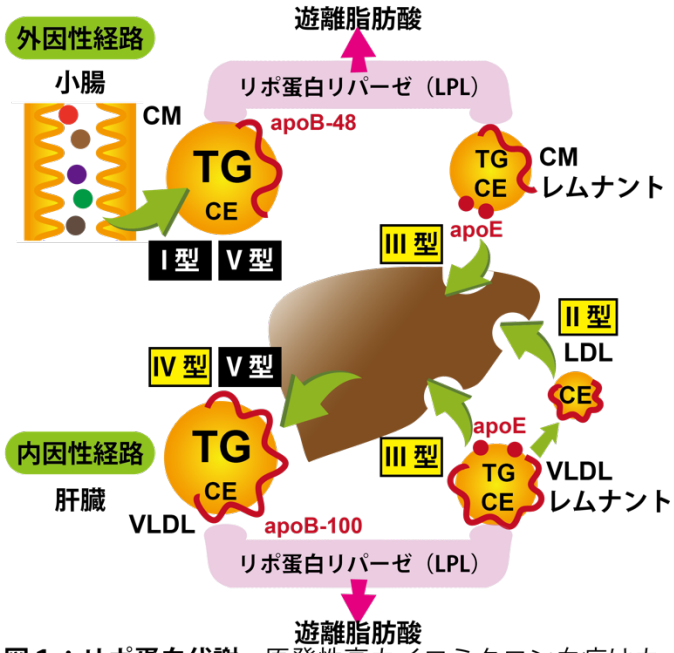


図１：リポ蛋白代謝　原発性高カイロミクロン血症はカイロミクロン（CM）が増加するⅠ型と、CM と VLDL が増加するⅤ型に分けられる。CM と VLDL は LPL により代謝される。

④ 疾患頻度

I型は非常に稀である。LPL経路の遺伝子（*LPL*、*APOC2*、*GPIHBP1*、*LMF1*、*APOA5*）の欠損症や異常症が知られているが、最も頻度の高いLPL欠損症の場合でも 50 万～100 万人に１人である。多くの場合、常染色体劣性遺伝である。稀に、LPL経路蛋白（LPL、APOC2、GPIHBP1）に対する自己抗体による場合がある。

V型はI型よりも頻度は高い。その頻度は環境要因に伴って変化するが、TG 2,000 mg/dl 以上のものは人口の約 0.02%（約 5,000～6,000 人に１人）との報告がある(5)。

⑤ 遺伝学（病因遺伝子、遺伝形式等）

高CM血症の最初の症例は 1932 年に報告された(5)。以後、原因遺伝子として、*LPL*（1960 年）、その補因子であるアポリポ蛋白C-II（*APOC2*）（1978 年）が同定され、最近ではLPL関連蛋白群（*APOA5*、*GPIHBP1*、*LMF1*）の欠損症や異常症が同定されている。しかし、原因遺伝子が不明のケースもかなり多い（I型の 33%、V型の 77%が原因遺伝子不明との報告もある）(8)。

1）*LPL*と*APOC2*

＊*LPL*欠損症（OMIM 238600）

1960 年の報告(9)以来約 150 個の遺伝子変異、日本人患者においても 30 個以上の変異が報告されている(9)。疾患頻度は、50 万人～100 万人に 1 人程度と言われている。

＊アポリポ蛋白C-II欠損症 (OMIM 207750)

貧血に対する輸血によって高TG血症が著明に改善した(血清TG値が 1,750 mg/dlから 196 mg/dlへ低下)ことが契機となり 1978 年にカナダで(10))、1979 年に日本(11)で発見され、以来現在までに世界でも 20 家系ほどの報告がある。*LPL*欠損症に比べると、高TG血症の程度は軽度（ホモの場合TG値は 500～10,000 mg/dl程度）で、症状の発現時期も遅く（これまでの報告では 13～60 歳で診断されている）、発疹性黄色腫や肝脾腫も少ない。しかしながら、成人になってからの急性膵炎は逆に*APOC2* 欠損症の方が頻度も多く、症状もより重症といわれている（64%で認めたとの報告もある(5)）。これは、高TG血症が重度な*LPL*欠損症などのケースの方が幼少期からしっかりと食事療法（脂肪制限食）がなされるが、成人期となってから発症する場合には、食事療法を守るのが難しいことが多いためと考えられている(5)。

2) 新たなLPL経路蛋白群（図２）

LPLの機能に必要な蛋白が近年同定されている。LPLは《step 1》脂肪細胞や筋細胞などの間質細胞で合成・分泌され、《step 2》血管内皮細胞の内部を通過し、《step 3》血管内皮細胞の血管内腔側の細胞膜表面に繋留し、《step 4》血中を流れるリポ蛋白のTGを水解する。これらの過程に必要な蛋白の欠損が、高CM血症の原因となることが分かってきている。《step 1》にはERシャペロン蛋白LMF1 (12)、《step 2》と《step 3》にはGPIHBP1(13,14)、《step 4》にはAPOA5(15)が必要であり、LMF1、GPIHBP1、APOA5 の異常は高CM血症の原因となる。

＊*GPIHBP1* 異常症 (OMIM 615947)

GPIHBP1 は 2003 年に同定され(13)、欠損マウスモデルでの機能解析から(14)、CM代謝における重要性が明らかとなった。その後、多くの*GPIHBP1* の遺伝子異常 (G56R, C65S, C65Y, C68G, Q115Pなど) がヒトの高CM血症の原因として見出されている(16) (17)。

＊*LMF1* 異常症(OMIM 246650)

2007 年に、LMF1 の欠損が高CM血症をきたすことが初めて報告された(12)。Y439X変異では、LPL活性の 93%低下、HL活性の約 50%低下をきたし、著しい高TG血症 (約 3,000 mg/dl) を呈する。W464X変異では、LPL活性、HL活性がそれぞれ 76%、27%減少する(18)。

＊アポリポ蛋白A5 異常症(OMIM 144650))

2000 年に比較ゲノム学的アプローチで*APOA5* 遺伝子が同定され (15)、2005 年に*APOA5* 遺伝子異常が高CM血症の原因となることが初めて報告された(19)。乳幼児期発症のI型を呈するケースも報告されているが(20)、多くの場合、環境要因（糖尿病、肥満、加齢、高炭水化物食、高脂肪食、飲酒、妊娠など）の影響を受けて、後天的に増悪しV型を呈する(21)。*APOA5* の遺伝子異常はIV型 (VLDLが蓄積) を呈することも多く、動脈硬化のリスクとなることも知られているため(22,23)、急性膵炎だけでなく動脈硬化予防にも注意が必要である。治療上は環境要因を抑えることが大切であり、ω-3 系多価不飽和脂肪酸製剤が有効なケースも報告されている(24)。

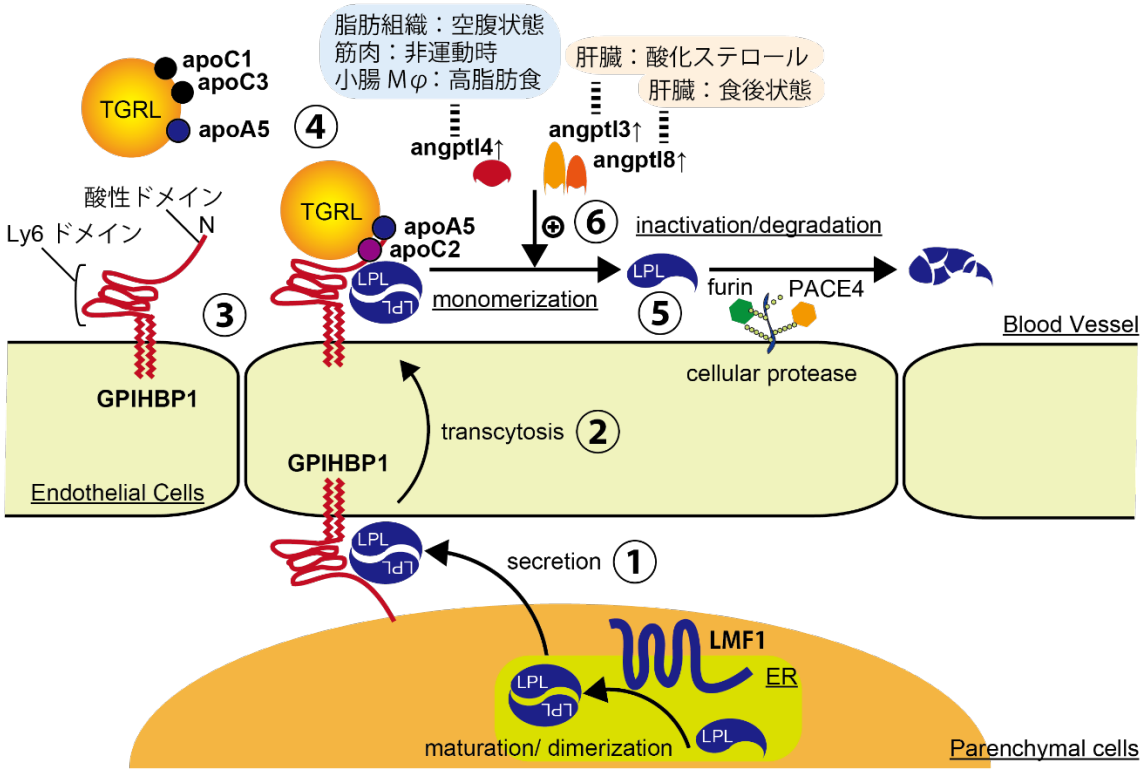


図２：LPL とその関連蛋白の異常は、高カイロミクロン血症の原因となる

LPL は、血管内皮細胞の血管内腔側に繋留し、CM や VLDL などの TG リッチリポ蛋白 (TGRL) を代謝している。この LPL の機能には以下のステップが必要である。
① 脂肪細胞や筋細胞などの間質細胞（Parenchymal cells）での LPL の合成と分泌（LPL の小胞体（ER）でのダイマー化／成熟が必要であり、これを促進する蛋白 LMF1 が必須）
② LPL のトランスサイトーシス（血管内皮細胞の間質側の GPIHBP1 が LPL を捕捉し、LPL を血管腔側へ移動）
③ LPL の血管腔側への繋留 (tethering)（GPIHBP1 が Ly6 ドメインと酸性ドメインで LPL と結合し LPL を血管内皮表面に繋留）
④ 血中の TGRL の血管内皮細胞表面への停留（margination）（GPIHBP1 は酸性ドメインで apoA5 を介して TGRL と結合（この反応は apoC1 や apoC3 によって阻害）。GPIHBP1 は TGRL と LPL の橋渡しをしている）
⑤ LPL の不活性化（モノマー化のあと細胞由来プロテアーゼ（furin (PCSK3), PACE4 (PCSK6) により分解され不活性化）。
⑥ ⑤の過程の angptl ファミリー蛋白（angptl3, angptl4, angptl8）による促進（angptl ファミリーはそれぞれ特徴的な転写制御を受けており、LPL 活性を様々な組織のニーズに合わせて調節している）

3）LPL経路蛋白群に対する自己抗体

遺伝子異常による高CM血症の他に、これらの蛋白に対する自己抗体による高CM血症が知られている。LPL、APOC2 に対する自己抗体（OMIM 118830）(25)の他に、最近、GPIHBP1 に対する自己抗体による高CM血症が報告された(26)。原因不明の高CM血症、膠原病合併の高CM血症の際はその可能性を考える。

原発性高CM血症が疑われる場合には、これらの遺伝子・蛋白異常を見分けるための検査や、可能であれば遺伝子検査を行うことが望ましい（表１）。またほとんどの場合劣性遺伝をとるため、近親婚の家族歴の聴取は重要であり、遺伝性疾患を疑う鍵となる。父と母の出身地を聞くことで血族結婚が判明することもある。

⑥ 病態（症状、合併症）

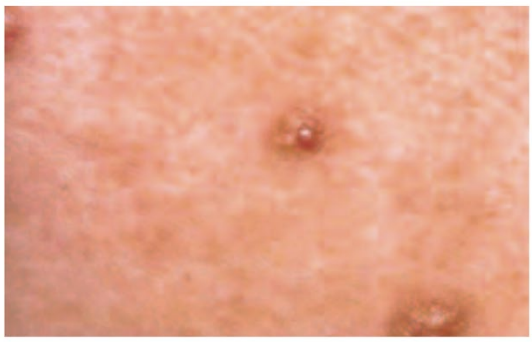
その原因となる遺伝子異常の重症度に応じて、あるいは脂肪摂取をどれだけ忌避しているかの個々人の違いに応じて、発症時期は幼小児期あるいは成人期と様々である(9)。環境要因（糖尿病の増悪、アルコール多飲、妊娠など）は増悪の契機となる。重症例では小児期から脂肪摂取後の上腹部痛を繰り返す。例えば、重度な*LPL*欠損症の場合、授乳中～幼少期などから、著明な高TG血症、膵炎（脂肪摂取時の腹痛発作に注意）、乳糜血清、網膜脂血症、発疹性黄色腫、肝脾腫などを呈する。患者の多くは授乳中～幼少期に発見される（*LPL*欠損症 43 症例のうち、13 症例は生後 1 年以内、22 症例は 10 歳未満、8 症例は 10 歳以後に見出されたとの報告もある(5)）。主要な症状を記す。

＊急性膵炎：血清TG値が 1,000 mg/dlを越えると急性膵炎の発症リスクが高まり、発症例ではほとんどが 2,000 mg/dlを超えているとされる。TG > 1,000 mg/dlの症例のうち、約20%程度で急性膵炎を発症するとの報告がある(6,27)。TGが 1,000 mg/dl以下でも、急性膵炎のリスクが増加することが報告されており、注意が必要である(28)。高TG血症による急性膵炎は、急性膵炎全体のうち 12～22%を占めるとの報告もあり稀ではないが(27,29) (5)、急性膵炎ではTG値が測定されていないことも多く、過小評価されている可能性もある。高CM血症による急性膵炎は、他の原因による急性膵炎と比べて、症状や臨床経過などの点に違いはない。腹痛、悪心、嘔吐、背部痛などの症状に気をつけ、急性膵炎の症例、頑固な腹痛に高TG血症を伴う症例では、高CM血症を鑑別する。

＊乳糜血清：採血した血液が白色ピンク上、そのまま置いておくと上層に白色のクリーム層が浮いてくる。例えば、4,000 mg/dlのTGを含む血清は、4%ミルクと同じような乳糜様外見を呈する(5)。CMは体内で最大のリポ蛋白（75-1,200 nm）であり、比重が軽いため、4℃、24 時間の静置でクリーム層となって上層に浮いてくる。ちなみに、I型高脂血症ではCM単独の増加を反映して下層は透明となるが、V型高脂血症ではVLDLも増加するため下層は白濁している。

＊網膜脂血症：眼底検査で、乳糜色の網膜血管を認める(30)（文献 30 に写真あり）。血清TG値が 4,000 mg/dlを超えると出現することが多い。視力には影響しない。

＊発疹性黄色腫：四肢伸側、臀部、肩などを好発部位として出現・消退する小さな（数mm程度の）ピンクがかった黄色い発疹である(31)（図３）。CMを貪食した皮膚のマクロファージ細胞によるものであり、通常TG値 2,000 mg/dl以上で出現、約半数の患者で認める。TG値改善後は、数週間から数ヶ月の経過で消退する。消退する経過では、TGが抜け、コレステロールエステルに富む、赤みがかった病変を呈する(5)。例えば小児ではこの症状により皮膚科で診断されることもある。



35歳男性。家族性Ⅰ型高脂血症（リポ蛋白リパーゼ欠損症）にみられた発疹性黄色腫。

（寺本民生氏提供）

図３：発疹性黄色腫

「動脈硬化性疾患予防のための脂質異常症治療ガイド 2013 年版」（日本動脈硬化学会）より引用。

＊肝腫大と脾腫：脂質を貪食した泡沫マクロファージ細胞の浸潤による。脾腫は、脂肪制限食などによる血清TG値の改善とともに、速やかに（1 週間以内程度）軽快する(5)。

＊その他希釈効果などによる検査値異常：偽性低Na血症、低アミラーゼ血症、Hb低値、ビリルビン高値(5)。

＊その他の合併症：呼吸困難（感）、神経学的症状（認知症、うつ病、記憶障害）の報告もある(5)。

⑦ 我が国の診断基準と診断方法の実際

表１に診断基準を示す(2)。

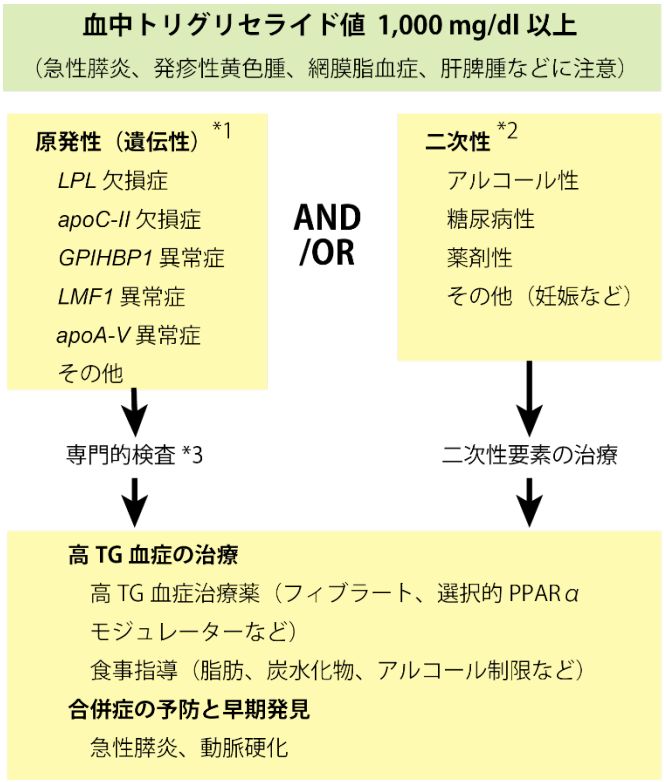
⑧ 鑑別疾患

鑑別疾患は表１に記載の通りである。

なお、二次性と思われる場合でも原発性の原因となる遺伝的素因が隠れている可能性があり注意する。

膠原病を合併している場合には、先に述べた自己抗体による高CM血症を鑑別する(25,26)。

妊娠中の著明な高TG血症の際は原発性高CM血症を鑑別する。妊娠は一般に高脂血症をきたすが（健常者においてもLDL-Cは 1.5 倍程度、TGは 2 倍程度増加する）(32)、原発性高CM血症の患者においては特に高TG血症の増悪と膵炎の合併に注意する。妊娠中の急性膵炎の約半数は高TG血症に起因するとの報告もある(33)。



*1,2 二次性と思われる中にも原発性が隠れていることがあり注意する。
*3 LPL 活性、apoC-II 蛋白、apoA-V 蛋白、自己抗体、遺伝子検査など。

図４：原発性高カイロミクロン血症の診断と治療のフローチャート

⑨ 現在の治療法

原発性高CM血症の治療は、急性膵炎の予防のために、TG 1,000 mg/dl以下を目指し(1)、食後でも1,500 mg/dlを超えないように(2)少しでも血中TG値を下げることが大切である。

LPL経路の異常を回復し得るような根治的な治療法は残念ながらない。ヒト*LPL*の機能獲得型多型 (S447X)をアデノ随伴ウイルスベクターにて一過性に発現するalipogene tiparvovec (Glybera®)が、2012 年に欧州初の遺伝子治療薬として*LPL*欠損症を対象として認可され(34)、臨床症状と膵炎発症率の軽減が期待されたが、極めて高額な薬価（110 万ユーロ）と効果不明確のため、2017 年に発売中止となっている。現時点では、環境要因の改善と、その効果は限定的であるが高TG血症治療薬（フィブラート、選択的PPARαモジュレーターなど）を用いる。

高TG血症の悪化の契機となる環境要因、生活背景はよく聴取する。食事（特に、脂肪、炭水化物やアルコールの摂取）、妊娠などの生理的変化、肥満症、糖尿病などの合併、服薬状況（薬剤性の可能性）には特に注意し、環境要因の改善につとめる。

これらの治療の効果は限定的であり、治療抵抗性で膵炎を繰り返してしまうことも多いが、脂肪摂取制限の遵守不良は合併症としての膵炎をより重症化させることから(5)、生活指導と服薬指導含め、難治性疾患としてのケアを生涯にわたって行うことが大切である。

＊脂肪摂取制限：１日 15～20g以下（総カロリーの 15%以下）。妊娠中の高CM血症に対して、妊娠中期や後期での１日２ g以下の脂肪制限が有効であり、新生児にも影響がなかったとの報告もある(5)。

＊中鎖脂肪酸（medium chain triglyceride（MCT））：小腸からの吸収の際にMCTはCMに乗らず直接門脈系に流入するため、乳児のMCTミルク、脱脂粉乳、大人でのMCTを使った料理がすすめられる。

＊炭水化物摂取制限：炭水化物制限はVLDLの産生を抑える。VLDLとCMは同じLPL経路で代謝されるため、VLDLの抑制はCM代謝の改善につながり得る(35)。

＊アルコール摂取制限：エタノールとして１日 20g以下が目安となるが、個人差があり、基本的には禁酒が望ましい。

＊薬物療法：TG降下薬（フィブラート、選択的PPARαモジュレーターなど）が有効な場合もある。基本的には高CM血症に有効な薬剤はないが、VLDL代謝の改善はCM代謝の改善につながり得る(35)。ω-3 系多価不飽和脂肪酸製剤で軽快するケースもあるが、魚油サプリメントによる高CM血症悪化の報告があり注意が必要である(1)。

＊二次性高CM血症の治療：高CM血症の原因となる後天的な要素を可能な限り除去する（糖尿病やアルコール多飲、肥満症の治療など）。極端な減量は、体重がリバウンドした際には、かえってより重度の高TG血症と急性膵炎を起こす危険があり、注意する。糖尿病合併の場合には、糖尿病治療によって高TG血症が軽快すること、糖尿病治療薬によってTG低下作用に差が出る可能性に留意して、治療薬を選択する。例えばピオグリタゾンが他剤より有効なケースなどもある。

＊急性膵炎の治療：通常の急性膵炎の治療（絶食、低カロリー輸液など）を行う（但し、脂肪製剤の投与や高カロリー輸液は一般的には行わない）。著しい高TG血症が急性膵炎の原因となっている場合には、血漿交換療法も治療の選択肢となる（米国アフェレーシス学会ガイドライン）(36)。他に難治性の再発性高TG血症性急性膵炎（HTGP）に対し、抗酸化療法が有効との報告もあるが(37)、一定した見解はない。特殊なケースでの治療法として、アポリポ蛋白C-II欠損症の場合には、急性膵炎などの緊急時に新鮮凍結血漿の輸血が有効である。アポリポ蛋白C-IIが補充されることにより、血中のTG値は速やかに低下する(10)。

⑩ 将来の展望

１）根本的な治療薬について

近年のゲノム研究から高TG血症と関連する遺伝子が多く同定されており、これらの遺伝子を標的としたアンチセンス核酸医薬、モノクローナル抗体製剤の中には、原発性高CM血症への有効性が示唆されているものもある。アポリポ蛋白C-III（*APOC3*）に対するアンチセンス核酸医薬（Volanesorsen（ISIS-APOCIIIRx, ISIS 304801））(38)、diacylglycerol acyltransferase 1（DGAT1）阻害薬(pradigastat)（39)、抗ANGPTL4抗体(40)、ANGPTL3に対する抗体やアンチセンス医薬(IONIS-ANGPTL3-LRx)(41,42)が開発されている。このうちVolanesorsenは、健常人でのphase 1、高TG血症患者でのphase 2を経て、*LPL*欠損症を含む高カイロミクロン血症患者での有効性も示されるなど(38)、今後の臨床応用が期待されていたが、副作用もあり、FDAの認可は得られていない。他に、MTP阻害薬（lomitapide）が高カイロミクロン血症の治療に有効な可能性もあり、長期的な有効性・安全性の検討結果が待たれる（43）。

２）原因遺伝子について

原発性高CM血症の多くは、まだ原因遺伝子が明らかでない(8)。このようなケースの遺伝子解析からは、新たな原因が見つかる可能性がある。例えば、*APOC2* の極度の発現低下も高カイロミクロン血症の原因となりうることが最近示唆された（アポリポ蛋白C-II低下症）(44)。新たな原因遺伝子は新たな治療法開発につながる可能性があり、病因の更なる解明が望まれる。

３）膵炎ハイリスクの指標について

TG ＞ 1,000 mg/dlの症例でも、すべてが急性膵炎となるわけではなく、約20%程度しか急性膵炎にならないとの報告もある(6,27)。血清TG値が 30,000 mg/dl近くでも急性膵炎にならないケースも報告されている(5)。一方で、マイルドな高TG血症（TG 1,000 mg/dl以下）も急性膵炎のリスクになりうる(28)。血清TG値と急性膵炎の重症度も必ずしも相関しない(45)。どのような臨床的特徴の高CM血症が膵炎のリスクが高いかがわかれば、そのような患者を重点的に治療することが可能となるであろう。

４）動脈硬化ハイリスクの指標について

高CM血症が動脈硬化のリスクとなるかについては、これまでも議論があったが(2)、疫学的には、著しいTG高値は急性膵炎のリスクであると同時に動脈硬化のリスクでもある(28)。遺伝疫学的研究からも、高TG血症や高CM血症をきたす遺伝子異常（*APOA5* など）は、動脈硬化のリスクともなることが報告されている(22,23)。例えば、*APOA5* は早発性冠動脈疾患のリスク遺伝子として*LDLR*（LDL受容体）に次ぐリスクであると報告されている(23)。高CM血症の動脈硬化惹起性は、原因となる遺伝子異常に依存している可能性もあり、今後の解明が待たれる。現時点での臨床的には、動脈硬化の合併に注意し、危険因子を管理することが重要となる。

おわりに

原発性高CM血症の原因遺伝子は完全には明らかではなく、根本的な治療法もなく、厳しい脂肪摂取制限などを生涯にわたり行なってもなお、急性膵炎を繰り返すケースも多い。このような背景から、原発性高CM血症は難病指定されている（表１）。原発性が疑われる場合には専門医に紹介し、専門的な検査をすすめることが望ましい。紹介基準としては、日本動脈硬化学会の「脂質異常症診療ガイド 2018 年版」にもある通り、急性膵炎のリスクの高くなるTG > 500 mg/dlが目安となり、随時でもTG>1,000 mg/dlは要注意である。厚労省を中心とした「原発性高脂血症に関する調査研究班」では、現在、PROLIPID研究という全国レベルでの原発性高脂血症患者の登録調査研究を行っている。希少疾患の疫学にはシステマティックな症例蓄積が必須である。膵炎や動脈硬化ハイリスク群を見分けるための診断指標同定、原因遺伝子の解明、新たな治療薬の開発などは喫緊の課題である。

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表１：原発性高カイロミクロン血症の診断基準（難病情報センターの診断基準に最新の情報をアップデートしたもの）

＜診断基準＞　Definite、Probableを対象とする。

必須条件：(1)及び(2)を認め、鑑別診断（下記D）が除外される。
(1)血清トリグリセリド値　1,000 mg/dL以上（空腹時採血(食後 12 時間以上)）
(2)カイロミクロンの証明（血清静置試験[*1]、超遠心法、電気泳動法、HPLC法による）
(*1: 血清を４℃で 24～48 時間静置した後に、血清の上清にクリーム層を認める）

Ａ．症状 主症状：１～４、副症状：５、６
１．繰り返す腹痛AND/OR急性膵炎
２．発疹性黄色腫
３．網膜脂血症の存在
４．肝腫大AND/OR脾腫大
５．呼吸困難感
６．神経精神症状（認知症、うつ病、記憶障害）

Ｂ．検査所見
１．LPL活性・蛋白の欠損あるいは著明な低下（正常の 10%以下）。
（ヘパリン静脈注射後血漿(注 1)、脂肪組織生検検体、単球由来マクロファージ。）
２．アポリポ蛋白C-IIの欠損あるいは著明な低下（正常の 10%以下）。
３．アポリポ蛋白A5 の欠損あるいは著明な低下（正常の 10%以下）。
４．LPL、ヘパリン、アポリポ蛋白C-IIに対する自己抗体の証明(注 2)。

Ｃ．遺伝学的検査
１．　リポ蛋白リパーゼ遺伝子の変異
２．　アポリポタンパクC-ＩＩ遺伝子の変異
３．　*GPIHBP1* 遺伝子の変異
４．　*LMF1* 遺伝子の変異
５．　アポリポタンパクA-V遺伝子の変異

Ｄ．鑑別診断
１．　III型高脂血症
２．　家族性複合型高脂血症（FCHL）
３．　二次性高脂血症（アルコール多飲、ネフローゼ症候群、神経性食思不振症、妊娠、糖尿病、リポジストロフィー、ウェーバー・クリスチャン（Weber-Christian）病、甲状腺機能低下症、先端巨大症、クッシング症候群、ネルソン症候群、薬剤（エストロゲン、ステロ

イド、利尿薬、βブロッカー、SSRIなど抗精神病薬、痙攣治療薬、HIV治療薬、免疫抑制剤など）、その他高TG血症を来す疾患（多発性骨髄腫、全身性エリテマトーデス（SLE）、悪性リンパ腫、サルコイドーシスなど））

＜診断のカテゴリー＞

Definite（確定診断）：必須条件に、ＢあるいはＣのいずれかの異常（疾患関連あり）が確認された場合。

Probable（臨床的診断）：必須条件に、Ａの主症状のいずれかを認める場合。

Possible（疑い例）：必須条件のみ、あるいは、必須条件にＡの副症状を認める場合。

（注１）活性型のLPLは毛細血管内皮細胞表面に静電的に結合して係留されているため、ヘパリンを静注することによって初めて流血中に出現する。そのため通常、ヘパリン（10～50 U/kg(2)、60～100 U/kg(5)）静注 10～15 分後の血漿中のLPL活性と蛋白量を測定して診断が行われる。GPIHBP1 欠損症の場合は、その前後のタイムポイントでの測定が有用である可能性もある。ヘパリン静注後血漿中の総リパーゼ活性のうちLPLによるものは約 1/3 で、残りのほとんどは肝性トリグリセリドリパーゼ（HTGL）によるものであるため、LPL活性の分別測定のためには抗LPL抗体や抗HTGL抗体が必要となるが、硫酸プロタミンや 1M NaClにてLPLを失活させる方法もある。安定した合成基質が必要とされるなど熟練を要したが、現在では研究用として測定キットも市販されており、また蛋白量の測定も一般臨床検査として採用されている。

（注２）本文中に記載の通り、最近GPIHBP1に対する自己抗体による高CM血症が報告された。

（執筆責任者：後藤田貴也、岡崎啓明）

脳腱黄色腫症

要約

脳腱黄色腫症は *CYP27A1* 遺伝子変異を原因とする常染色体劣性の遺伝性疾患である．*CYP27A1* 遺伝子は 27-水酸化酵素をコードしており，脳腱黄色腫症患者では本酵素活性が著しく低下している．その結果，血清コレスタノールが上昇し，脳，脊髄，腱，水晶体，血管などの全身臓器にコレスタノールが沈着することにより，様々な臓器障害をきたす．本症の臨床症状は，腱黄色腫，新生児期の胆汁うっ滞，小児期の難治性下痢，若年性白内障・冠動脈疾患・骨粗鬆症といった全身症状と，精神発達遅滞・認知症，小脳性運動失調，てんかん，錐体路症状，錐体外路症状，末梢神経障害といった神経症状に大別される．病型には，多彩な臨床症状を呈する古典型，痙性対麻痺を主徴とする脊髄型，神経症状を認めない非神経型，新生児胆汁うっ滞型がある．診断は，臨床症状から本症を疑い血清コレスタノール値の上昇を確認する．*CYP27A1* 遺伝子検査により確定診断を行うことが望ましい．治療としてはケノデオキシコール酸の有効性が確立している．早期治療により良好な経過をとりうるが，治療が遅れると重篤な後遺症を残す． 脳腱黄色腫症は治療可能な疾患であり，早期診断・治療が非常に重要である．

はじめに

脳腱黄色腫症は古くから知られている脂質代謝異常症であるが，その臨床像は多様であり未診断例が非常に多い．本症はケノデオキシコール酸などによる疾患修飾療法が可能な疾患であり，早期診断・治療が非常に重要である．本稿では，最近実施された本邦における全国調査結果[1)]，最新の診断基準・診療ガイドライン[2)]を含め，脳腱黄色腫症についての最近の知見を概説する．

疾患の概要（特徴・合併症・自然予後など）

脳腱黄色腫症は，*CYP27A1* 遺伝子変異を原因とする常染色体劣性の遺伝性疾患で[3-6)]，主にコレスタノールが全身臓器に沈着することにより様々な臓器障害が惹起される．臨床病

型は，多彩な臨床症状を呈する古典型[7-10]，痙性対麻痺を主徴とする脊髄型[1,8,11-14]，神経症状を認めない非神経型[1]，新生児胆汁うっ滞型[9,15-17])に分類される（表 1）[1,2]．典型的な古典型脳腱黄色腫症は，小児期に慢性の下痢，白内障，精神発達遅滞／退行，てんかん，歩行障害などで発症することが多い．腱黄色腫（図 1）は 20 歳代に生じることが多くアキレス腱に好発するが，黄色腫を認めない例も稀ではない．若年性の骨粗鬆症や冠動脈疾患の合併も多い．未治療のまま経過すると進行性の神経症状により，高度の日常生活動作障害を呈する．

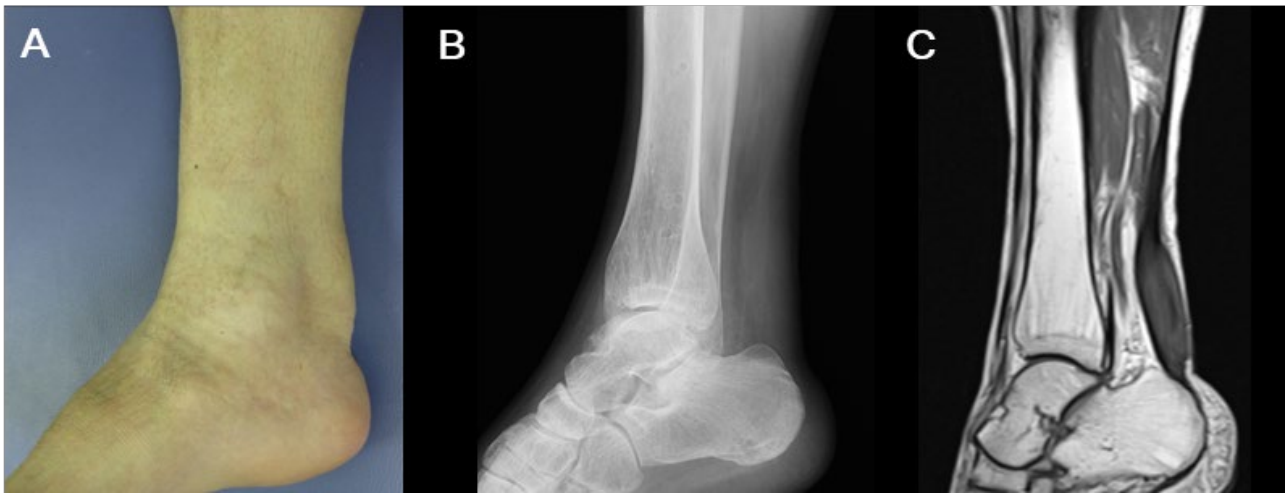

図 1．脳腱黄色腫患者のアキレス腱黄色腫（Intern Med 53: 2725-2729, 2014[18]より転載）．
（A）肉眼所見．（B）単純レントゲン．（C）MRI T1 強調像．

表１．脳腱黄色腫症の病型

病　型	特　徴
古典型	小児期に下痢や白内障で発症することが多く，腱黄色腫，冠動脈疾患，骨粗鬆症，進行性の神経・精神症状など多彩な臨床症状を呈する病型. 神経・精神症状としては，精神発達遅滞，認知機能障害，小脳症状，錐体路症状，錐体外路症状，けいれん，脊髄性感覚障害，末梢神経障害などを認める.
脊髄型	成人期発症で，亜急性から慢性に経過する痙性対麻痺を主症状とする病型. 血清コレスタノール値は古典型よりも低値であることが多い.
非神経型	腱黄色腫など非神経症状のみを呈する病型. 家族性高コレステロール血症やシトステロール血症との鑑別が必要.
新生児胆汁うっ滞型	新生児期新生児～乳児期の遷延性黄疸・胆汁うっ滞を呈する病型. 将来的に他の病型に移行する可能性がある.

疾患頻度

「脳腱黄色腫症の実態把握と診療ガイドライン作成に関する研究」班が実施した全国調査では，2012 年 9 月～2015 年 8 月の 3 年間に日本全国で 40 例の脳腱黄色腫症患者の存在が確認された[1)]．また，これまでに本邦から約 60 例の本症患者の報告がある．一方，ExAC (The Exome Aggregation Consortium)のデータベースを用いた *CYP27A1* 遺伝子変異の検討による本症の頻度は，東アジア人で 64,267～64,712 人に 1 人と推測されており[19)]，本邦の潜在的な患者数は 1,000 人以上である可能性がある．現在 PROLIPID という全国レベルでの原発性高脂血症患者の登録調査研究が実施されており，脳腱黄色腫症に関しても今年度から登録が開始される.

遺伝学

CYP27A1 が脳腱黄色腫症の原因遺伝子であり，患者は *CYP27A1* 遺伝子変異をホモ接合体または複合ヘテロ接合体で有する．これまでに 50 種類以上の変異が報告されており，ミスセンス変異が 65%，ナンセンス変異が 20%，欠失・挿入変異が 16%，スプライス変異が 18%を占める[20]．日本人では，c.1214G＞A (p.R405Q)が 31.6%，c.1421G＞A (p.R474Q)が 26.3%，c.435G＞T (p.G145=)が 15.8%と頻度が高いことが全国調査で明らかになっている[1]．本症の遺伝形式は常染色体劣性であり，ヘテロ接合体の保因者が臨床症状を呈した報告はない．

病態

CYP27A1 遺伝子は，27-水酸化酵素をコードしており，脳腱黄色腫症の患者では本酵素活性が著しく低下している．27-水酸化酵素は，肝臓における一次胆汁酸の合成に必須の酵素であり，酵素欠損によりケノデオキシコール酸などの胆汁酸の合成障害をきたす（図 2）．また，ケノデオキシコール酸によるコレステロール分解へのネガティブフィードバックが消失するため，コレスタノール・胆汁アルコールの産生が助長される（図 2）[21]．上昇したコレスタノールが脳，脊髄，腱，水晶体，血管などの全身臓器に沈着し，様々な臓器障害を惹起する．下痢や胆汁うっ滞は，ケノデオキシコール酸の欠乏や胆汁アルコールの上昇などの機序によると推測される．

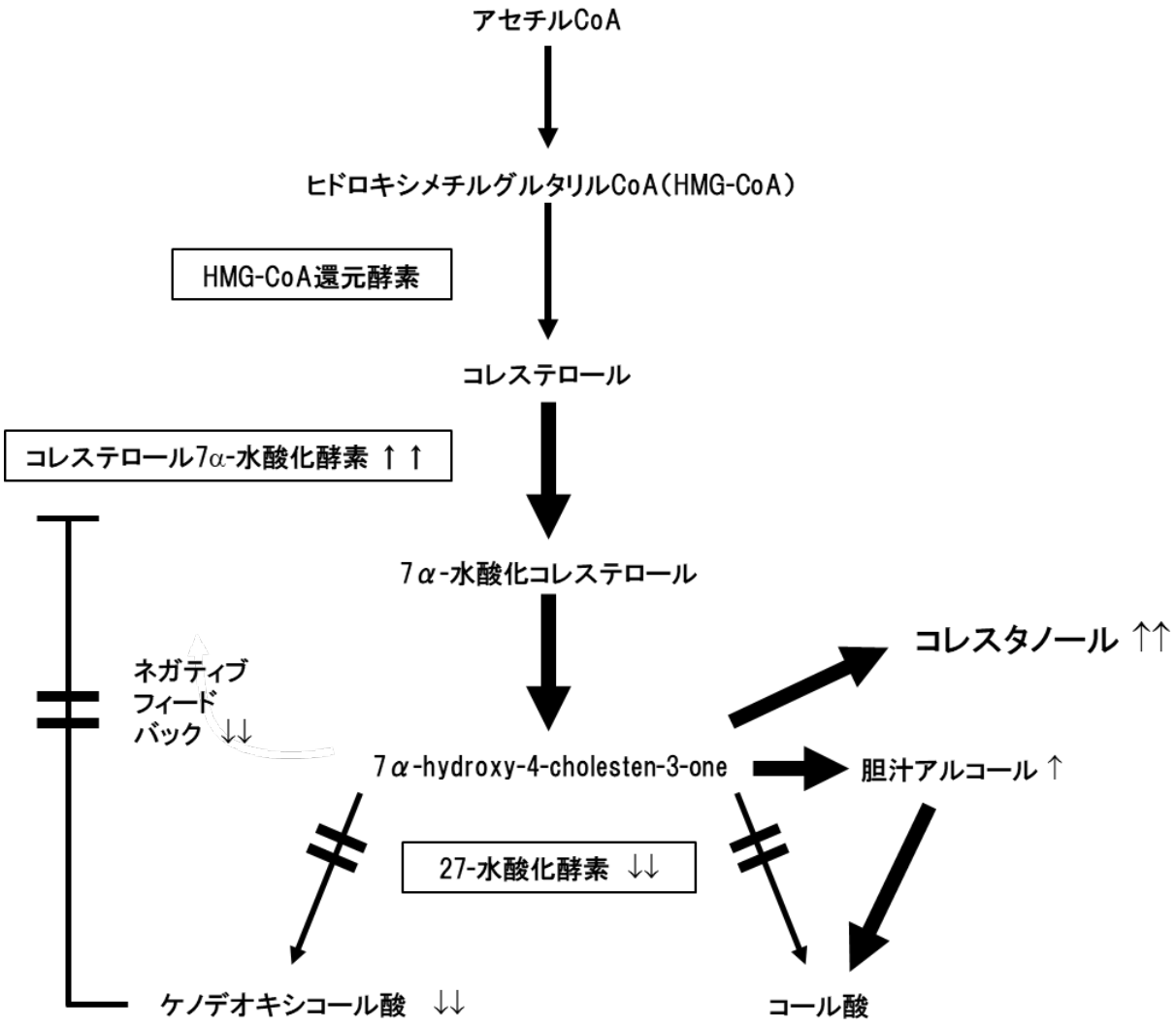

図 2 脳腱黄色腫症の病態（脳腱黄色腫症診療ガイドライン 2018[2)]より転載）

本症患者は *CYP27A1* 遺伝子変異により 27-水酸化酵素活性が著減している．その結果，ケノデオキシコール酸の産生が低下し，血清中コレスタノールが上昇する．ケノデオキシコール酸低下によりコレステロール 7α-水酸化酵素へのネガティブフィードバックが減少するため，血清中コレスタノールは更に上昇する．上昇したコレスタノールが全身臓器に沈着し臓器障害を惹起する．

我が国の診断基準と診断方法の実際

現在指定難病の認定に用いられている旧診断基準は難病センターのホームページ（http://www.nanbyou.or.jp/upload_files/File/263-201704-kijyun.pdf）で参照可能である．2018 年に改訂された新しい診断基準[1,2]を表 2 に示す．

表２．脳腱黄色腫症の診断基準

A 症状
1. 腱黄色腫
2. 進行性の神経症状*または精神発達遅滞
3. 若年発症の白内障
4. 若年発症の冠動脈疾患
5. 小児～若年発症の慢性の下痢
6. 若年発症の骨粗鬆症
7. 新生児～乳児期の遷延性黄疸・胆汁うっ滞
*進行性の神経症状としては，認知機能障害，小脳症状，錐体路症状，錐体外路症状，けいれん，脊髄性感覚障害，末梢神経障害などの頻度が高い
B 生化学的検査所見
血清コレスタノール濃度 4.5 μg/mL 以上
（健常者の平均値 ± SD： 2.35 ± 0.73 μg/mL）
C 遺伝学的検査
CYP27A1 遺伝子の変異
（変異をホモ接合体または複合ヘテロ接合体で認める）

D 鑑別診断

以下の疾患による血清コレスタノール高値を除外する.

- 家族性高コレステロール血症
- シトステロール血症
- 閉塞性胆道疾患
- 甲状腺機能低下症

上記疾患の鑑別が困難な場合や上記疾患と脳腱黄色腫症の合併が否定できない場合は, *CYP27A1* 遺伝子検査を実施する. *CYP27A1* 遺伝子の病原性変異が確認された場合は, 上記の疾患を合併していても脳腱黄色腫症の診断が可能である.

＜診断のカテゴリー＞

Definite： A の 1 項目以上＋B + C+ D

Probable： A の 1 項目以上＋B + D

Possible： A の 1 項目以上＋B

腱黄色腫, 進行性の神経症状または精神発達遅滞, 若年発症の白内障・下痢・冠動脈疾患・骨粗鬆症, 新生児～乳児期の遷延性黄疸・胆汁うっ滞など本症を疑う症状を認めた場合, 血清コレスタノールの測定を行う. 血清コレスタノールは外注検査が可能であるが保険収載はされていない. 血清コレスタノールが上昇（4.5 μg/mL 以上）しており, 他疾患が否定されれば Probable, さらに *CYP27A1* 遺伝子の変異が証明されれば Definite の診断となる.

鑑別診断

家族性高コレステロール血症とシトステロール血症は，腱黄色腫と血清コレスタノール高値を呈するため，脳腱黄色腫症の重要な鑑別疾患である．但し，これらの疾患では，神経・精神症状，胆汁うっ滞，慢性の下痢，白内障，骨粗鬆症を呈することはほとんどないため，これらの症状を認める場合は脳腱黄色腫症が強く疑われる．また，脳腱黄色腫症では，家族性高コレステロール血症やシトステロール血症のような著明な高 LDL コレステロール血症を呈する事はない．この他，閉塞性胆道疾患や甲状腺機能低下症で血清コレスタノールが上昇する場合があり鑑別が必要である．神経症状の観点からは，脊髄小脳変性症や痙性対麻痺との鑑別が重要である．原因が特定できない小脳性運動失調症や痙性麻痺の症例，特に MRI で小脳歯状核，淡蒼球，皮質脊髄路，小脳脚，脳室周囲白質（図 3A）[1,7,22,23]，または頚髄～胸髄の側索および後索（図 3B）[11,12]に T2 強調像高信号を認める症例では，本症を疑い血清コレスタノールの測定を実施する必要がある．また，原因が特定できない新生児～乳児期の遷延性黄疸・胆汁うっ滞でも本症を念頭に精査を進める必要がある．

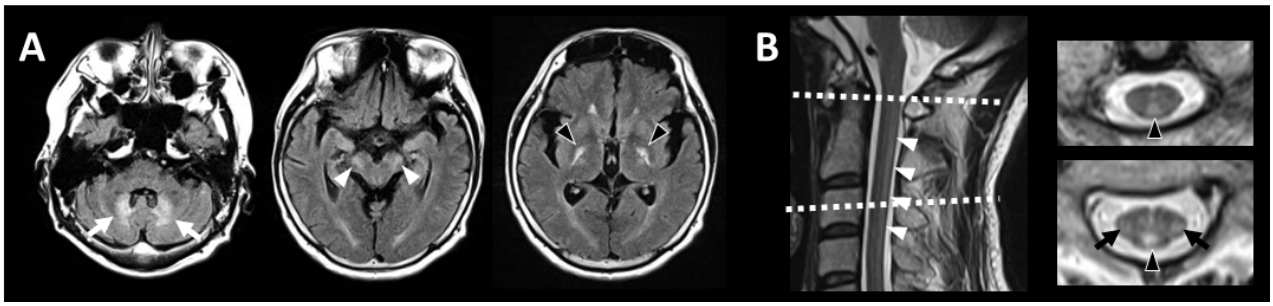

図 3　脳腱黄色腫症患者の MRI 所見　(A) 脳 MRI FLAIR 画像（Intern Med 53: 2725-2729, 2014[18]より転載）．小脳歯状核（白矢印），皮質脊髄路（白矢頭），淡蒼球（黒矢頭）に高信号を認める．(B) 脊髄 MRI T2 強調画像（神経内科 86：368-373, 2017[24]より転載）．頚髄後索（黒矢頭）および側索（黒矢印）に長軸方向に長い高信号（白矢頭）を認める．

現在の治療法

疾患修飾療法の中心は，著減しているケノデオキシコール酸の補充（保険適応外）である．ケノデオキシコール酸投与により胆汁酸合成経路の律速酵素であるコレステロール 7α-水酸化酵素へのネガティブフィードバック（図 2）が正常化し，血清コレスタノールの上昇や尿中への胆汁アルコール排泄増加といった生化学的検査異常が改善する．また，その結果として組織へのコレスタノールの蓄積が抑制される．早期治療により臨床症状の改善も期待できる[1,25-29]．ケノデオキシコール酸の投与量は成人例では 750 mg/日[26]，小児例では 15 mg/kg/日[29]が推奨されている[2]．HMG-CoA 還元酵素阻害薬（スタチン製剤，保険適応外）[1,27,30,31]もコレスタノールの産生を抑制することが知られており，多くの症例で治療に用いられているが，臨床的な有用性のエビデンスは十分に蓄積されていない．LDL アフェレシス（保険適応外）も血清コレスタノールを低下させることが可能であるが[1,32-34]，約 2 週間で治療前値に戻ってしまう[34]ことからケノデオキシコール酸やスタチン製剤による治療効果が不十分な例に実施を検討する．

将来展望

現在本邦で，脳腱黄色腫症に対するケノデオキシコール酸の治験が計画されており，近い将来保険適応になる可能性がある．本邦で実施した全国調査の結果では，本症の診断までに平均で 16.5 ± 13.5 年を要しており，特に小児期の未診断例が多いとが明らかになっている[1]．現状では，診断・治療の遅れにより重篤な神経系の後遺症を残している患者が多い．今後，発症早期に診断・治療介入することで本症患者の予後が改善すると期待される．

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無ベータリポ蛋白血症(無βリポ蛋白血症)

① 要約

無βリポ蛋白血症(ABL)は常染色体劣性遺伝形式を示す稀な疾患である.アポ B 含有リポ蛋白が欠損し，著明な低脂血症を呈する．ミクロソームトリグリセライド転送蛋白(MTP, 遺伝子名 *MTTP*) の欠損（ホモ接合体）により，肝臓における血中への VLDL 分泌，腸管におけるカイロミクロン形成による脂肪吸収が障害される．有棘赤血球症を認め，脂溶性ビタミンの吸収障害により，網膜色素変性症，神経障害を呈する（図１）．MTP 欠損の証明には，*MTTP* 遺伝子変異の同定が必要である．脂溶性ビタミンの大量補充療法が唯一の治療法である．なお,家族性低βリポ蛋白血症 1(FHBL1)のホモ接合体の重症例は ABL 同様の臨床像を呈する．検査所見上は鑑別困難であり，ABL では 1 親等親族には低脂血症を認めないが，FHBL1 ホモ接合体の 1 親等親族には中等度の低脂血症を認めることが参考所見となる．

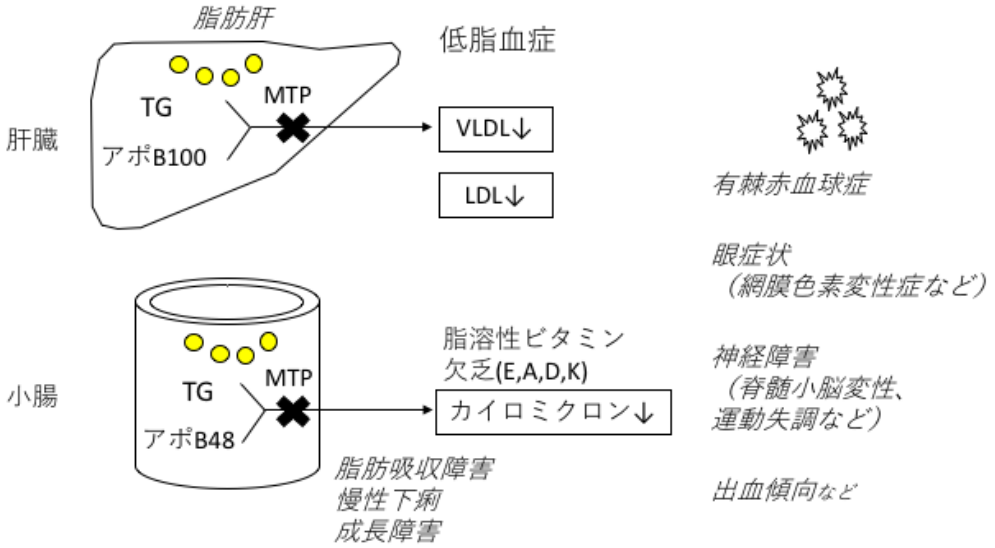

図１.無ベータリポ蛋白血症
ミクロソームトリグリセライド転送蛋白（MTP, 遺伝子名*MTTP*）は肝臓や小腸で働き、VLDLやカイロミクロンの合成を助ける酵素である。その欠損（ホモ接合体）は、ベータリポ蛋白とよばれるこれらのアポB含有リポ蛋白の合成・分泌障害に起因する低脂血症を来すだけでなく、トリグリセライド（TG）が分泌されずに細胞内にとどまることに起因する脂肪肝や、脂肪・脂溶性ビタミン吸収障害に起因する様々な合併症（斜体で表示）の原因となる。

② はじめに

無βリポ蛋白血症(abetalipoproteinemia ； ABL)はアポ B 含有リポ蛋白であるカイロミクロン，VLDL，LDL が欠如して著明な低脂血症を呈する稀な遺伝性疾患である．1950 年に Bassen と Kornzweig により有棘赤血球・網膜色素変性症・運動失調を呈する症例として報告され（1)，Bassen-Kornzweig 症候群とも呼ばれる．1960 年にこの疾患に罹患した患者の血清総コレステロ

ールが主に β リポ蛋白分画で低下していることが報告され(2)，無 β リポ蛋白血症とよばれるようになった．アポ B 含有リポ蛋白の合成に必須なミクロソームトリグリセライド転送蛋白（microsomal triglyceride transfer protein ； MTP）活性の欠損が 1992 年に報告された(3)．1993 年には MTP のサブユニットの 1 つがクローニングされ，その遺伝子（遺伝子名 *MTTP*）異常が ABL 患者で報告された(4)．本症は MTP 欠損による疾患である（図１）．

③ 疾患の概要(特徴・合併症・自然予後等)

出生時は無症状であるが，授乳開始後から，嘔吐，腹部膨満，脂肪吸収障害による下痢が生じ，栄養障害による成長障害がみられる(2)．脂肪の多い食事を避けることにより，消化器症状は軽減する(2)．小腸上皮細胞の細胞質には脂肪滴が充満し，消化管内視鏡では，小腸の絨毛上皮が白色調を呈し，snow white duodenum とよばれる．慢性の脂肪吸収障害により，脂溶性ビタミンであるビタミン E，A，D，K は低値を示す．脂溶性ビタミンの欠乏により，思春期までに多彩な神経症状や網膜色素変性などの眼症状を呈する。神経症状は，脊髄小脳変性が特徴で主にビタミン E 欠乏によるとされ，10 歳(～20 歳)頃までに始まる。深部腱反射の低下が初発症状で、早ければ 2～3 歳で出現することが多い．その後，振動覚や位置覚も障害され，失調性歩行となる．しばしば Romberg 徴候を伴う．未治療例の多くは 30 歳前に自力歩行が困難になる．推尺異常や構語障害等の運動障害を伴い，重症例では骨格筋が拘縮し，凹足・内反尖足・脊柱後側弯症を呈するに至るとされる．他に，末梢神経障害，筋症状も報告されている(2)．眼症状は，ビタミン E 欠乏とビタミン A 欠乏によるとされ，網膜色素変性症が特徴的である．最初に夜盲や色覚異常がみられる．次第に視力低下や視野障害を来すこともある．また，有棘赤血球(acanthocyte)を 50%以上の赤血球で認め，連銭形成が阻害されるため，血沈は著明に延長する．貧血も報告されており，脂肪吸収障害に続発する鉄，葉酸，その他の栄養素の欠乏によるものとされている(2,5)．肝臓では，VLDL の合成・分泌が障害され，肝臓に脂肪が蓄積し脂肪肝になる．脂肪肝炎や肝硬変を合併したケースも報告されており，注意が必要である(6)．この中には中鎖脂肪(medium-chain triglyceride: MCT)投与が肝硬変を誘発した可能性のあるケースもあり，MCT 投与にあたっては注意が必要である(2)．その他，ビタミン K 欠乏による出血傾向(プロトロンビン時間延長)や心筋症による不整脈死の報告もある．進行したケースでは神経・筋障害による自立歩行困難，失明などにより ADL が著しく低下する．ビタミン補充による症状や予後の改善が報告されている．成人期から始めても有効との報告もあるが，症状の回復は期待しにくいため，早期治療が大切である(2)．治療奏功例で 60 代-70 代まで生存しているという報告もある(5,7,8)．また，妊孕性が保たれていることが報告されている(2,9)．

④ 疾患頻度

100 万人に 1 人以下とされている(10).世界で約 100 例の症例報告がある(11). 本邦では, 1983 年 Akamatsu らにより第 1 例が報告され(12), 以後 10 家系程度が報告されている.遺伝子診断で確定がついているものとしては, 3 例の変異が報告されている(13,14).

⑤ 遺伝学(病因遺伝子、遺伝形式等)

*MTTP*遺伝子変異により発症し, 常染色体劣性遺伝形式を呈する. 30 以上の *MTTP*変異が報告されている(10). 約 3 分の 1 に両親の血族結婚を認め, 男女比は概ね 1:1 である(11) (3:2 との報告もある(2)).

⑥ 病態

肝臓ではアポ B100 を含有する VLDL が産生され, 小腸ではアポ B48 を含有するカイロミクロンが産生される. 本症では MTP の遺伝的欠損により, これらの過程が障害されるため, VLDL さらに LDL が欠如するとともに, 腸管から吸収される脂肪からカイロミクロンが産生できない. そのため, 著明な低脂血症を呈する.カイロミクロンは脂肪や脂溶性ビタミンの吸収を担っているため, その産生障害は, 慢性的な下痢と脂溶性ビタミンの欠乏状態を来たす. 脂肪吸収障害による栄養障害, 脂溶性ビタミン吸収障害に伴う網膜色素変性や神経障害に伴う ADL 低下が特に問題となる.

⑦ 我が国の診断基準と診断方法の実際

診断基準を表 1 に示す.多くの症例では,乳幼児期に脂肪便や発育障害で診断される.脂溶性ビタミン欠乏による神経症状で発見される場合や成人後の健診で偶然低脂血症を診断されることもある(13). 血中総コレステロール(TC)低値(50mg/dl 未満), 血中トリグリセライド(TG)低値(15mg/dl 未満)の場合で, 他の低脂血症が除外できれば本症が疑われる. (ただし、TC, TG 値は症例によるばらつきが大きく,本疾患が MTP 欠損によるアポ B 含有リポ蛋白の分泌障害に起因することを考えると,本来的には LDL-C, アポ B によるスクリーニングの方が望ましい.既報の症例は、LDL-C ＜ 15 mg/dl, アポ B ＜ 10 mg/dl の範囲にあることから (6, 11, 13, 14) ,LDL-C ＜ 15 mg/dl, アポ B ＜ 10 mg/dl をスクリーニング基準とするのが望ましい (ただし典型例ではアポ B ＜ 5 mg/dl)) .

症状としては, 脂肪便や慢性下痢, 神経症状の有無, 網膜色素変性症の有無を確認する. 検査としては, 血中アポ B 濃度が欠損レベル(5mg/dl 未満)であることを確認する. また有棘赤血球は 50%以上の赤血球に認める. MTP 欠損の証明には, *MTTP*遺伝子変異の同定が必要である.

⑧ 鑑別疾患

二次性低βリポ蛋白血症として，種々の疾患の慢性経過および終末期において低 LDL 血症が出現する．高頻度の疾患として，肝硬変を代表とする慢性肝疾患，甲状腺機能亢進症，慢性膵炎などによる腸管脂肪吸収障害，貧血を来す血液疾患なども LDL が低下することがよく知られている．家族性低βリポタンパク血症 1(familial hypobetalipoproteinemia ； FHBL1)は常染色体優性遺伝形式であり，アポ B 蛋白の遺伝子異常による短縮アポ B が主たる原因である．ヘテロ接合体(3000 人に 1 人程度)では網膜色素変性や神経障害をきたすことは無いが，ホモ接合体(100 万人に 1 人以下)の重症例では無 β リポ蛋白血症同様の臨床像を呈する．本人の検査所見上は鑑別困難であり，ABL では 1 親等親族には低脂血症を認めないが，FHBL1 ホモ接合体の 1 親等親族には中等度の低脂血症を認めることが参考所見となる．その他に乳幼児の低コレステロール血症に下痢，嘔吐，成長障害を伴う遺伝性疾患の鑑別としてカイロミクロン停滞病(Anderson 病)がある．非常にまれな疾患で，常染色体劣性遺伝を呈する．カイロミクロンの分泌に重要な Sar1b(secretion-associated and Ras-related GTPase 1B)をコードする *SAR1B* 遺伝子の変異により，カイロミクロン(およびアポ B48)が分泌されず，脂肪便，成長障害，低コレステロール血症を呈する(15)．血中トリグリセライド値は正常である．

⑨ 現在の治療法

治療の概要を表２に示す(8)．下痢を回避するためには脂肪の摂取制限が必要である．総カロリー摂取の 30%以下（あるいは 1 日 15～20 g 以内（小児では 5g/日以内から始める））に脂肪摂取を制限する(2,7,8,10,11,16)．乳児の栄養障害には，カイロミクロンを経ずに吸収される MCT を投与することがあるが必須ではなく，肝硬変の誘発には注意する必要がある(2,11)．また，必須脂肪酸が不足しないように配慮する (8)．ビタミン E の経口大量補充療法は，神経症状の発症及び進展遅延に推奨されている(2,10)．但し，血中ビタミン E レベルは正常化せず，正常下限の 30%までにとどまるといわれている(5,11)．また、ビタミン E の補充は，その他の脂溶性ビタミンの競合的吸収阻害を来たすことにより，ビタミン K 欠乏などを助長する可能性があるため注意が必要である(11)．ビタミン E と共にビタミン A の大量投与は，眼症状の予防に有効である(2,10)．ビタミン D・ビタミン K・鉄・葉酸の補充が必要な場合もあるため血中濃度をモニターする(2,5,7,10,16)．ビタミン A やビタミン K の補充の場合には，補充によって血中濃度が正常化するといわれている(2,5)．ビタミン A 毒性には注意する必要がある(8)．血中ビタミン A 値が正常であるにも関わらず，ビタミン A 補充後にビタミン A 毒性を来たしたケースが報告されている(8)．ビタミン A の治療目標は，毒性を避けるため正常下限にすべきとされ(8)，ビタミン A 補充にあたっては血中βカロテン濃度をモニターしながら補充量を調節することが推奨されている(5,7,8)．妊婦や妊娠の可能性のある女性の場合にはビタミン A 毒性に特に留意し，投与量が過剰とならないように，まずは補充量を 50%に減量し，βカロテンやビタミン A の血中濃度

をモニターし投与量を調節しながら補充する(7,8). ビタミン A は必須のビタミンであるため, 妊娠中であっても補充を中止してはならない(8).

経過観察にあたり, Hegele らの推奨する経過観察の概要を表 3 に示す(8).

⑩ 将来の展望

脂溶性ビタミンの経口大量補充療法が唯一の治療法であるが対症療法にとどまる. 根治治療は小腸や肝臓における MTP の発現回復であるが, 現時点では技術的に困難であり, 画期的な治療法の開発が望まれる. 稀な疾患であるため疾患データベースによる遺伝子変異, 症状, 合併症, 治療状況, 予後についての情報蓄積も重要な課題である. これらの情報を活用して, 例えば遺伝子変異の種類による疾患の重症度の予測や, 臨床的特徴をふまえた最適な治療法の選択が可能となれば, 患者へのメリットは大きい.

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表１　無 β リポタンパク血症の診断基準

必須項目

・血中総コレステロール 50mg/dL 未満

・血中トリグリセリド値 15mg/dL 未満

Ａ．症状

１．脂肪便又は慢性下痢

２．神経症状（運動失調,痙性麻痺,末梢神経障害による知覚低下や腱反射消失など）

３．網膜色素変性症（夜盲,視野狭窄,視力低下など）

Ｂ．検査所見

１．血中アポＢ濃度 5mg/dL 未満

２．有棘赤血球の存在

Ｃ．鑑別診断

以下の疾患を鑑別する。

家族性低 β リポタンパク血症,カイロミクロン停滞病（アンダーソン（Anderson）病）,甲状腺機能亢進症

※家族性低βリポタンパク血症ホモ接合体との確実な鑑別は,本人のデータのみでは困難であり遺伝子変異の同定を要するが,以下の所見を参考に鑑別可能である.

・１～２親等親族のコレステロール低値

本症は常染色体劣性遺伝であり１親等家族に軽度低脂血症を認めないが,家族性低 β リポタンパク血症は常染色体共優性遺伝であるため,ホモ接合体の１親等親族（ヘテロ接合体）に正常の 1/2 程度の低脂血症を認める.両親・兄弟の血清脂質・血中アポＢ濃度、脂溶性ビタミン濃度の測定も参考になる.

Ｄ．遺伝学的検査

MTTP 遺伝子の変異

＜診断のカテゴリー＞

Definite：必須項目を満たす例で,Ａ・Ｂの各１項目以上を満たしＣの鑑別すべき疾患を除外し,Ｄを満たすもの.

Probable：必須項目を満たす例で,Ａ・Ｂの３項目以上（Ｂの１項目を含む）を満たし,Ｃの鑑別すべき疾患を除外したもの.

表 2　治療概要(文献 8 より改変引用)		
症状	治療	検討点など
成長障害	適切なカロリー摂取を確保[1] （極度の低栄養では MCT 投与を検討(2,7)）	栄養士に紹介を検討する MCT 投与の際は肝障害･肝硬変の誘発に注意し,長期投与は避ける(2,11)
脂肪便	低脂肪食 ・総カロリーの 10-20%(8) ・総カロリーの 30%以下(7,10) ・15-20 g/日以内(2,16) ・小児では 5 g/日以内から始める(11)	長鎖脂肪酸は避ける
	経口必須脂肪酸の補充（7,8,11）	耐容内のティースプーン１杯以下の多価不飽和脂肪酸の豊富な油(大豆油やオリーブ油など)(7,8,11)
線維化を伴わない脂肪肝	脂肪制限	
肝線維化，かつ/または肝硬変	（肝移植されたケースもある(17)）	早期診断・早期治療がなされれば非常にまれな合併症である
脂溶性ビタミン欠乏	ビタミンE[2] ・100-300 IU/kg/日(7,8,10,11) ・1,000-2,000 mg/日(幼児)、5,000-10,000 mg/日(学童期以降の小児から成人)(2) ・2,400-12,000 IU/日(5,16)	ビタミン補充は，経口投与をするべきである（脂溶性ビタミンの経静脈投与は必要ない）. ビタミン E の補充は,その他の脂溶性ビタミンの競合的吸収阻害を来たすことにより,ビタミン K 欠乏などを助長する可能性があるため注意が必要である(10).
	ビタミンA[3] ・100-400 IU/kg/日(5,7,8,16)	
	ビタミンK ・5-35 mg/週(5,7,8,16)	
	ビタミンD[4] ・800-1,200 IU/日(7,8)	
貧血	軽度の貧血は一般的に治療の必要はないが,時に脂溶性ビタミンに加え	

	て、ビタミンB12、鉄、葉酸の投与を検討(2,5,7,10,16)	
INR 上昇	ビタミンK補充(上記参照)	
視力異常	ビタミンEやビタミンA補充(上記参照)は，視力障害の進行を停止し，眼の合併症進展を予防(2,8,10)	
構音障害	言語聴覚療法	ビタミン E 早期補充により，構音障害はまれ
運動失調	集中的なリハビリテーション(または協調性障害の理学療法)	神経科医，理学療法医，理学・作業療法士からなる集学的チームによる最善の治療
	転倒防止のため杖/歩行器	
	必要があれば，電動車いすに乗るために住宅改修	
	食事補助具や着衣用のフック	
	体重コントロール(肥満は，歩行と移動困難を悪化させるため)	
甲状腺機能低下症	甲状腺ホルモン補充による標準治療	

1 適切な治療で，正常の成長速度が達成されうるが，治療後でも十分な成長をするとは限らない(7,8).

2 ビタミンEの単位は，トコフェロール酢酸エステル 1 mg を 1 単位(IU)と定められている．本邦で使用可能なビタミン E 製剤は,トコフェロール酢酸エステルとトコフェロールニコチン酸エステルである．トコフェロール酢酸エステル 1 mg は 1 IU，トコフェロールニコチン酸エステル 1 mg は 0.88 IU に相当する．なお、血中ビタミンEレベルは正常化せず，正常下限の 30%までにとどまるといわれている(5,11).

3 ビタミン A 毒性の可能性は低いが,血中ビタミン A 値が正常であるにも関わらず,ビタミン A 補充後にビタミン A 毒性を来たしたケースが報告されており注意が必要．ビタミン A の治療目標は，毒性を避けるため正常下限にすべきとされ(8)．ビタミンA補充にあたっては血中βカロテン濃度をモニターしながら補充量を調節することが推奨されている(5,7,8)．妊婦や妊娠の可能性のある女性の場合にはビタミン A 毒性に特に留意し,投与量が過剰とならないように,まずは補充量を 50%に減量し,βカロテンやビタミンAの血中濃度をモニターし投与量を調節しながら補充する(7,8)． ビタミンAは必須のビタミンであるため,妊娠中であっても補充を中止してはならない(8).

4 本邦で使用可能なビタミンD製剤は,活性型ビタミンD製剤であり，天然型ビタミンDは薬価収載されていない.

表 3 経過観察概要(文献 8 より改変引用)		
	評価	頻度
全身	成長パラメータの評価	診察毎
胃腸系	脂質[1]	数年毎
	肝機能[2]	毎年
	脂溶性ビタミン[3]	
	肝臓エコー	３年毎
血液系	全血算(complete blood count)	毎年
	INR	
	網状赤血球数	
内分泌系	血清カルシウム，リン，尿酸	
	血清 TSH	
眼科	眼科的評価	6-12 ヶ月毎
神経系	神経学的評価	6-12 ヶ月毎
その他	骨密度(DXA)、心エコー	3 年毎 (7)

1 脂質評価は一般的に総コレステロール，トリグリセライド，LDL コレステロール，HDL コレステロール，アポ B，アポ AI

2 AST，ALT，γGTP，総ビリルビンと直接ビリルビン，ALP，アルブミン

3 ビタミン A(レチノール)，βカロテン， 25-OH ビタミン D，ビタミン E，ビタミン K（他に、脂肪吸収障害に伴って二次的に欠乏・不足しうるとされるビタミン B12,鉄,葉酸;欠乏により神経障害を来たす可能性のあるビタミン（B6、B12）など）(2,5,7,10,16)

（執筆責任者：岡崎啓明、高橋学）

資料4

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Homozygous Familial Hypercholesterolemia

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Familial hypercholesterolemia (FH) is an inherited disorder with retarded clearance of plasma LDL caused by mutations of the genes involved in the LDL receptor-mediated pathway and most of them exhibit autosomal dominant inheritance. Homozygotes of FH (HoFH) may have plasma LDL-C levels, which are at least twice as high as those of heterozygous FH (HeFH) and therefore four times higher than normal levels. Prevalence of HoFH had been estimated as 1 in 1,000,000 before but more recent genetic analysis surveys predict 1 in 170,000 to 300,000. Since LDL receptor activity is severely impaired, HoFH patients do not or very poorly respond to medications to enhance activity, such as statins, and have a poorer prognosis compared to HeFH. HoFH should therefore be clinically distinguished from HeFH. Thorough family studies and genetic analysis are recommended for their accurate diagnosis.

Fatal cardiovascular complications could develop even in the first decade of life for HoFH, so aggressive lipid-lowering therapy should be initiated as early as possible. Direct removal of plasma LDL by lipoprotein apheresis has been the principal measure for these patients. However, this treatment alone may not achieve stable LDL-C target levels and combination with drugs should be considered. The lipid-lowering effects of statins and PCSK9 inhibitors substantially vary depending on the remaining LDL receptor activity of individual patients. On the other hand, the action an MTP inhibitor is independent of LDL receptor activity, and it is effective in most HoFH cases.

This review summarizes the key clinical issues of HoFH as well as insurance coverage available under the Japanese public healthcare system.

Key words: **Homozygous familial hypercholesterolemia, Family study, Genetic diagnosis, Lipoprotein apheresis, MTP inhibitor, PCSK9 inhibitor, Cutaneous and Tendon Xanthoma, Aortic Supra-valvular stenosis**

Introduction

Familial hypercholesterolemia (FH) is an inherited disorder of lipoprotein metabolism caused by mutations of the genes involved in the LDL receptor-mediated pathway for cellular uptake of LDL. Most FH patients show an autosomal dominant trait. Hyper-LDL-cholesterolemia remains throughout their lives and causes premature coronary heart disease unless properly treated[1-3].

Early diagnosis and initiation of lipid-lowering therapy is essential for preventing development of cardiovascular complications, even in Japan where cardiovascular disease is not the leading cause of death and its prevalence among FH patients seems to be somewhat lower than in Western countries. Heterozygous FH (HeFH) patients who carry the mutated gene in a single allele have plasma LDL cholesterol (LDL-C) levels double normal or higher and may experience the first cardiovascular event as

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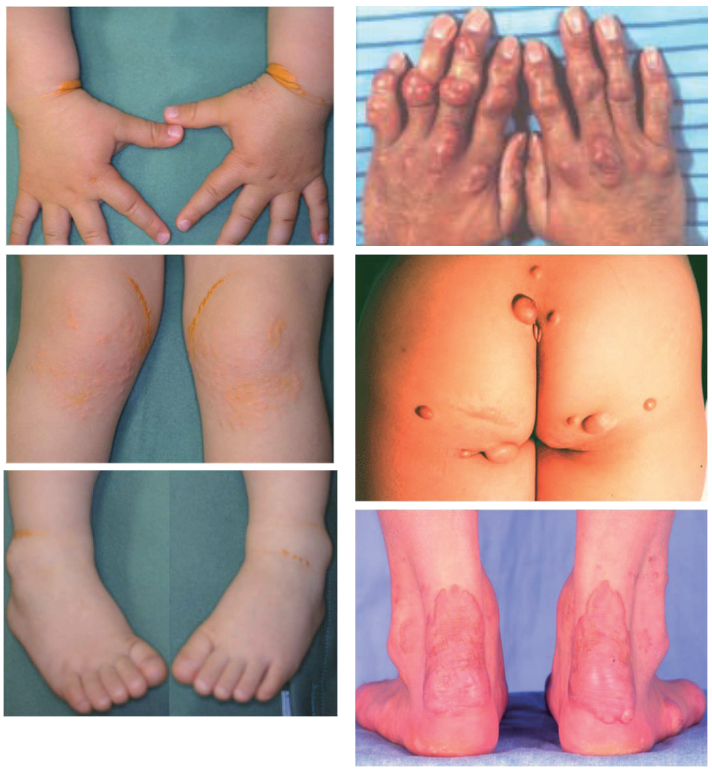

A 3-year-old patient: wrists, knees, ankles

Adult cases: fingers, buttocks, Achilles tendon

Fig. 1. Cutaneous and Tendon Xanthomas in HoFH

Presence of cutaneous xanthomas from childhood is strongly suggestive of HoFH, and tendon xanthomas are generally prominent in adults with HoFH.

early as their thirties. With mutations in both alleles, homozygous FH (HoFH) exhibits LDL-C levels twice those of HeFH, or even higher, and patients develop cardiovascular complications even in the first decade of their lives. Most HoFH is refractory to statins and other standard lipid-lowering drugs as most of them depend on remaining LDL receptor activity. Thus, HoFH has a poor prognosis compared to HeFH and therefore, earlier diagnosis and more aggressive treatments are required to prevent premature death.

1. Clinical Manifestations of HoFH

Familial hypercholesterolemia (FH) is a disease with a triad of clinical characteristics: elevated LDL-C, cutaneous and/or tendon xanthomas, and premature atherosclerotic cardiovascular disease (ASCVD). A genetic defect in LDL receptor function is the cause of FH, and activity of the LDL receptor is completely or almost completely absent in HoFH patients. HoFH includes homozygotes or compound/double heterozygotes of autosomal-dominant disease-causing mutations in the related genes, and their parents are HeFH, but there are rare exceptions that exhibit autosomal recessive inheritance[4, 5].

1) Elevated LDL-C Levels

HoFH patients have very high LDL-C levels from birth, which puts them at very high-risk of coronary heart disease. Plasma LDL-C levels are more than 500 mg/dL in many cases of genetically confirmed HoFH, but there is considerable variation in lipid levels among patients. Those with LDL-C levels over 370 mg/dL (or total cholesterol levels over 450 mg/dL) in the fasting steady state should consult with specialists as they are probably cases of HoFH.

2) Cutaneous and Tendinous Xanthomas (Fig. 1)

Characteristic cutaneous xanthomas that have developed since infancy are physical findings suggestive of HoFH. They are commonly found on the extensor surfaces of the elbows/knees and wrist/gluteal regions and parents often take a child to a

doctor for the first visit because of them[6]. Tendon xanthomas are pathognomonic for both HeFH and HoFH, but not apparent during childhood and gradually appear around puberty. Xanthomas can be repressed or made to regress with continuous aggressive lipid-lowering treatment.

3) ASCVD

The prognosis for untreated HoFH is extremely poor. It is difficult for patients to live beyond 30 years without treatment. The LDL-C accumulation threshold hypothesis, which uses a calculation of [LDL-C x years of life], has been proposed as a rational explanation for the coronary risk of FH, and according to it, the coronary threshold of HoFH would be around 11 years old even for individuals with lower LDL-C levels[7]. Angina or myocardial infarction from infancy, as well as aortic supravalvular and/or valvular stenosis are often noted in HoFH **(Fig. 2)**, and may become the main cause of death in patients. Even with substantially effective treatment, systemic atherosclerosis, with such manifestations as aortic aneurysms, peripheral artery disease, and cerebrovascular disease, develops along with aging. Aggressive LDL-lowering treatments should be started as young as possible to prevent these atherosclerotic complications.

2. Prevalence

In the 1970s, prevalence of HeFH was estimated as 1 in 500 in the general population, and accordingly, that of HoFH as 1 in 1,000,000 [8]. However, more recent molecular genetic studies have revealed that FH is more common than previously expected. HeFH is now estimated as 1 in 200 to 300 and HoFH as 1 in 170,000 to 300,000 in many countries including Japan[9-13].

3. Genetics

LDL receptor-related disease-causing mutations are identified only in 60 to 80% of clinically diagnosed HeFH[14-16]. Most of them are in the LDL receptor gene (*LDLR*), and those in apolipoprotein B-100 (coded as *APOB* gene), the main ligand for the LDL receptor, have also been reported mainly in Caucasian populations[17]. In 2003, gain-of-function mutations in *PCSK9*, the gene coding proprotein convertase subtilistin/kexin-type 9 and enhancer of LDL receptor degradation, were found. This was considered to be the second major FH-related gene, explaining 5% of HeFH in Japan[18].

Families with FH caused by mutations in *LDLR*, *APOB*, and *PCSK9* all show autosomal dominant inheritance. Since *LDLR* accounts for the majority of the FH mutations, most individuals with HoFH are "true homozygotes" or "compound heterozygotes" for two different mutations in *LDLR*. Some patients are "double heterozygotes", having combined mutations in *LDLR* and *PCSK9* [4], for example. The parents of HoFH children who are "true or compound heterozygotes" mostly show the HeFH phenotype. On the other hand, the family traits of HoFH "double heterozygotes" may not apparently exhibit simple Mendelian inheritance since the heterozygotes for PCSK9 show a variety of phenotypes.

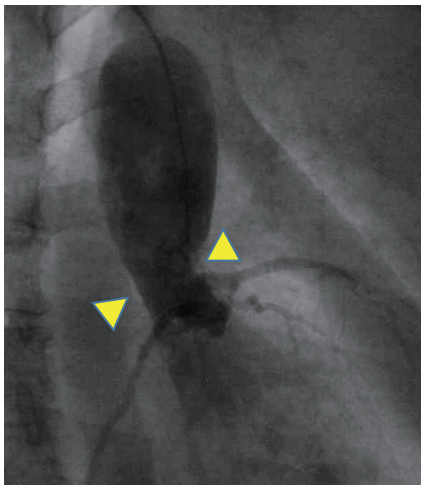

Fig. 2. Aortic Supra-valvular stenosis in HoFH

Supra-valvular stenosis is a pathognomonic finding of HoFH, and one of the causes of premature cardiac death in this disease.

It should be noted that HeFH is underdiagnosed and undertreated in the general population[3]. In the background of one suspected case of HoFH, there are many family members with HeFH , and they must be properly cared for in time to prevent their premature death.

Besides the mutations discussed above, those causing, autosomal recessive hypercholesterolemia (ARH), a rare unique type of FH have been reported in Japan[4, 5]. ARH is caused by mutations in a gene coding low-density lipoprotein receptor adaptor protein 1 (*LDLRAP1*). LDLRAP1 is an adaptor protein making a complex with clathrin and LDL receptors for efficient endocytosis of LDL receptors. Heterozygous carriers of this mutation do not exhibit the HeFH phenotype so it apparently shows autosomal recessive inheritance. If the parents in a probable case of HoFH have normolipidemia, ARH may be considered.

Disease-causing mutations cannot be identified in 20% to 40% of clinically diagnosed HeFH[19]. This may be due to still-unknown FH-related genes or limitations of analytic technologies. A clinical

Table 1. Diagnostic criteria for FH in children

1. Elevated serum LDL cholesterol levels: untreated LDL-C level of ≥ 140 mg/dL (If total cholesterol level is ≥ 220 mg/dL, measure LDL-C level)
2. Family history of FH or premature CAD (within second-degree relatives)
• Secondary hyperlipidemia should be ruled out.
• If a patient meets both of the above-mentioned criteria, FH is diagnosed.
• As LDL-C levels fluctuate during growth due to dietary and hormonal influences, careful examination is required.
• Clinical symptoms and findings including angina, xanthomas, and corneal arcus are rare in heterozygous FH children. Therefore, family history of FH is important in making diagnosis
• Premature CAD is defined as occurrence of CAD in men < 55 years old or in women < 65 years old.
• Homozygous FH should be suspected if patient has xanthomas.

Table 2. Diagnostic criteria for heterozygous FH in adults (15 years of age or older)

1. Hyper-LDL-cholesterolemia (an untreated LDL-C level of >=180 mg/dL)
2. Tendon xanthoma (tendon xanthoma on the backs of the hands, elbows, knees, etc. or Achilles tendon hypertrophy) or xanthoma tuberosum
3. Family history of FH or premature CAD (within the patient's second-degree relatives)
• The diagnosis should be made after excluding secondary hyperlipidemia.
• If a patient meets two or more of the above-mentioned criteria, the condition should be diagnosed as FH. In cases of suspected FH, obtaining a diagnosis using genetic testing is desirable.
• Xanthoma palpebrarum is not included in xanthoma tuberosum.
• Achilles tendon hypertrophy is diagnosed if the Achilles tendon thickness is >=9 mm on X- ray imaging.
• An LDL-C level of >=250 mg/dL strongly suggests FH.
• If a patient is already receiving drug therapy, the lipid level that led to treatment should be used as the reference for diagnosis.
• Premature CAD is defined as the occurrence of CAD in men < 55 years of age or women < 65 years of age, respectively.
• If FH is diagnosed, it is preferable to also examine the patient's family members.

diagnosis of typical HoFH cannot be excluded even if two pathogenic FH gene variants are not identified. A substantial portion of HeFH cases without "known" FH-gene mutations could be "polygenic hypercholesterolemia"[20] or "oligogenic FH"[21-23], though these concepts of FH have not become established. Although genetic analysis provides a definitive diagnosis of HoFH, the possibility of such cases cannot be excluded. Therefore, clinical assessment including thorough physical examination and familial studies is essential. For information, Japanese public healthcare insurance does not cover the expenses for HoFH genetic testing as of February 2021.

4. Pathophysiology

LDL receptor activity is completely or nearly all lost in HoFH. Severely elevated LDL-C levels from birth (more exactly, from fetal period[24]) often cause fatal cardiovascular disease even in infancy. As an example of cholesterol deposition in tissues, pathognomonic skin xanthomas develop from infancy in HoFH and tendon xanthomas become apparent later, and they are more prominent than those in HeFH.

5. Diagnostic Criteria in Japan

1) Clinical Diagnosis

A clinical diagnosis of HoFH can be made on the basis of skin or tendon xanthomas since infancy, and untreated LDL-C levels of twice those of HeFH or higher. Diagnostic criteria for FH in Japanese guidelines apply not only HeFH but also HoFH[1, 4] **(Table 1, Table 2)**. In cases with very high LDL-C and/or prominent xanthomas, HoFH should be suspected[25, 26].

Skin xanthomas since infancy are pathognomonic for HoFH, and sometimes the chief complaint for the first consultation with doctors[4] **(Fig. 1)**. Skin xanthomas in pediatric HoFH are frequently found in flexures of the wrist and ankles, and also in other regions having mechanical stress. Tendon xanthomas are more prominent than in HeFH[27], but become apparent later than skin xanthomas.

Typical HoFH exhibits total cholesterol levels of more than 600 mg/dL in total[1], but there is considerable overlapping of levels between HoFH and severe HeFH[28]. LDL-C levels over 370 mg/dL (or total cholesterol levels over 450 mg/dL) in the fasting steady state would be sufficient for a diagnosis of probable HoFH and the patient should be referred to

specialists. In pediatric patients, plasma LDL-C levels may fluctuate and should be measured multiple times.

Measurement of LDL receptor activity in the fibroblasts of patients provides useful information in diagnosing HoFH, but is currently not routinely available at the laboratories of commercial or research facilities in Japan. Assaying LDL receptor activity in lymphocytes is feasible[29] but less reliable than fibroblast measurements.

2) Genetic Diagnosis

Genetic testing is recommended for suspected HoFH cases, but is not covered by Japanese public healthcare insurance as of February 2021. Genetic diagnosis indicates the potential efficacy of drug treatment and thereby therapeutic strategies[30, 31]. Conversely, drug ineffectiveness (for example, refractory to PCSK9 inhibitors) may suggest the HoFH genotype so genetic tests should be considered in such cases[32].

The possibility of detecting an FH-causative mutation in HeFH is 60 to 80%. Therefore, diagnosis should be carefully made together with clinical examinations and detailed familial studies even in cases of suspected HoFH where the mutations detected are apparently in 0 alleles or only 1 allele, because a genetic test does not exclude the possibility of HoFH due to unknown gene mutations. Consultation with experienced specialists is required in such cases.

6. Screening/Follow-Up for ASCVD

Most HoFH patients may die of ASCVD before 30 years old if untreated[33, 34]. Once HoFH is suspected, extensive examination for ASCVD should be carried out. In HoFH, the potentially fatal disorders of angina pectoris, myocardial infarction, and aortic supra-valvular and valvular stenosis could occur even in childhood **(Fig. 2)**. Aortic supra-valvular and valvular stenosis in HoFH is sometimes difficult to treat and lethal[35]. If patients are left untreated until around 20 years old, ASCVD risk is extremely high. Heart and aortic disease proceeds and systemic atherosclerosis develops later in life.

Non-invasive tests such as cardiac ultrasonography, carotid ultrasonography, and electrocardiograms should be conducted first, and enhanced CT for the aorta and coronary artery and coronary angiography should be considered when necessary[36]. Exercise stress tests should be carefully performed with consideration for patient safety.

7. Differential Diagnosis

A differential diagnosis should be made using high LDL-C levels and prominent xanthomas. LDL-C may be elevated to HoFH levels by secondary hypercholesterolemia such as hypothyroidism or nephrotic syndrome. Xanthomas may develop due to hypercholesterolemia in primary biliary cholangitis. Sitosterolemia, caused by the ATP-binding cassette transporter ABCG5/ABCG8 gene (*ABCG5/ABCG8*) mutations[37], sometimes exhibits elevation of LDL-C and skin xanthomas comparable to HoFH during the suckling stage[38]. Although LDL-C elevation and skin xanthomas subside after weaning from breastfeeding, elevated levels of plasma plant-sterols (including sitosterol) persist in these patients. There is also cerebrotendinous xanthomatosis (CTX), an autosomal recessive disease caused by sterol 27-hydroxylase gene (*CYP27A*) mutations, which is characterized by prominent xanthomatosis in the tendon and brain and sometimes accompanied by central nervous symptoms (mental retardation, cognitive impairment, or motor ataxia)[39]. CTX is clinically diagnosed by elevated plasma cholestanol levels. A differential diagnosis should be carefully made because these diseases require specific therapeutic approaches.

8. Treatment of HoFH

HoFH patients may suffer fatal ASCVD from infancy so initiation of aggressive LDL-C lowering as early as possible is essential for preventing their premature deaths[1, 4] **(Fig. 3, Fig. 4)**. Specific therapeutic strategies for preventing ASCVD development in individual cases should be planned in addition to LDL lowering.

Patients as well as their families will be burdened by various sources of stress such as anxiety about prognosis, concern about heredity, and costs of treatments. Supportive information should be provided, including that on possible financial aid, the therapeutic options available, and genetic counseling. Financial aid is available under The Program for Designated Intractable Diseases of the Japanese public healthcare system. Pediatric FH patients can receive support separately under The Program of Medical Aid for Chronic Pediatric Diseases of Specified Categories, which covers both HeFH and HoFH. In practice, consultation with specialists should strongly be advised.

1) Adult HoFH (15 years of age or older)

The LDL-C management goal is less than 100 mg/dL in primary prevention, and less than 70 mg/dL in secondary prevention[1] in the Japanese guideline **(Fig. 3)**. Medication should start with statins at appropriate doses[40], followed by increasing them to maximal tolerated doses and combination with other

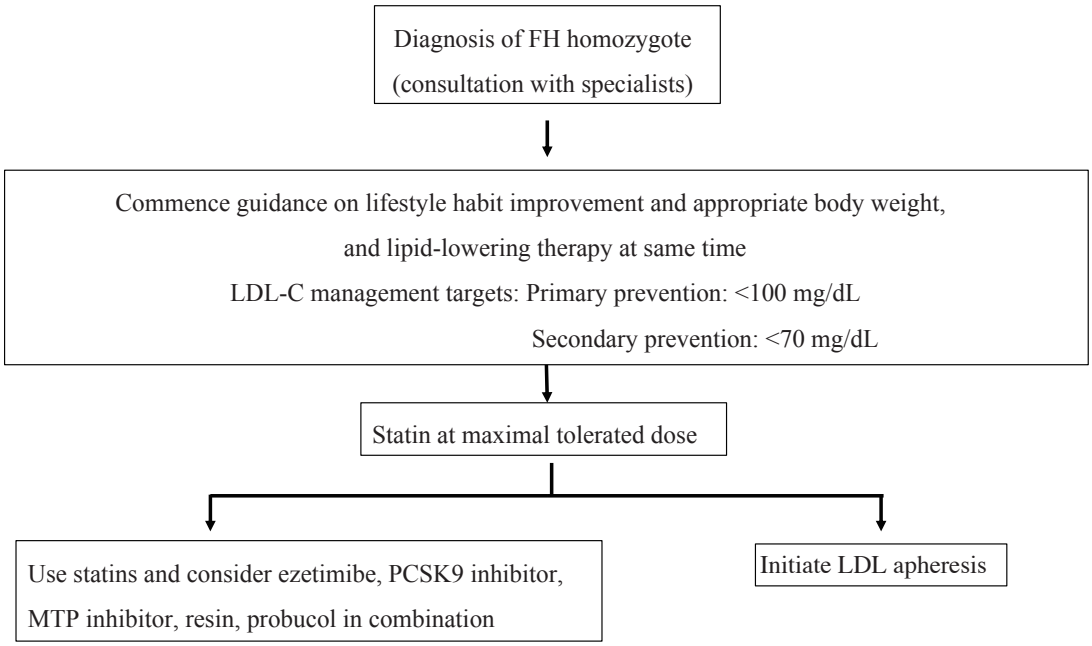

Fig. 3. Algorithm for treatment of adult (15 years of age or older) FH homozygotes

In HoFH, powerful LDL-C lowering therapy is required from a young age to prevent the onset and progression of CAD. Combination of lipid-lowering drugs, including MTP inhibitor, and lipoprotein apheresis is required in many patients with HoFH.
(Adapted from Guidelines for Diagnosis and Treatment of Familial Hypercholesterolemia 20171) "LDL apheresis" means "lipoprotein apheresis" in this review)

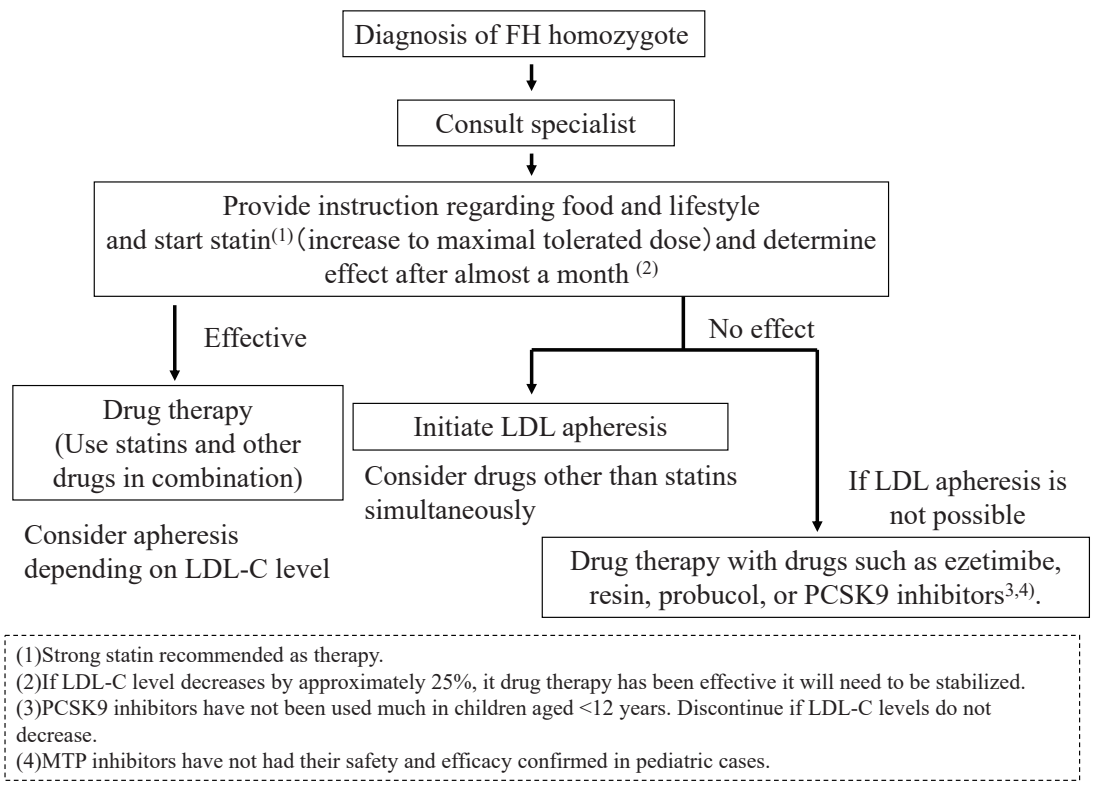

Fig. 4. Algorithm for treatment of pediatric FH homozygotes

Lifestyle interventions and maximally tolerated statin therapy should be started at the initial diagnosis. Since LDL-C targets are rarely achieved, lipoprotein apheresis therapy is recommended, and should be commenced by age 5 ideally.

drugs[41-43]. Achievement of these goals with drug treatment only is, however, not easy in HoFH.

Statins, ezetimibe and PCSK9 inhibitors all act by enhancing LDL receptor activity[44, 45], so their effectiveness depends on residual LDL receptor activity in the individual HoFH patient. Many HoFH patients are refractory to these drugs. However, if any of them are effective in lowering LDL-C, they should be continued together with the additional treatments described below.

MTP inhibitors (lomitapide) are a class of oral drug that is independent of LDL receptor activity. Clinically, they are indicated only for HoFH, and a decrease in LDL-C to approximately half of the pretreatment level can be achieved in many HoFH cases, if tolerated[46-49]. The main adverse effects are gastrointestinal symptoms and liver enzyme elevation accompanied by fat accumulation, similar to the symptoms observed in patients with MTP deficiency[50]. The MTP inhibitor should be started with the lowest dose, taking adequate measures in accordance with nutritional guidance (restricted fat and alcohol intake), and then the dose should be carefully increased gradually.

Lipoprotein apheresis directly removes LDL from plasma through selective absorption or filtration of LDL using an extra-corporal circulation system, and this has been the core therapy for HoFH to date[51-53]. LDL-C levels can be precisely decreased by this procedure, depending upon the treated plasma volume, when properly performed. Lipoprotein apheresis not only removes LDL but also has potential pleiotropic effects in preventing atherosclerosis through removal of cell adhesion molecules[54], coagulation factors[55], and inflammatory cytokines[56]. Lipoprotein apheresis for HoFH once every 1 to 2 weeks is covered by Japanese public healthcare insurance. The use of ACE inhibitors is contra-indicated for patients treated by lipoprotein apheresis with the Liposorber system and selective absorption of LDL by dextran sulfate-cellulose because shock may occur due to an increase in bradykinin activation.

Another option is liver transplantation. While this is highly invasive, it has been shown be a feasible therapeutic option for reversing atherosclerotic changes in HoFH patients that are uncontrollable with conservative therapy[57, 58].

2) Pediatric HoFH

Even in the suckling stage, children with HoFH must be referred to specialists for initiation of lipid-lowering therapy, as this is the key to a better prognosis[4]. The target LDL-C level should be the same as for adult HoFH in secondary prevention (though not clearly stated in the current pediatric guideline[4]). In pediatric HeFH, it is set at less than 140 mg/dL for primary prevention.

Statins and life-style interventions must be started at the time of diagnosis. Statins must be up-titrated and efficacy should be evaluated within a 1-month interval in order to titrate up to the maximal tolerated doses. Combination therapy with ezetimibe, bile sequestering resins, and PCSK9 inhibitors should be considered. These strategies may be effective in cases where there is a response in residual LDL receptor activity. Probucol should also be considered as it could reduce LDL in HoFH due to an unknown mechanism. Administration of an MTP inhibitor could be considered but only with extreme caution because no results of clinical trials in children have been reported. Drug therapy should be conducted until it becomes possible to commence lipoprotein apheresis.

In any case, lipoprotein apheresis must be considered since LDL-C targets are seldom achieved in HoFH only with drug treatment. This extracorporeal circulation therapy is generally commenced at the age of 5 or older, though it has reportedly been started in a patient who was 3.5 years old. In Japan, the main method is selective LDL absorption by dextran sulfate cellulose. However, with the aim of reducing extracorporeal volume, simple plasma exchange can be selected for children with a bodyweight under 30 kg.

3) Treatment during Pregnancy in HoFH

Female HoFH patients could be treated in the same way as for secondary prevention on reaching childbearing age. During pregnancy, LDL and VLDL are generally increased, and continuation of LDL-lowering therapy would be important. Statins and many other drugs are contraindicated during pregnancy and breastfeeding, and only bile sequestering resins can be used, taking proper care, but their LDL-lowering effects are limited[59]. It has been reported that lipoprotein apheresis is effective and feasible during pregnancy, and a case of cardiovascular death caused by suspension of apheresis during pregnancy[60] has been reported. Consultation with experienced specialists is recommended for pregnancy in HoFH.

Future Perspectives

Therapeutic options are still limited for HoFH, and all-out efforts should be made to achieve the best combination of feasible therapies in many cases. However, each therapeutic strategy has its advantages

and disadvantages so new therapies are awaited.

Inclisiran, a new siRNA drug that inhibits translation of PCSK9, is being developed[61]. As the effect of one injection lasts 6 months to 1 year, this drug may be a good option for HoFH patients who respond to PCSK9 inhibitors. Inclisiran was approved in the European Union in December 2020.

Evinacumab, an anti-ANGPTL3 antibody, is a new class of drug that is reportedly effective even in HoFH[62], and clinical trials are ongoing in Japan and other countries[63]. The LDL-C lowering effect of evinacumab is independent of LDL receptor activity.

Mipomersen (Kynamro), an antisense drug for the *APOB* gene, has moderate LDL-lowering effects but has the adverse effects of liver damage and injection site reactions. It was approved by the FDA for HoFH in 2013 [64] but rejected by the European Medicines Agency, and FDA approval was eventually withdrawn in 2019.

Gene therapy for HoFH has been investigated, but is still in the experimental stage. Since HoFH is a relatively rare disease, even if approved, demand for therapies would not be very high anywhere in the world. Lomitapide had been approved only for the treatment of HoFH in just 38 countries as of March 2021, including those in North and South America, the European Economic Area, and only Japan in East Asia. Lipoprotein-apheresis, which requires specific equipment, is available in a limited number of countries. Wider availability of therapeutic measures for HoFH should encourage its more active diagnosis worldwide.

Early diagnosis of FH is essential for preventing premature death in patients, whether they are hetero- or homozygotes[65-67]. Universal screening of plasma lipid levels during childhood has been trialed in some parts of Japan and we expect that such trials on local universal screening will lead to a nationwide system. In addition, reverse cascade screening, in which family members are screened on the basis of child probands, and continued worldwide registry research should improve the effectiveness of finding FH[68-76].

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Conflicts of Interest

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Review

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Current Status of Familial LCAT Deficiency in Japan

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Lecithin cholesterol acyltransferase (LCAT) is a lipid-modification enzyme that catalyzes the transfer of the acyl chain from the second position of lecithin to the hydroxyl group of cholesterol (FC) on plasma lipoproteins to form cholesteryl acylester and lysolecithin. Familial LCAT deficiency is an intractable autosomal recessive disorder caused by inherited dysfunction of the LCAT enzyme. The disease appears in two different phenotypes depending on the position of the gene mutation: familial LCAT deficiency (FLD, OMIM 245900) that lacks esterification activity on both HDL and ApoB-containing lipoproteins, and fish-eye disease (FED, OMIM 136120) that lacks activity only on HDL. Impaired metabolism of cholesterol and phospholipids due to LCAT dysfunction results in abnormal concentrations, composition and morphology of plasma lipoproteins and further causes ectopic lipid accumulation and/or abnormal lipid composition in certain tissues/cells, and serious dysfunction and complications in certain organs. Marked reduction of plasma HDL-cholesterol (HDL-C) and corneal opacity are common clinical manifestations of FLD and FED. FLD is also accompanied by anemia, proteinuria and progressive renal failure that eventually requires hemodialysis. Replacement therapy with the LCAT enzyme should prevent progression of serious complications, particularly renal dysfunction and corneal opacity. A clinical research project aiming at gene/cell therapy is currently underway.

Key words: **Lecithin cholesterol acyltransferase, Low HDL-cholesterol, Abnormal LDL, Corneal opacity, Proteinuria, Enzyme replacement therapy**

Introduction

The enzyme that esterifies cholesterol in human blood plasma was discovered in 1962 [1]. The reaction was determined to be an acyl transfer reaction from phosphatidylcholine (lecithin) associated with HDL. The enzyme was named LCAT, and the physiological role proposed for it was creating a gradient of cholesterol content between the HDL surface and cell membrane to generate efflux of cell cholesterol[2]. At around the same time, a patient with deficiency of this enzyme was identified in Norway. A 33-year-old woman in a hospital in Oslo was suspected of having chronic nephritis due to proteinuria and exhibited corneal opacity, anemia, and slight hypoalbuminemia, though renal function was normal. Renal biopsy revealed presence of foam cells in the glomerular tufts. Plasma total cholesterol and triglyceride levels were high but most of the cholesterol was found not to be esterified and further biochemical analyses

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demonstrated that the patient was deficient in LCAT activity. Similar signs and symptoms were also noted in her sister, suggesting a hereditary disorder. Therefore, the disorder was named familial LCAT deficiency (FLD, OMIM 245900) by Norum and Gjone[1]. The classical form of this disease exhibits plasma LCAT activity of less than 10% of normal whereas, in partial deficiency the decrease may be 15 to 40%. In FLD, there is lack of esterification activity on both HDL and ApoB-containing lipoproteins. Later, a subtype of this disease was found and named fish-eye disease (FED, OMIM 136120), where esterification is inactive only on HDL[3]. Both FLD and FED are caused by *LCAT* gene mutations. The profile and progression of the accompanying symptoms vary depending on the extent of LCAT activity impairment. In this review, the clinical and biochemical features, genetic backgrounds and current treatment of this hereditary disease are summarized and, referring to cases reported in Japan, clinical practice guidelines for Japan are proposed.

Background Mechanism for Clinical Findings of Familial LCAT Deficiency and Fish-Eye Disease

LCAT is the enzyme that acyl-esterifies cholesterol in plasma, which reduces unesterified cholesterol on the HDL surface to generate efflux of cell cholesterol to HDL. This comprises an important part of cholesterol transport from peripheral organs and cells to the liver for its catabolism. LCAT dysfunction disrupts this process, resulting in marked reduction of HDL-C and deformation of HDL particles due to lack of their major core lipid, cholesteryl acyl-ester. Impaired turnover of cellular cholesterol leads to its accumulation in cells in the cornea, bone marrow, liver, spleen, and glomerular basement membrane of the kidney[4, 5]. It is visible from the abnormal shape of erythrocytes[4, 5]. The clinical prognosis of LCAT deficiency is largely dependent on progression of renal dysfunction[4, 5]. Both FLD and FED are commonly screened for by low plasma HDL-C level and corneal opacity[4, 5].

1) Dyslipidemia

LCAT catalyzes acylesterification of cholesterol on plasma lipoproteins in the steady state, both on α-lipoproteins (HDL) (α-activity) and β-lipoproteins (LDL and VLDL) (β activity). The reaction requires the presence of helical apolipoproteins such as apolipoprotein (apo) A-I and E. It takes place on HDL, where particles are initially assembled as disc-like particles from extracellular helical apolipoproteins such as apoA-I with cellular phospholipid and cholesterol (nascent HDL or preβ-HDL), to generate the core and make particles spherical (mature HDL). This process maintains the efflux of cholesterol from cells to HDL. The reaction also takes place on apoB lipoproteins (β-lipoproteins), which should provide additional efflux of cell cholesterol. Lack of LCAT activity therefore causes a marked decrease in HDL-C and "immature" HDL remains in plasma appearing as rouleaux under electron microscopic observation. Owing to this abnormal HDL, plasma apoA-I and apoA-II, the first and second major apolipoproteins, also decrease. Thus, among FLD plasma lipoproteins, the percentage of esterified cholesterol in total cholesterol (CE/TC) is markedly low. There are also abnormal findings for LDL fractions in ultracentrifugation analysis[6] due to lack of the LCAT reaction, in which three subtypes of particles with different lipid compositions are evident. They are LpX particles, which are called FC-rich, PL-rich and TG-poor particles, and have a larger size (40 nm-60 nm). A large subtype of LDL rich in TG and PL (Lp8)[7] was identified by gel filtration HPLC analysis as a specific subtype for FLD. However, the exact mechanism for generating these abnormal LDL particles is not fully understood. Moreover, specific changes in LDL in FED are not clearly defined.

2) Corneal Opacity

FC and phospholipids accumulate excessively in the cornea due to lack of the LCAT reaction. Corneal turbidity is observed from early childhood in both FLD and FED, with patients presenting severe visual impairment and requiring corneal transplantation. Corneal opacity is frequently observed not only in LCAT deficiency but also in other HDL-deficiencies such as those related to apoA-I and ABCA1 (Tangier disease)[8]. Electron microscopic studies have shown that corneas from FLD patients are similar to those of patients with familial apoA1 deficiency[9-13]. In a patient with Tangier disease, very mild corneal clouding (usually requiring a slit-lamp examination for detection) has been reported, with less abundant extracellular corneal stromal deposits and cholesterol/phospholipid accumulation than in FED[14]. Since FED is usually not accompanied by renal dysfunction, the underlying mechanisms for corneal opacity and renal dysfunction may differ. Since the largest particle size capable of diffusing through the central stromal matrix is about 12 nm[15], it is unlikely that LDL and/or LpX infiltrate into the corneal stroma. On the other hand, small to normal-sized spherical HDL particles are found only in very small amounts in FLD and FED and Tangier disease[16-18]. As cholesterol is

synthesized in the cornea[19] reduced removal is a possible cause of its accumulation.

3) Hemolytic Anemia

Abnormally shaped erythrocytes, called target red blood cells, appear in LCAT deficiency due to the abnormal lipid composition of the cell membranes, which sometimes leads to hemolytic anemia, perhaps due to their fragility[20, 21]. The half-life of red blood cells is approximately half that of healthy people.

4) Splenomegaly

Splenomegaly with sea-blue histiocytosis has been reported[22, 23] in some FLD patients presenting abnormal lipid profiles. The histiocytes contained cytoplasmic vacuoles and membrane-like structures resembling rose petals, indicating that they were composed of phospholipid-containing membranes.

5) Proteinuria and Renal Dysfunction

Proteinuria is detected relatively early in the life of patients and frequently develops into progressive renal failure at 40 to 50 years of age, and eventually requires hemodialysis[24, 25]. It has been reported that proteinuria occurred in FLD patients at 3 years of age[26]. As kidney damage does not generally develop in FED, renal biopsy may be useful for differential diagnosis of the subtypes of LCAT deficiency. Renal lesions begin with deposition of lipid in the glomerular basement membrane, and later in the mesangium and capillary subendothelium. LpX particles, abnormal lipoprotein particles identified in the LDL fractions of FLD, have been considered to be a causative factor of renal damage in many studies[5, 27-29]. Recently, large TG-rich LDL (Lp8)[7] has been reported to be associated with the progression of renal dysfunction. It has also been reported that oxidized lecithin in the LDL of patients causes renal dysfunction[30]. In addition, lipoproteins containing apoE have been shown to be taken up by renal glomerular mesangial cells, causing excessive lipid deposition, possibly leading to renal dysfunction[31]. ApoE is a physiological LCAT activator in β-activity on LDL/VLDL particles[32], and effect of *apoE* genotype on clinical manifestations has been reported[33, 34], although further analyses are required to draw a definitive conclusion. In mice, LpX is taken up by glomerular endothelial cells, podocytes, and mesangial cells, it causes dysfunction in glomerular endothelial cells, and increases secretion of inflammatory cytokines[35]. Recent follow-up studies of families with an FLD mutation for a median of 12 years showed that eGFR deteriorated among homozygous family members at an average annual rate of 3.56 mL/min/1.73 m^2, whereas deterioration in heterozygous members and family controls was 1.33 and 0.68 mL/min/1.73 m^2, respectively[36]. A recent Italian cohort study in which 18 FLD patients (12 males and 6 females) were followed up for 12 ± 8.5 years reported that renal events (dialysis, kidney transplant, or death due to renal complications) occur at a median age of 46 years[37].

6) Atherosclerosis

Based on the inverse association between cardiovascular risk and plasma HDL-C levels found in epidemiological studies and the proposed function of LCAT in cholesterol transport, it is conceivable that the risk of cardiovascular events is increased in genetic low HDL-C patients. However, studies on FLD patients have produced inconsistent findings regarding a correlation between LCAT activity and atherosclerosis[38, 39]. Recently, Italian and Dutch research groups assessed subclinical atherosclerosis using carotid intima-media thickness in 74 patients with heterozygous mutations leading to the FLD and FED phenotypes[40]. Carriers of *LCAT* mutations leading to FLD exhibited less carotid atherosclerosis, whereas carriers of those leading to FED showed marginally more atherosclerosis. Thus, the clinical significance of the function of HDL[41] and other LCAT-associated lipoproteins[7] in the progression of atherosclerosis has not been established from the findings in FLD and FED. Also, no significant information in this regard has been reported in Japanese FLD and FED patients.

Disease Prevalence and Genetics

FLD and FED are autosomal recessive inherited diseases caused by mutations of the *LCAT* gene located in the short arm of chromosome 16. In Japan, the prevalence of these diseases is extremely low so the exact rate of mutation is unknown. **Fig. 1** shows previously identified *LCAT* gene mutations in patients according to The Human Gene Mutation Database[42], showing great diversity in the positions of mutations causing dysfunction of LCAT. An association between position and extent or nature of dysfunction has not been well established. A report by the Ministry of Health, Labor and Welfare Research Group described 13 types of mutations identified in Japan[43] by 2004. Since the report, a further 7 mutations of the *LCAT* gene have been identified as causative mutations of FLD or FED in Japan[34, 44-46]; 5 of them were novel mutations and 2 had already been reported in patients in other countries. Mutations occurring in Japanese are summarized in **Table 1**.

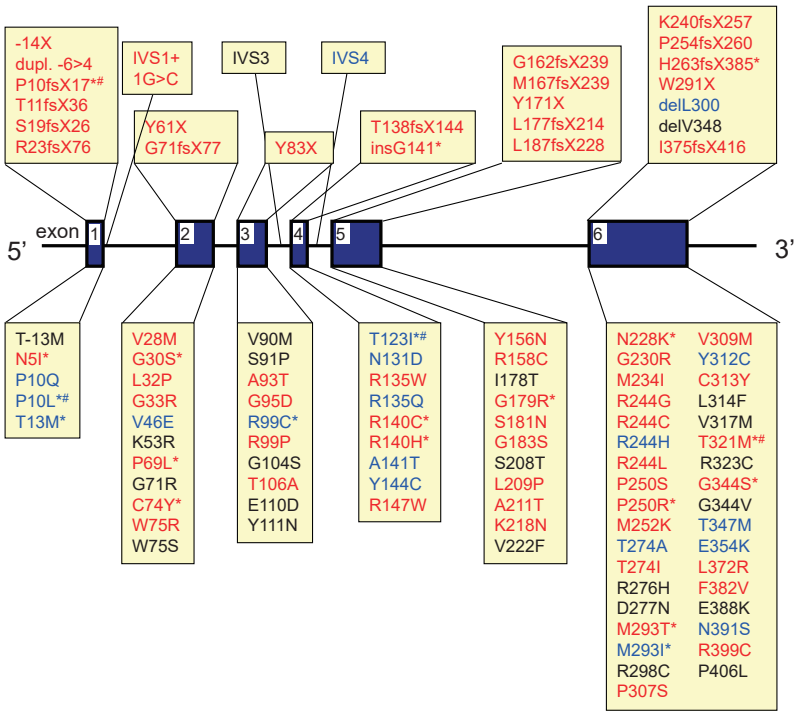

Fig. 1. Previously identified mutations in *LCAT* gene

The *LCAT* gene is composed of six exons. Mutations identified so far are depicted according to The Human Gene Mutation Database (HGMD®) (http://www.hgmd.cf.ac.uk/ac/index.php). Numbers of amino acid residues are expressed based on mature LCAT protein after signal peptide (24 amino acid residues) is cleaved. Mutations in red and bule are causative mutations identified in familial LCAT deficiency (FLD) and fish-eye disease (FED), respectively. The * symbol indicates a mutation reported in Japan, and the # symbol indicates a mutation identified in Japan as well as other countries. Mutations shown in black are variants of uncertain significance found by such as genome-wide nucleotide sequencing of clinical samples.

Table 1. Mutations identified in patients in Japan

Exon	Mutation	Codon	Amino acid substitution	Phenotype
1	c.86A>T	5	Asn>Ile	FLD
1	c.101insC	10	Pro10fsTer17	FLD
1	c.101C>T	10	Pro>Leu	FED
1	c.110C>T	13	Thr>Met	FED
2	c.160G>A	30	Gly>Ser	FLD
2	c.278C>T	69	Pro>Leu	FLD
2	c.293G>A	74	Cys>Tyr	FLD
3	c.367C>T	99	Arg>Cys	FED
4	c.440C>T	123	Thr>Ile	FED
4	c.490C>T	140	Arg>Cys	FLD
4	c.491G>A	140	Arg>His	FLD
4	c.493insGGC	141	ins Gly	FLD
5	c.607G>C	179	Gly>Arg	FLD
6	c.756C>A	228	Asn>Lys	FLD
6	c.821C>G	250	Pro>Arg	FLD
6	c.862del	264	His263fsTer385	FLD
6	c.950T>C	293	Met>Thr	FLD
6	c.951G>A	293	Met>Ile	FED
6	c.1034C>T	321	Thr>Met	FLD
6	c.1102G>A	344	Gly>Ser	FLD

Mutations identified in Japanese patients are summarized. Note that numbering of amino acid residues is based on mature LCAT protein in which 24 signal peptide sequence is removed.

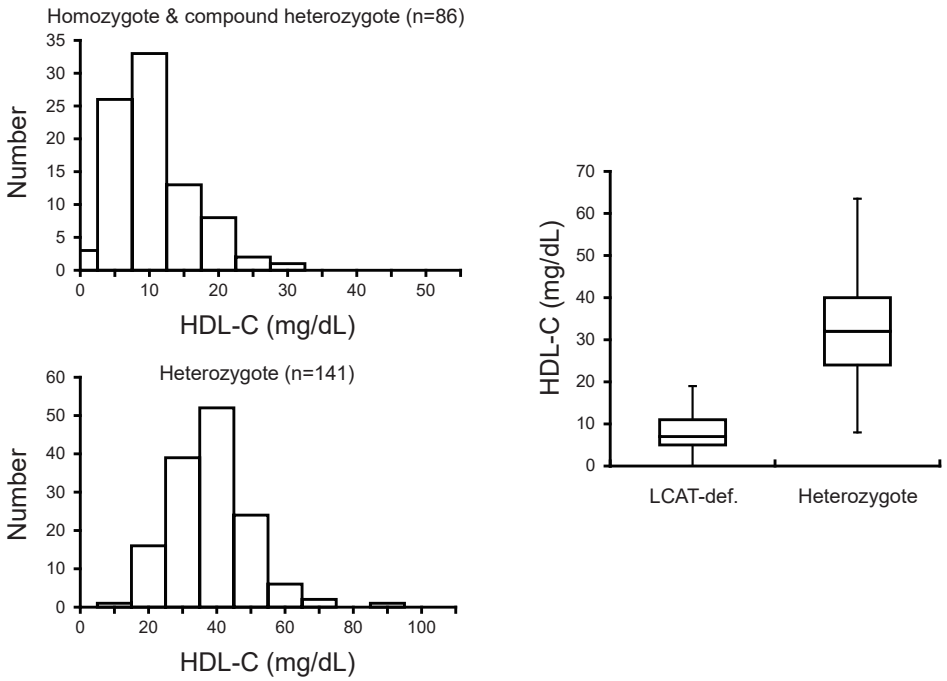

Fig. 2. Distribution of HDL-C in patients

Clinical levels of HDL-C available from published data (until Aug. 2019) for homozygous and compound heterozygous patients (n=86) and heterozygotes (n=141) have been collected and their distribution is shown in the figure. Note that their assay methods are not taken into consideration in the data distribution.

Clinical Examinations and Diagnostic Approach to LCAT Deficiency in Japan

The main clinical findings in FLD and FED are corneal opacity and low HDL-C. They are the key signs for suspecting these diseases. Proteinuria and/or anemia are also observed in many cases of FLD, but not in FED.

1) Lipid Examination

HDL-C values reported in the literature are summarized for homozygous and compound heterozygous FLD patients (n=86) in **Fig. 2** (until Aug. 2019). More than 72% of patients exhibited HDL-C levels less than 10 mg/dL. However, 3.5 % had levels higher than 20 mg/dL though the assay methods were not standardized. When a patient has an HDL-C level less than 25 mg/dL and corneal opacity, LCAT activity analysis should be considered (proposed by the Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Diseases of the Ministry of Health, Labour and Welfare of Japan in 2020). In assays, since α-activity represents LCAT activity using synthetic HDL (specific for HDL) as a substrate[47], measured levels are largely decreased in all plasma samples from patients with FLD or FED and may be below the detection limit in both. Cholesterol esterification rate (CER)[48] represents total esterification activity, including β-activity (specific for β-lipoproteins) and α-activity. As β-activity is also disrupted in FLD but not much in FED, measured levels are usually more decreased in FLD, compared with FED, which is useful for distinguishing FLD and FED. However, these assays are not routinely available in the clinical laboratories of regular hospitals in Japan. Therefore, the CE/TC ratio in plasma is a useful alternative for distinguishing FLD and FED. CE/TC is always reduced in FLD but not in FED and partial LCAT deficiency. ApoA-I and apoA-II are also significantly reduced due to the reduced HDL levels in FLD and FED. In the electrophoretic analysis of lipoproteins (agarose or polyacrylamide), LCAT dysfunction results in the appearance of abnormal lipoproteins, including LpX and IDL. Large and triglyceride-rich LDL (Lp8) is identified through HPLC gel filtration analysis of lipoproteins[7].

2) Ophthalmic Examination

Corneal opacity **(Fig. 3A)** is recognized in most LCAT deficiency patients. Grayish white granular spots are observed in corneal layers excluding the epithelium by the slit-lamp test. To assess the extent of corneal opacity, a contrast sensitivity test[49] is useful.

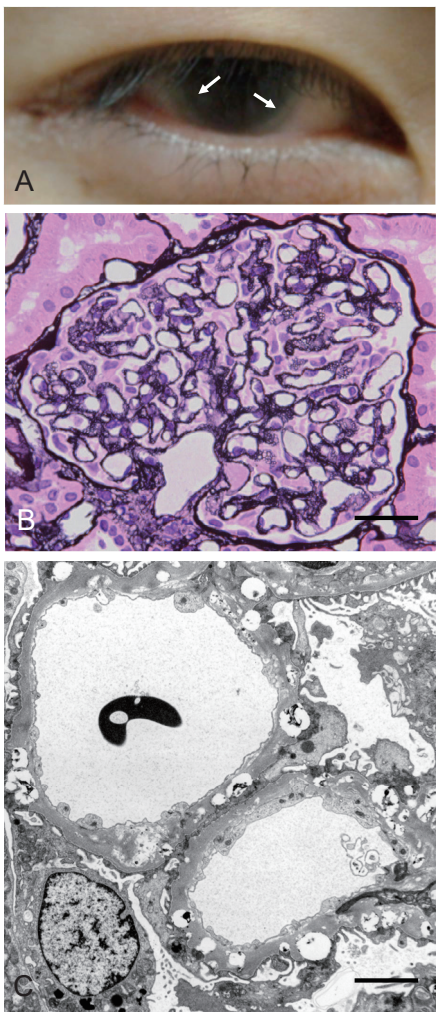

Fig. 3. Case with LCAT deficiency manifesting as corneal opacities and proteinuria (patient from ref. 31)

A) Corneal opacities in right eye (arrows).
B) Light microscopic findings for renal biopsy (Periodic acid methenamine silver stain). Thickened with bubbly, vacuolated, and honeycomb appearance. (Bar = 10 μm)
C) Electron microscopic findings for renal biopsy. Electron micrograph shows glomerular epimembranous, intramembranous, and subendothelial lipid droplets. Electron-lucent deposits with an electron-dense core can be observed in the glomerular basement membrane and mesangial matrix. (Bar = 2 μm)

3) Renal Examination

When proteinuria is present in patients with decreased LCAT activity who present with corneal opacity, renal biopsy may be considered **(Fig. 3B and 3C)**. Deposition of FC and phospholipids in the subendothelium of glomerular basement membrane is often observed. Accumulation of foam cells and thickening of Bowman's sac and glomerular basement membrane are also observed. Electron microscopy reveals an extensive high electron density membrane structure in the capillary lumen, basement membrane, and mesangial region[50].

4) Hematological Examination

Mild hemolytic anemia is present in many cases of FLD. A blood count shows a decreased hemoglobin level. HbA1c and haptoglobin levels are also decreased. Red blood cells with an abnormal appearance (called "target cells", "knizocytes", "stomatocytes", or "spherostomatocytes") are observed in FLD due to cholesterol accumulation in the cell membranes.

5) Gene Analysis

Genetic analysis is useful for the final diagnosis, combined with the results of the above examinations. The recessive inheritance format is determined through identification of mutations in the *LCAT* gene of the FLD or FED patients.

Differential Diagnosis

1) Hereditary Low HDL-Cholesterolemia (Tangier Disease, Familial Hypo-Alpha-Lipoproteinemia and ApoA-I Deficiency)

Patients with apoA-I deficiency and Tangier disease have a marked reduction in plasma HDL-C levels, which are generally lower than those in FLD and FED. Corneal opacity is also observed in these diseases[8]. The apo A-I level is about 30-50 mg/dL in patients with FLD or FED, but levels in Tangier disease are more markedly decreased (less than 10 mg/dL). Thus, the plasma apolipoprotein A-I concentration is useful for the differential diagnosis of these diseases. However, genetic analysis may be needed for final differentiation of diseases with hereditary low HDL-cholesterolemia.

2) Immune-Mediated LCAT Deficiency

There have been reports of patients exhibiting marked reduction in plasma HDL-C and renal dysfunction, similar to those in genetic LCAT deficiency, but are due to the presence of autoantibodies against LCAT protein[51, 52]. Immune-mediated LCAT deficiency is sometimes found through a gradual decrease in HDL-C. Testing for the antibodies and investigation of family history are necessary for differentiating this disorder from genetic LCAT deficiency, especially FLD.

3) Liver Disease (Liver Cirrhosis and Fulminant Hepatitis), Biliary Tract Obstruction, Malnutrition, or Cachexia

LCAT is an enzyme produced in the liver, so its biosynthesis is susceptible to hepatic damage. It is thus necessary to differentiate FLD and FED from

conditions where there is a secondary decrease in the enzyme due to serious liver dysfunction[53].

4) Drug-Induced Low HDL-Cholesterolemia (Probucol and Probucol/Fibrates)

Probucol has been found to reduce plasma HDL by inhibiting ABCA1 activity. In addition, it has been reported that plasma HDL is reduced to an extreme degree when probucol is taken with fibrate, even when fibrate is initiated after discontinuing probucol[54-56]. Patient histories need to be examined for use of these medications.

Since it is a designated intractable disease, diagnostic criteria for familial LCAT deficiency were previously proposed by the research group of the Ministry of Health, Labor and Welfare of Japan. The guidelines have been updated based on additionally accumulated Japanese clinical and laboratory data by a dyslipidemia research group supported by a grant from the Ministry of Health, Labor and Welfare **(Table 2)**.

Table 2. Diagnostic criteria for Japan proposed by research group of Ministry of Health, Labor and Welfare

A. Required item
1. Blood HDL-C level less than 25 mg/dL
2. Decrease in cholesteryl ester/TC ratio (CE/TC) (60% or less)

B. Symptom
1. Proteinuria, renal dysfunction
2. Corneal opacities

C. Laboratory findings
Blood and biochemical examination findings
1. Anemia (hemoglobin level, less than 11 g/dL)
2. Abnormalities in morphology of red blood cells (called "target cells", "knizocytes", "stomatocytes", or "spherostomatocytes")
3. Appearance of abnormal lipoproteins (LpX, IDL, or large TG rich LDL)

Ophthalmic examination findings
Decreased contrast sensitivity

D. Differential diagnosis
Differentiate from following diseases.
1. Other hereditary low HDL-cholesterolemia (Tangier disease, apolipoprotein AI deficiency)
2. Secondary LCAT deficiency (pathophysiology showing decreased protein synthesis such as liver disease (hepatic cirrhosis, fulminant hepatitis), biliary obstruction, malnutrition, cachexia, and autoimmune LCAT deficiency with underlying disease)
3. Secondary low HDL-cholesterolemia (After surgery, hepatopathy (especially cirrhosis, severe hepatitis, including convalescent stage), acute phase of systemic inflammatory disease, debilitating diseases such as cancer. history of oral probucol within the past 6 months, probucol and fibrate combination (including prescription after discontinuation of probucol))

E. Genetic testing
1. Mutation of *LCAT* gene

In a clinical sample in which two essential items are satisfied, the following determinations are made.
Definite: A disease that meets one or more of B and C and excludes any disease to be differentiated from in D, and satisfies E
Probable: Disease that meets one or more of B and C and excludes any disease that should be differentiated from in D

Current Treatment

There is no currently approved effective treatment for FLD and FED. Effective treatments would be replacement with normal or recombinant LCAT enzymes and gene therapy, and they are now under development. To mitigate renal dysfunction, a low-fat diet and renoprotective drugs, such as angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), are prescribed.

1) Diet

There has been a study on the FLD siblings where the younger brother, who was put on a low calorie intake (1900 Cal) with fat restriction (25 g/day), did not develop proteinuria while his elder brother having a total calorie intake of 2500 Cal and fat intake of 65 g/day did[57]. Together with those of other studies[46, 58], these findings indicate that development of renal dysfunction can be delayed by a low-fat diet. A low-fat diet may lead to a decrease in abnormal lipoproteins associated with LCAT deficiency as well as reduced renal damage, although it may not be effective in all cases[59].

2) Blood Transfusion Therapy

Fresh blood (whole blood or plasma) transfusion therapy has been reported to be effective for LCAT replacement[60, 61]. An increase in LCAT activity was observed, but it returned to the pre-transfusion level within one week, indicating that it is difficult to maintain a therapeutic level.

3) Drug Treatment

There is no definitive drug treatment for alleviating decreased or defective LCAT activity in FLD. Drug therapy, combined with diet, has been attempted with the purpose of preventing or mitigating the deterioration in renal function. ACE inhibitors reportedly reduced proteinuria after one

year of treatment[26]. Also, combination therapy of nicotinic acid and fenofibrate lead to a reduction in LpX and an associated reduction in albuminuria in a patient[62]. In addition, high-dose ARB with statin was reported to stabilize the progression of renal dysfunction[63]. Results for corticosteroid treatment (with ACE inhibitor) suggested that reduced inflammatory responses lead to a decrease in proteinuria in a patient[64].

4) Recombinant hLCAT Protein (rhLCAT) Replacement Therapy

A clinical trial on rhLCAT has been conducted in the United States[65]. High-dose rhLCAT (9.0 mg/kg) improved anemia and renal function to some degree with improvement in lipid parameters, including an increase in HDL-C but there was a return to the pre-treatment status by 2 weeks after administration, and the supply of rhLCAT became insufficient during the trial. As with other enzyme replacement therapies, it is necessary to continue administration. Another clinical trial has been conducted to evaluate the safety, pharmacokinetics and pharmacodynamics of rhLCAT in subjects with stable coronary artery disease (NCT02601560)[66]. It was reported that antibodies against rhLCAT appeared in some of the participants on the highest dose of rhLCAT.

5) Gene Therapy

A gene therapy-mediated continuous supply of LCAT would improve patient QOL by reducing the frequency of hospital visits and administration of therapy. No gene therapy has received regulatory approval anywhere. In Japan, the first in-human study on gene therapy/regenerative medicine via auto-transplantation of *LCAT* gene-transduced preadipocytes has been approved by the Ministry of Health, Labor and Welfare, under the Act on Securement of Safety of Regenerative Medicine[67]. The first patient has been followed up for more than three years since transplantation at Chiba University Hospital. It was well-tolerated. The second clinical trial was started in 2020 for the purpose of obtaining regulatory approval in Japan.

6) Organ Transplantation

Kidney transplantation to treat renal dysfunction and corneal transplantation to remedy visual impairment are performed, but the risk of recurrence is inevitably high. In recent years, single-donor sequential kidney and liver transplantation has been performed in one patient[68]. During the 5-year follow-up period, the function of the transplanted organs was maintained, but dyslipidemia recurred within 1 year after liver transplantation.

Future Perspectives

Our current understanding of familial LCAT deficiency and its complications is summarized in this review based on information from the literature, including that from Japan. More than 100 *LCAT* mutations have been identified in the world, but mechanisms of development of subsequent complications remain to be elucidated. A better understanding of the pathophysiology of this disease will be necessary to make further progress in treatment. We hope that this review will be helpful for clinicians in performing diagnosis and medical care for patients suspected of having the disease in Japan.

The diagnosis of the subtypes of this rare genetic disease, FLD and FED, requires the involvement of multiple departments such as lipid metabolism, nephrology, and ophthalmology. Also, the onset of severe renal dysfunction is relatively late (40 to 50 years old). These could be reasons for the delay in diagnosis. Measurement of LCAT activity and genetic testing for FLD and FED are not covered by National Health Insurance in Japan, and this also makes it difficult for physicians to diagnose patients with the disease.

Currently, LCAT enzyme replacement therapy by means of transfusion of a recombinant preparation or gene/cell therapy is under development. We hope that these treatments are put into practice in near future, and improve patients' survival and QOL.

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Diagnosis and Management of Sitosterolemia 2021

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Sitosterolemia is an inherited metabolic disorder characterized by increased levels of plant sterols, such as sitosterol. This disease is caused by loss-of-function genetic mutations in ATP-binding cassette (ABC) subfamily G member 5 or member 8 (*ABCG5* or *ABCG8*, respectively), both of which play important roles in selective excretion of plant sterols from the liver and intestine, leading to failure to prevent absorption of food plant sterols. This disorder has been considered to be extremely rare. However, accumulated clinical data as well as genetics suggest the possibility of a much higher prevalence. Its clinical manifestations resemble those observed in patients with familial hypercholesterolemia (FH), including tendon xanthomas, hyper LDL-cholesterolemia, and premature coronary atherosclerosis. We provide an overview of this recessive genetic disease, diagnostic as well as therapeutic tips, and the latest diagnostic criteria in Japan.

Key words: **Sitosterolemia, ABCG5, ABCG8, Familial hypercholesterolemia**

Introduction

Sitosterolemia (OMIM #210250, and #618666) is an autosomal recessive disorder of lipid metabolism characterized by increased absorption and decreased biliary excretion of plant sterols and cholesterol, resulting in prominently elevated serum concentrations of plant sterols, such as sitosterol, campesterol, and stigmasterol **(Fig. 1)**[1, 2]. This condition was first described by Bhattacharyya and Connor in 1974 [3]. Patients with sitosterolemia primarily exhibit tendinous and tuberous xanthomas and premature coronary atherosclerosis, resembling these characteristics in patients with familial hypercholesterolemia (FH)[4-9]. Severity of the phenotypes of sitosterolemia appears to be more variable than for FH possibly due to its greater dependency on dietary sterol intake[10, 11]. In addition, they have a wider variety, which includes hemolysis, splenomegaly, platelet abnormalities, and arthralgia/arthritis[12]. This disease is caused by biallelic (homozygous/compound heterozygous) loss-of-function (LOF) mutations in either ATP-binding cassette (ABC) subfamily G member 5 or member 8 (*ABCG5* and *ABCG8*, respectively) that play an important role in excreting sterols from the liver and intestine **(Fig. 1)**[13, 14]. Therefore, increased absorption of plant sterols from the intestine and their decreased secretion from the liver are the primary cause of sitosterolemia[15, 16]. Several (adaptive) secondary changes in lipid metabolism have been found to be associated with the accelerated sterol absorption; for

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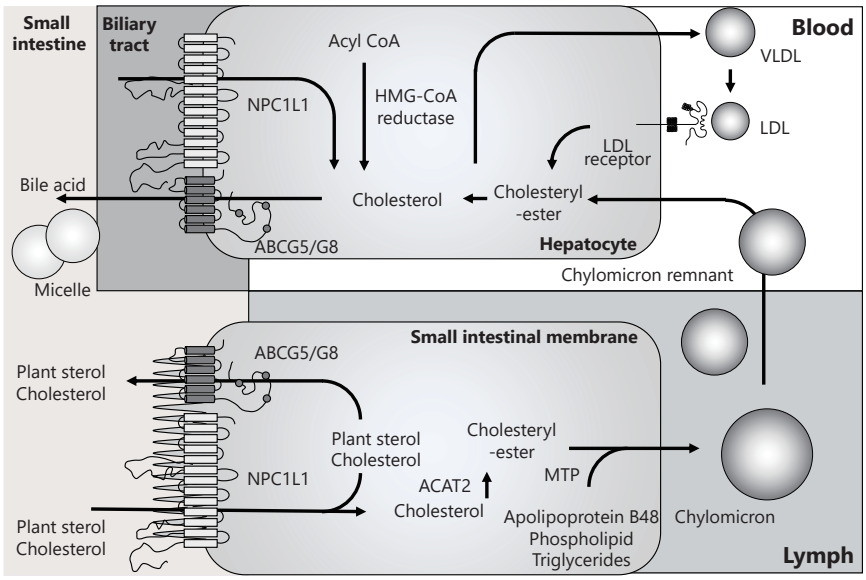

Fig. 1. Schema of sterol metabolism focusing on ABCG5/8 and NPC1L1

In the intestine, plant sterols and cholesterol are absorbed via NPC1L1, while they are excreted via ABCG5/8. The same pattern is observed in hepatocytes.

example, altered solubilization of sterols in intestinal micelles, increased activity of acyl CoA: cholesterol acyltransferase (ACAT), and changes in intracellular transport processes of sterols.

Sitosterolemia used to be considered an extremely rare disorder but recent studies indicate the possibility of a much higher prevalence in the general population[6-10].

Based on the pathophysiology of this disease, ezetimibe, an inhibitor of Niemann-Pick C1 Like 1 (NPC1L1) that mediates absorption of dietary cholesterol in the intestine[17], has been shown to be effective in reducing serum sitosterol as well as cholesterol in sitosterolemic patients, together with dietary management to restrict intake of these sterols[18, 19]. In this review article, we discuss the current understanding of sitosterolemia, its diagnostic criteria, and future perspectives.

Plant Sterols

Plant sterols (sitosterol, campesterol, and stigmasterol) are sterol molecules naturally contained at low levels in plant foods such as fruits, vegetables, nuts and cereals[20]. Sitosterol is usually the most abundant plant sterol in the diet[2] and the average Japanese diet and Western diets contain similar amounts of cholesterol and plant sterols. Although approximately 50% of dietary cholesterol is absorbed, less than 5% of plant sterols is absorbed in normal individuals[21-24], resulting in lower levels of plant sterols than cholesterol in the body. In a recent investigation of plasma concentrations of plant sterols in 667,718 subjects, they seemed to be dependent on age, gender, and apolipoprotein E genotype[25].

Accumulation of plant sterols in patients with sitosterolemia would contribute to atherogenesis. However, dietary intake of plant sterols is generally considered beneficial for normal individuals as they competitively inhibit cholesterol absorption, which is then selectively excreted resulting in lower cholesterol levels[26]. The European Atherosclerosis Society Consensus Panel currently recommends taking plant sterols for patients with a relatively high risk for cardiovascular disease and/or statin intolerance[20]. In addition, the proinflammatory properties of sitosterol appear to be much weaker than those of cholesterol[27].

Epidemiology

Sitosterolemia has long been considered an extremely rare disorder. Indeed, only 45 sitosterolemic subjects were reported in a review article published in 2003 [28]. Its autosomal recessive inheritance may have caused us to think it is a rare disease. However, the Exome Aggregation Consortium (ExAC) Exome Browser, a public genetic database, has suggested that 1 in ~220 general individuals have LOF mutations in the *ABCG5* or *ABCG8* gene[29]. Therefore, a rough estimate of the number of homozygous/compound

heterozygous patients with sitosterolemia is 1 in ~200,000 general individuals. Moreover, a recent study has shown that a certain proportion of patients clinically diagnosed as FH could in fact have sitosterolemia[30]. Accordingly, this disorder appears to be much more prevalent than previously thought.

Genetic Backgrounds and Pathophysiology

In 2001, the cause of this disease was identified as double LOF mutations in the *ABCG5* or *ABCG8* gene[13, 14]. So far, most patients with recognized sitosterolemia have come from consanguineous marriages, which has lead to homozygous mutations in the *ABCG5* or *ABCG8* gene. However, recent advances in genetic analysis have revealed that there are also a number of cases with compound heterozygous mutations in the *ABCG5* and *ABCG8* genes. Relatively common pathogenic mutations are c.1166G>A/p.Arg389His, and c.1256G>A/p.Arg419His in *ABCG5* gene[31-33].

The ABCG5 and ABCG8 proteins form heterodimers and act as a complex, which functions as a transporter of sterols in the bile and intestine. Accordingly, patients with sitosterolemia exhibit either homozygous or compound heterozygous mutations in the *ABCG5* or *ABCG8* gene. Besides the above mutations, Tada *et al.* previously reported a unique case of sitosterolemia caused by double heterozygous mutations in the *ABCG5* and *ABCG8* genes, suggesting that specific combinations of mutations and/or quite deleterious heterozygous mutations may cause sitosterolemia[34].

Recent genome-wide association studies (GWAS) indicated that the *ABCG5* and *ABCG8* genes are significantly associated with LDL cholesterol levels and increased prevalence of coronary artery disease (CAD)[35, 36], suggesting that these genes contribute to high LDL cholesterol and high plant sterol levels in plasma and risk for CAD among the general population as well. In addition, Tada *et al.* have recently shown that deleterious mutations of the *ABCG5* or *ABCG8* gene contribute substantially to mimicking and exacerbation of the FH phenotype[30].

Clinical Manifestations

Individuals suffering from sitosterolemia primarily present with tendinous and tuberous xanthomas and premature coronary atherosclerosis, resembling those in FH. Therefore, a certain proportion of patients with sitosterolemia could be misdiagnosed as FH due to tendon xanthomas and elevated LDL cholesterol[30]. However, the severity of LDL cholesterol elevation and xanthomas appears to be more variable in sitosterolemia than in FH. In a case of myocardial infarction in a 25-year-old woman previously described by Kawamura *et al.*[9], Achilles tendon xanthomas, as well as significantly elevated LDL cholesterol levels and sitosterol levels were found, and she was initially misdiagnosed as FH. However, consideration of the recessive pattern of inheritance, great responsiveness to dietary counseling together with statin plus ezetimibe (LDL cholesterol was reduced from 220 mg/dl to 55 mg/dl) lead to the accurate diagnosis of sitosterolemia.

Typical cases in infancy have also been described. LDL cholesterol levels in FH tend to be constantly high, whereas those in sitosterolemia may vary with the latest dietary intake of sterols. The most extreme cases have been infants who are breastfeeding. They have been found to have cutaneous xanthomas associated with significant elevation in LDL cholesterol levels, resembling those in homozygous FH,[6, 37, 38]. It has been noted that weaning alone can reduce their LDL cholesterol levels, causing the cutaneous xanthomas to regress, despite sitosterol levels that remain significantly elevated. These observations suggest that they are quite vulnerable to a sterol-rich diet, and that dietary management is very important in infants with sitosterolemia. However, we have experienced several independent infantile cases of transient hypercholesterolemia associated with breastfeeding without any signs of cutaneous xanthomas, where the patients turned out to be carriers of heterozygous mutations of the *ABCG5* gene (data not shown). Thus, it appears that some infantile cases of "breastfed hypercholesterolemia" can be explained by heterozygous mutations of the *ABCG5* gene.

In addition, a variety of other phenotypes, such as hemolysis, splenomegaly, platelet abnormalities, arthralgia/arthritis have been documented among patients with sitosterolemia, and some of them have been shown to be associated with accumulation of sitosterol in an animal model[39]. The underlying mechanism responsible for the hematologic abnormalities observed in some patients with sitosterolemia appears to be accumulation of circulating sterols in blood cell membranes, leading to abnormal morphology and function[40]. Regarding arthralgia/arthritis, the case of a sitosterolemic patient who also had a history of recurrent arthritis has been described. Whole exome sequencing analysis revealed that this patient had another concomitant genetic disorder that had caused familial Mediterranean fever where arthritis is documented as one of the major manifestations[7].

Since sitosterolemia is a recessive disorder, in

many cases there is a consanguineous marriage in the background. This could lead to the coincidence of other recessive genetic disorders, although there is no clear evidence suggesting an association between their genotypes or inheritance patterns and the severity or variety of sitosterolemia phenotypes. Comprehensive genetic analyses in such patients could shed light on the causal (genetic) backgrounds of their phenotypes.

Sitosterol or Cholesterol?

Sitosterolemia was named for the significant elevation in serum sitosterol level in this disease. As sitosterol and other plant sterols have been shown to accumulate in atherosclerotic lesions of patients with sitosterolemia[4, 41], lowering serum sitosterol has long been considered to be a target for therapy. However, a causative relationship between marked elevation of sitosterol in serum and its tissue deposition and development of atherosclerotic cardiovascular diseases remains to be demonstrated. The results of studies regarding an association between serum sitosterol levels and atherosclerosis have been controversial[42-45].

Currently available data as well as the fact that sitosterolemic patients with premature atherosclerotic cardiovascular diseases tend to exhibit hyper-LDL cholesterolemia suggest that LDL cholesterol, rather than sitosterol is the main causal factor for atherogenicity. Therefore, further studies assessing the role of sitosterol in the development of atherosclerosis are needed

Diagnostic Criteria

Diagnostic criteria for sitosterolemia in Japan are described in **Table 1**. Serum sitosterol levels could be measured using high-sensitive gas chromatography. Their reference ranges in Japanese individuals have been determined as 0.99 - 3.88 μg/mL in males, and 1.03 - 4.45 μg/mL in females[46]. It is vitally important to perform differential diagnosis to distinguish it from FH **(Fig. 2A)**, autosomal recessive hypercholesterolemia (ARH) **(Fig. 2B, 2C)** and cerebrotendinous xanthomatosis (CTX) **(Fig. 2D, 2E)**. It is not easy to make a differential clinical diagnosis of sitosterolemia **(Fig. 2F, 2G)** just based on physical manifestations[47-50].

Diagnostic Tips for Sitosterolemia

As stated above, patients with sitosterolemia typically exhibit tendinous and tuberous xanthomas and premature coronary atherosclerosis, resembling the manifestations of FH. Therefore, patients with premature coronary atherosclerosis should be examined to see whether they have a special genetic background including that for sitosterolemia. Absence of a family history of hypercholesterolemia as well as premature CAD is likely to indicate sitosterolemia rather than FH. However, it is of note that some patients with sitosterolemia have a family history of hypercholesterolemia and tendon xanthomas despite its recessive pattern of inheritance. The tendon xanthomas of sitosterolemia tend to be more severe than those of heterozygous FH, despite lower levels of LDL cholesterol. Thus, sitosterolemia should be considered in differential diagnosis for heterozygous FH, which is now considered a relatively frequent genetic metabolic disease. In addition, LDL cholesterol levels of sitosterolemic patients tend to vary dramatically depending on their latest dietary intake of plant sterols, and this would be useful information in making a clinical diagnosis of this disease. ARH and CTX are extremely rare autosomal recessive diseases, and almost all patients with these diseases are from consanguineous marriages. It is sometimes quite difficult to differentiate sitosterolemia from ARH based on a single assessment; however, responsiveness to dietary counseling differs between sitosterolemia and ARH. On the other hand, patients with CTX can be differentiated from those with sitosterolemia based on several factors, such as absence of hypercholesterolemia, chronic diarrhea during childhood, juvenile cataracts, and neurological symptoms[49].

Table 1. Diagnostic criteria

A. Clinical manifestations
1. Cutaneous or tendon xanthomas
2. Premature coronary artery disease (male < 45 yr, female < 55 yr)
B. Laboratory testing
1. Serum sitosterol ≥ 1 mg/dL (10 μg/mL)
C. Differential diagnosis
Exclude familial hypercholesterolemia and cerebrotendinous xanthomatosis
D. Genetic analysis
Pathogenic mutations in ABCG5 or ABCG8 gene

Definite: fulfills A-1, B-1, C, and D
Probable: fulfills A-1, B-1, and C
Possible: fulfills A-1, A-2, and B-1

Management of Sitosterolemia

Restriction of plant sterols as well as cholesterol should be the first line strategy. Sitosterolemic patients should avoid plant sterol-rich foods, such as corn oil,

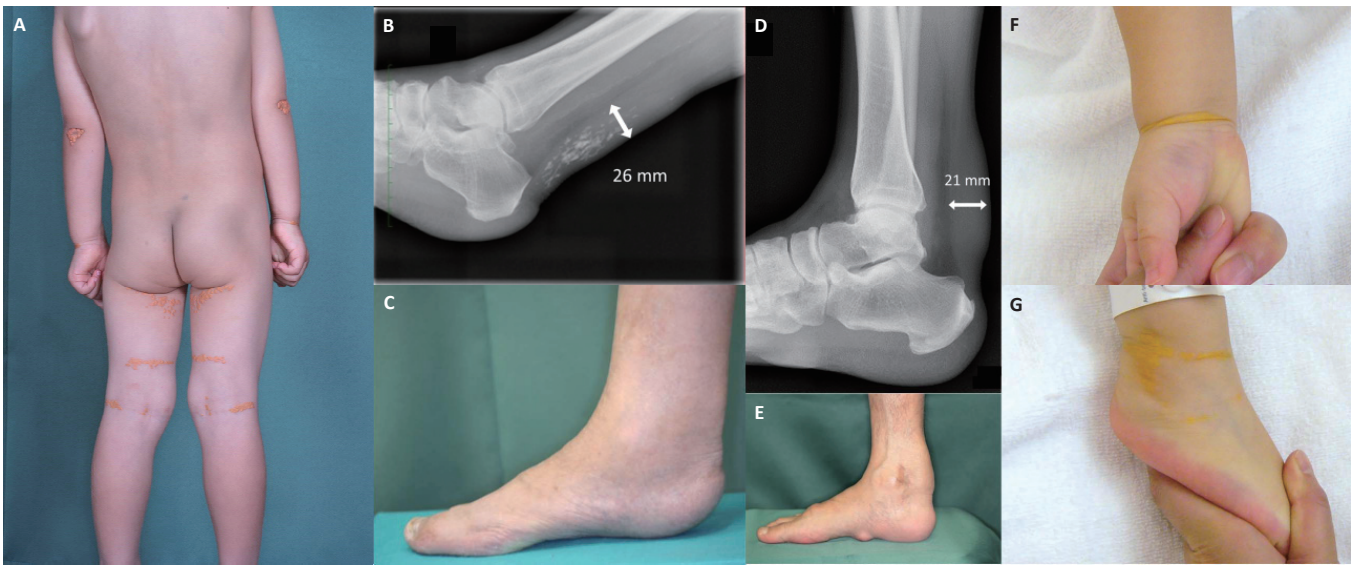

Fig. 2. Xanthomas in patients with dyslipidemias

(A) Systemic xanthomas in a patient with homozygous FH (3-year-old boy)
(B) X-ray of Achilles' tendon in a patient with ARH (67-year-male)
(C) Achilles' tendon xanthomas in a patient with ARH (67-year-male)
(D) X-ray of Achilles' tendon in a patient with CTX (63-year-male)
(E) Achilles' tendon xanthomas in a patient with CTX (63-year-male)
(F) Xanthomas at the ankle in a patient with sitosterolemia (1-year-old girl)
(G) Xanthomas at the wrist in a patient with sitosterolemia (1-year-old girl)

sesame seeds, peanuts, soybeans, rapeseed oil, sesame oil, rice oil, margarine, avocado, chocolate, and shellfish, whereas, other vegetables and fruits, such as potato, carrot, and apple contain less plant sterols[51]. In addition to plant sterols, they also need to avoid cholesterol-rich foods, including animal liver and eggs. Regarding medication, ezetimibe and bile-acid sequestrant resins have been established as standard therapies because the primary cause of this disease is increased absorption of plant sterols from the intestine and their decreased secretion from the liver[15]. Both could reduce sitosterol (~ 20% by ezetimibe, and ~ 30% by resins)[18, 52] and LDL cholesterol in sitosterolemia. Ezetimibe has also been shown to favorably increase platelet count[19].

Patients with sitosterolemia usually do not respond to statins because HMG-CoA reductase activity is already maximally inhibited[52]. However, statins are effective in reducing LDL cholesterol, at least in some sitosterolemic patients[9, 45], although they may increase sitosterol levels in others[53]. Considering the lack of a clear association between sitosterol levels and frequency of atherosclerotic cardiovascular disease[44], as well as the fact that some patients with sitosterolemia are treated with statins due to being misdiagnosed with FH[30], statins could at least be used for patients in a secondary prevention setting. For patients with advanced atherosclerotic lesions and resistance to the standard treatments mentioned above, LDL apheresis could be considered if applicable, although it is not officially covered by the Japanese national health insurance[8].

Liver transplantation was performed in a case of sitosterolemia with liver cirrhosis and reportedly resulted in a dramatic reduction in serum plant sterol levels[54]. Regarding target levels of LDL cholesterol, there is plenty of clinical evidence suggesting that lowering LDL cholesterol is associated with reduced risk for atherosclerotic cardiovascular diseases. In addition, sitosterolemia has been considered as a phenocopy of FH and therefore, the target LDL cholesterol level should be the same as that of FH. However, there has been no definite evidence for an association of sitosterol lowering and prevention of atherosclerotic cardiovascular diseases so far. Accordingly, LDL cholesterol, rather than sitosterol, should be the main biomarker when treating patients with sitosterolemia. Dietary restriction of plant sterols, ezetimibe, and bile-acid sequestrant resins have been shown to reduce both LDL cholesterol and sitosterol levels and thus these strategies should be considered as standard treatment for patients with sitosterolemia. The plant sterol content of foods and food ingredients varies widely from 7 mg/100 g in potatoes and

tomatoes to 686-952 mg/100 g in corn oil[55]. It is therefore rational to recommend patients with sitosterolemia and reduced function of ABCG5 or ABCG8 to avoid vegetables rich in plant sterols.

Conclusions and Perspectives

Sitosterolemia is a monogenic disorder that has been considered rather rare. However, its prevalence may currently be substantially underestimated[56], so we should be more careful to identify this disease among hypercholesterolemic patients with xanthomas. In particular, to raise awareness of sitosterolemia among pediatricians and dermatologists, education for them focusing on its typical manifestations is important. Measurement of serum sitosterol is not covered by Japanese national health insurance but we firmly believe that it is reasonable for it to be covered now that we have reference data for serum sitosterol levels among Japanese healthy individuals as well as patients with sitosterolemia. Ideally, prospective randomized controlled trials investigating if specific lowering of serum sitosterol leads to reduced risk for atherosclerotic cardiovascular diseases should be performed. More large-scale observational studies attempting to demonstrate an independent association between sitosterol levels and atherosclerotic cardiovascular diseases are also needed.

To establish the clinical importance of this disease for public health, more accurate prevalence and clinical manifestation data should be accumulated, supported by the health insurance system and comprehensive genetic analyses. Diagnostic criteria of sitosterolemia proposed by the Japanese Ministry of Health, Labor and Welfare scientific research team for hyperlipidemia would facilitate the accumulation of such data on this unique disorder.

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Conflicts of Interest

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Current Diagnosis and Management of Tangier Disease

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Tangier disease is a genetic disorder characterized by an absence or extremely low level of high-density lipoprotein (HDL)-cholesterol (HDL-C). It is caused by a dysfunctional mutation of the ATP-binding cassette transporter A1 (*ABCA1*) gene, the mandatory gene for generation of HDL particles from cellular cholesterol and phospholipids, and it appears in an autosomal recessive hereditary profile. To date, 35 cases have been reported in Japan and 109 cases outside Japan. With dysfunctional mutations in both alleles (homozygotes or compound heterozygotes), the HDL-C level is mostly less than 5 mg/dL and there is 10 mg/dL or less of apolipoprotein A-I (apoA-I), the major protein component of HDL. In patients with Tangier disease, major physical findings are orange-colored pharyngeal tonsils, hepatosplenomegaly, corneal opacity, lymphadenopathy, and peripheral neuropathy. Although patients tend to have decreased low-density lipoprotein (LDL)-cholesterol (LDL-C) levels, premature coronary artery disease is frequently observed. No specific curative treatment is currently available, so early identification of patients and preventing atherosclerosis development are crucial. Management of risk factors other than low HDL-C is also important, such as LDL-C levels, hypertension and smoking. Additionally, treatment for glucose intolerance might be required because impaired insulin secretion from pancreatic beta cells has occasionally been reported.

Key words: **Tangier disease, HDL, Reverse cholesterol transport, ABCA1, Cholesterol efflux, Orange tonsil, Atherosclerosis**

Introduction

Tangier disease is an autosomal recessive disease characterized by extremely low levels or absence of high-density lipoprotein (HDL)-cholesterol (HDL-C) and apolipoprotein A-I (apoA-I)[1]. The disease was named after Tangier Island in Chesapeake Bay, Virginia, USA, where the first case was discovered in 1960 and reported in 1961[2]. In 1991, generation of HDL particles through the direct action of helical HDL apoproteins on cells was first reported[3], and this was found to be deficient in cells derived from a patient with Tangier disease in 1995[4]. Eventually, ATP binding cassette transporter A1 (*ABCA1*) was identified as the gene responsible for this action and for Tangier disease in 1999[5-7]. Sequential progress in the investigation of HDL biosynthesis showed that HDL particles generated through ABCA1-dependent interaction of apolipoproteins with cells are the main source of plasma HDL. Patients with homozygous or compound heterozygous mutations in the *ABCA1* gene display the phenotype of Tangier disease and heterozygotes have decreases in HDL-cholesterol to various extents.

1. Disease Frequency

The number of cases of Tangier disease reported by 2020 was 35 in Japan and 109 in other countries (possibly including duplicates), indicating that it is a rather rare disease[8, 9]. However, the frequency of dysfunctional mutations in the *ABCA1* gene in the general population is not clear. A recent article using the Exome Aggregation Consortium database reported that 1 in 400 individuals in the general population is a heterozygote for a loss-of-function variant in the *ABCA1* gene on the basis of allele frequencies (frameshift, nonsense and splicing only; not missense), indicating a global prevalence of Tangier disease of at

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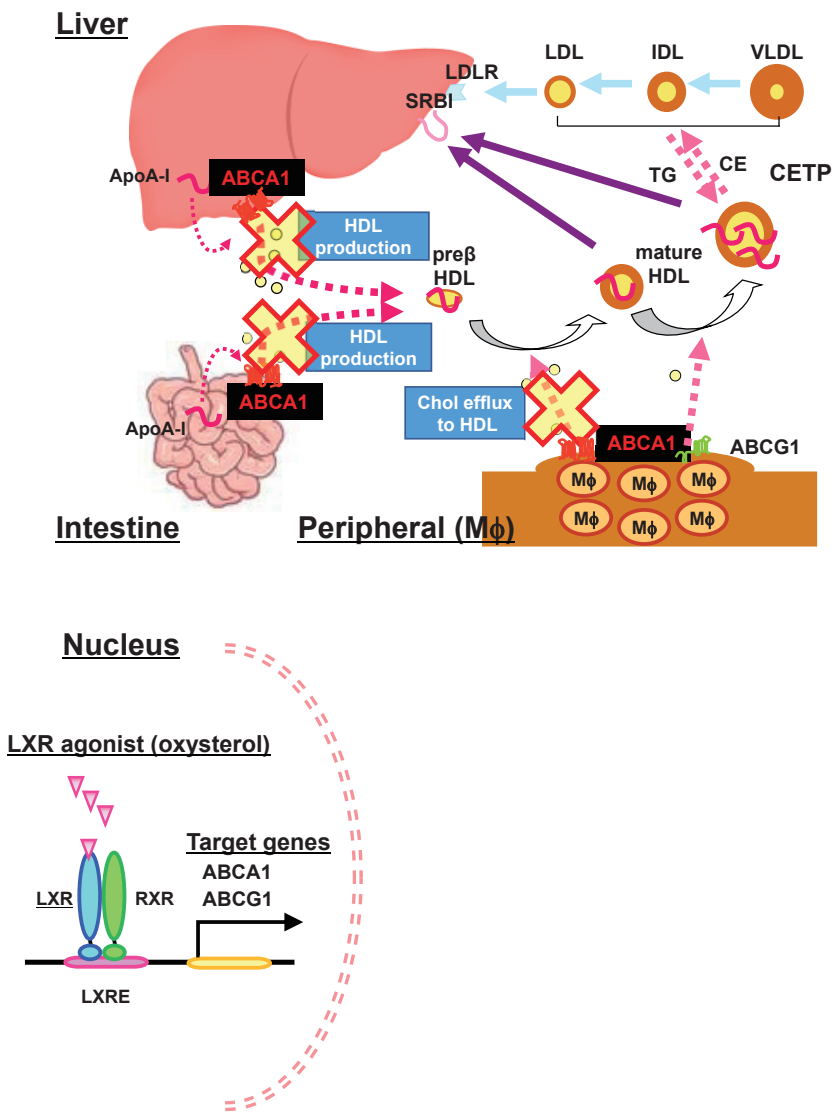

Fig. 1. Roles of ABCA1 in formation of HDL particles, reverse cholesterol transport and pathogenesis of Tangier disease

least 1 in 640,000[10]. It therefore seems that a substantial number of cases might go undiagnosed.

2. Genetic Backgrounds and Pathophysiology

ABCA1 is a member of the ATP-binding cassette transporter membrane protein family. It is an essential factor for generation of nascent HDL particles with extracellular helical apolipoproteins, through transport of cellular phospholipids and cholesterol (Fig. 1). This process is the major source of plasma HDL and one of the major mechanisms of cholesterol export from cells. It may be essential for final processing of cholesterol in mammalian somatic cells that are unable to catabolize cholesterol molecules. Peripheral cells sense intra-cellular cholesterol levels and increase ABCA1 expression for its excretion[11], while it undergoes bidirectional control in hepatocytes to prevent cholesterol recovered from peripheral cells flowing back into blood plasma[12, 13]. With functional deficiency in ABCA1, spherical HDL particles are not produced resulting in extremely low plasma HDL-C levels, which, in Tangier disease patients, are about one third of the normal level. The reason for this is unclear but it has been postulated that a substantial portion of cholesterol molecules in LDL in human plasma are those which have been acyl-esterified in HDL and transferred to VLDL/LDL and that a severe decrease in HDL cholesterol may lead to a decrease in LDL-C level.

In Tangier disease patients, cellular cholesterol export is impaired due to ABCA1 deficiency in peripheral cells, including macrophages and Schwann

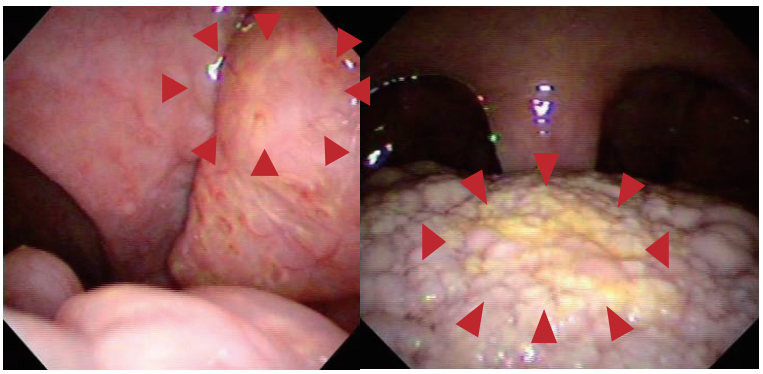

Fig. 2. Orange-colored tonsils observed in male patient with Tangier disease in his 50s
Arrow heads indicate palatine tonsil (left panel) and lingual tonsil (right panel). Reproduced from reference [8].

cells. Cholesterol therefore accumulates in these cells, causing orange-colored pharyngeal tonsillar swelling, corneal opacity, hepatosplenomegaly, lymphadenopathy and peripheral neuropathy. However, impairment of the initial stage of reverse cholesterol transport should be considered to be a risk for developing atherosclerotic diseases even though plasma LDL-C concentrations could be reduced.

ABCA1 appears to destabilize the raft structure, a cholesterol-rich domain of the plasma membrane[14, 15], its deficiency leads to an increase in "lipid" rafts and it has been suggested that this increases secretion of inflammatory cytokines[16]. It has also been reported that the insulinogenic index decreases due to cholesterol accumulation in pancreatic β-cells, which often accompanies glucose intolerance[17, 18]. These metabolic disorders are collectively involved in the development of premature coronary artery disease[8].

In early studies of Tangier disease, Schaefer et al. revealed the kinetics of plasma lipoprotein metabolism using externally labeled injected HDL and found that that apoA-I was catabolized at a much greater fractional rate in patients[19]. Their data, however, should be reinterpreted in terms of external HDL catabolism on the basis of ABCA1 deficiency. A recent study using human pluripotent stem cell-derived hepatocytes has demonstrated that ABCA1 deficiency increases angiopoietin-like protein 3 secretion, which is consistent with increased triglyceride in the plasma of Tangier patients[20].

3. Clinical Manifestations

3.1. Abnormal Plasma Lipoproteins

Plasma HDL-C is mostly low, at 5 mg/dL or less (mean of identified cases 3 ± 3 mg/dL), and the apoA-I concentration is 10 mg/dL or less[21]. Plasma LDL-C is also reduced, to around 37% of the average normal level. The appearance of remnant lipoprotein particles (intermediate products between VLDL and LDL) rich in triglycerides has been reported and this was found to result in abnormal small, dense LDL particles[21]. In subjects with heterozygous mutations of the *ABCA1* gene, plasma HDL-C and apoA-I levels are often reduced to about 50% of that in normal subjects, though the extent of HDL-C decline is not consistent.

3.2. Physical Findings

Impairment of HDL biogenesis results in reduced cholesterol export, which leads to lipid accumulation in cells. A typical finding of this disorder is orange-colored tonsils **(Fig. 2)**[8]. The tonsils of patients are lobulated and swollen and present a bright orange or yellow-grey surface. A history of recurrent tonsillitis or tonsillectomy is often noted. In addition, splenomegaly and associated thrombocytopenia and/or reticulocyte hyperplasia may be present **(Fig. 3)**. Hepatomegaly is also observed in about one-third of cases, but liver dysfunction is not usually present[22]. There is also cholesterol accumulation in other organs, such as lymph nodes, thymus, intestinal mucosa, and skin. Its accumulation in the cornea causes corneal opacity.

3.3. Peripheral Neuropathy

Various peripheral neuropathies, ranging from mild to severe, have been reported. Sensory, motor or mixed disorders appear transiently or persistently. Reduced deep perception and tendon reflexes are rare. Peripheral neuropathy appears as a recurrent asymmetric disorder of peripheral nerves including cranial nerves, as neuropathy with symmetry in the lower limbs, or syringomyelia-like peripheral neuropathy[23, 24].

3.4. Cardiovascular Diseases

It has been reported that 12 out of 35 patients

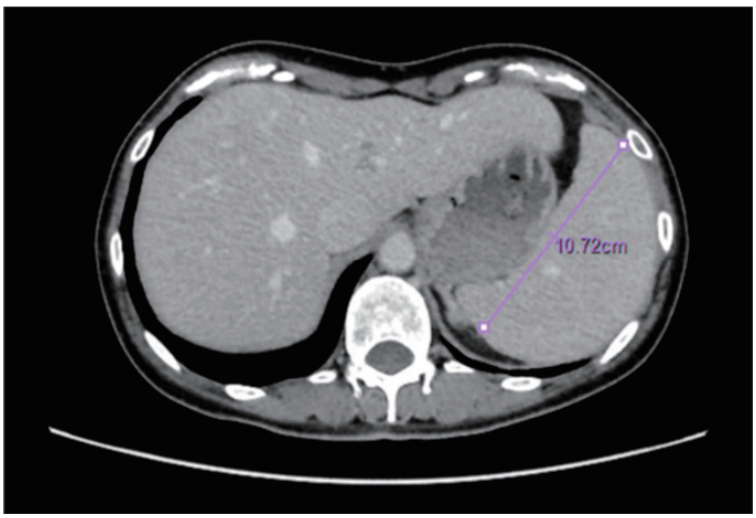

Fig. 3. Abdominal CT scan of splenomegaly in female patient with Tangier disease in her 40s
The photo was kindly provided by one of the co-authors, Prof. Yasushi Ishigaki (Iwate Medical University).

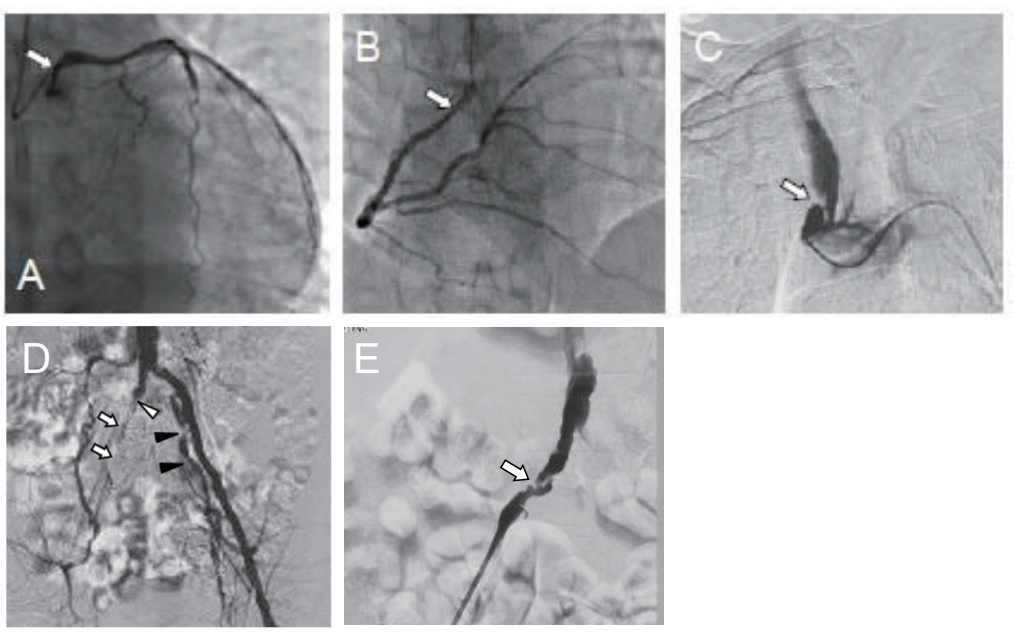

Fig. 4. Advanced systemic atherosclerotic lesions in male patient with Tangier disease in his 50s
Arrows indicate stenosis or occlusion of the artery.
A: left coronary artery, B: right coronary artery, C: brachiocephalic artery, D: left iliac artery, E: right external iliac artery [8].

(34.3%) in Japan and 34 out of 109 patients (31.2%) in other countries had some type of cardiovascular disease, suggesting accelerated atherogenicity in Tangier disease **(Fig. 4)**[8]. A previous case study using intravascular ultrasound (IVUS) revealed diffuse calcified coronary artery lesions[25], which might have been affected by HDL deficiency and glucose intolerance[17].

4. Diagnostic Criteria and Differential Diagnosis

Diagnostic criteria for Tangier disease are given in **Table 1** and the flow chart for differential diagnosis of hypo-HDL-cholesterolemia is shown in **Fig. 5**, based on discussions by the Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Diseases of Japan's Ministry of Health, Labour and Welfare.

Inherited diseases that lead to hypo-HDL-

Table 1. Diagnostic criteria

A. Required laboratory test results
1. Plasma (serum) HDL-cholesterol less than 25 mg/dL
2. Plasma (serum) apoA-I concentration less than 20 mg/dL
B. Clinical symptoms
1. Orange-colored tonsillar swelling
2. Hepatomegaly and/or splenomegaly
3. Corneal opacity
4. Peripheral neuropathy
5. Cardiovascular disease
C. Differential diagnosis
The following diseases should be excluded;
LCAT deficiency, apoA-I deficiency and secondary hypo-HDL-cholesterolemia*
D. Genetic testing**
Identification of pathogenic mutations in the *ABCA1* gene
< Diagnostic category >
Definite: Patients should satisfy both of required laboratory test results (A) AND at least one clinical symptom of (B) AND should be excluded for the diseases of differential diagnosis (C) AND should be positive for genetic testing (D).
Probable: Patients should satisfy both of required laboratory test results (A) AND at least two clinical symptoms of (B) AND should be excluded for the diseases of differential diagnosis (C).
Tangier disease can be diagnosed if patients are categorized "Definite" or "Probable".

*Secondary hypo-HDL-cholesterolemia: After surgery, liver disorders (especially liver cirrhosis and severe hepatitis, including convalescent stage), acute phase of systemic inflammatory disease, debilitating diseases such as cancer, history of oral probucol within the past 6 months, and combined probucol and fibrate (including fibrate administration after discontinuation of probucol).
**When differential diagnosis is difficult, genetic testing for *ABCA1* mutations should be performed. The diagnosis can be definite if pathogenic mutations in the *ABCA1* gene are identified.

cholesterolemia (Familial hypoalphalipoproteinemia) include classical lecithin: cholesterol acyltransferase (LCAT) deficiency, fish-eye disease, and familial apoA-I deficiency. Corneal opacity is commonly observed in these diseases, but tonsillar swelling and peripheral neuropathy are specific to Tangier disease, and xanthomas are found only in familial apoA-I deficiency[24, 26].

Care should be taken to exclude secondary hypo-HDL-cholesterolemia, such as in severe liver diseases, especially liver cirrhosis, and drug-induced hypo-HDL-cholesterolemia, most frequently due to combination of probucol and fibrates. It should be noted that probucol may continue to influence lipid profiles for several months after discontinuation, so HDL-C may be significantly reduced by switching from probucol to fibrates or permafibrate, a selective peroxisome proliferator-activated receptor alpha modulator (SPPARMα), in some cases.

5. Current Management of Tangier Disease

Based on the patients identified in Japan to date, there seem to be no distinct differences in clinical or genetic profiles with patients in other countries[8, 9]. No curative treatment, such as gene therapy for the *ABCA1* gene, has yet been established. Since extremely enhanced risk of atherosclerotic diseases is the major clinical problem, patients should be carefully monitored for presence of atherosclerotic lesions through regular testing including exercise electrocardiography, echocardiography and computed tomography coronary angiography[8]. The management of atherosclerotic risk factors, such as hypertension, smoking and diabetes mellitus, is crucial,[27]. Plasma LDL-C levels are generally low in patients with Tangier disease but if this is not the case, they should be reduced through administration of statins or other means. Impairment of the insulinogenic index should be estimated using a 75 g oral glucose tolerance test[17].

Conclusions and Future Perspectives

Gene therapy for *ABCA1* gene may have the greatest potential for Tangier disease. There is the possibility that restoration of ABCA1 expression in the liver would raise serum HDL-C levels but this might not be enough to recover cellular cholesterol efflux and suppress extra lipid accumulation in cells in atherogenic lesions such as macrophages, smooth muscle cells and endothelial cells. It may not be easy to develop a fundamental therapy for Tangier disease.

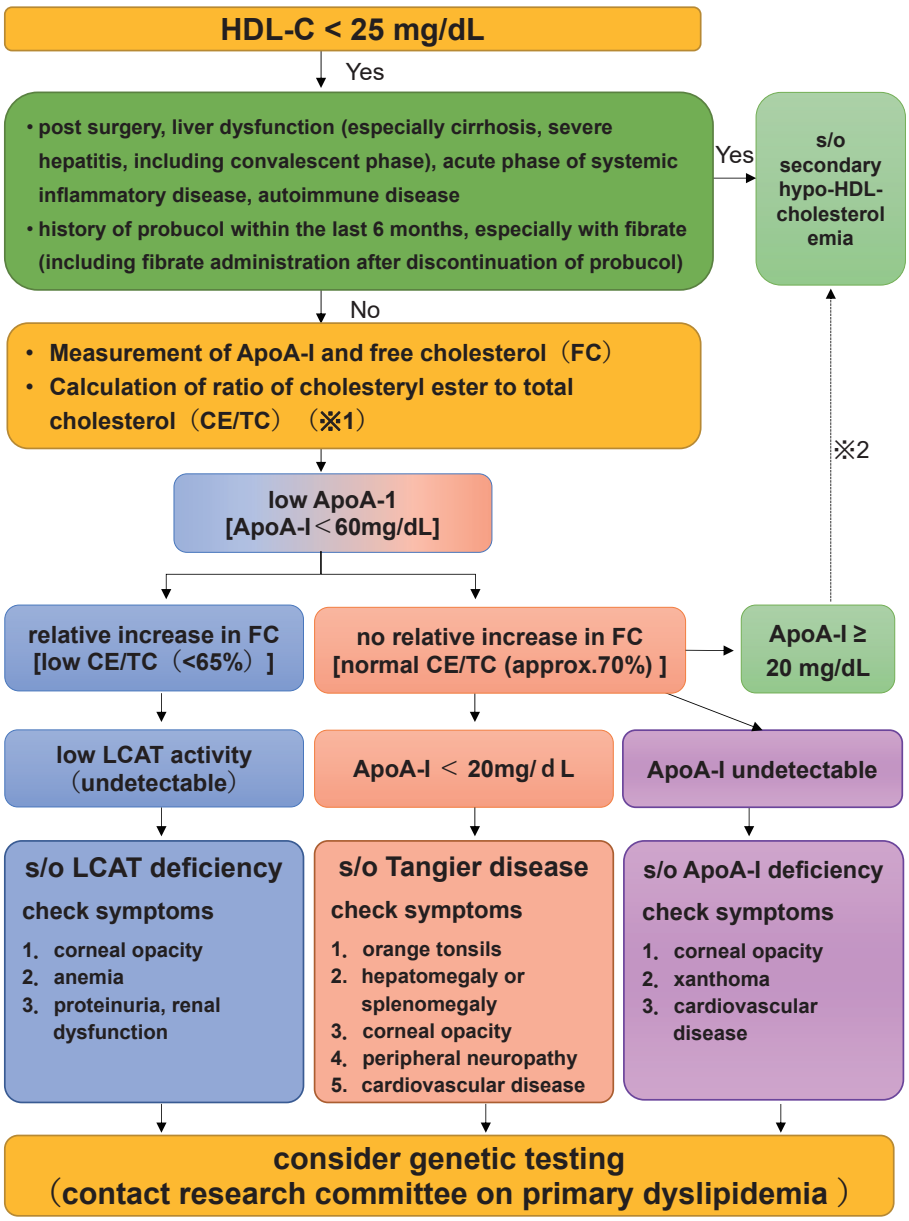

Fig. 5. Differential diagnosis flow chart for hypo-HDL-cholesterolemia

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Conflicts of Interest

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Current Diagnosis and Management of Primary Chylomicronemia

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Primary chylomicronemia (PCM) is a rare and intractable disease characterized by marked accumulation of chylomicrons in plasma. The levels of plasma triglycerides (TGs) typically range from 1,000 - 15,000 mg/dL or higher.

PCM is caused by defects in the lipoprotein lipase (LPL) pathway due to genetic mutations, autoantibodies, or unidentified causes. The monogenic type is typically inherited as an autosomal recessive trait with loss-of-function mutations in LPL pathway genes (*LPL*, *LMF1*, *GPIHBP1*, *APOC2*, and *APOA5*). Secondary/environmental factors (diabetes, alcohol intake, pregnancy, etc.) often exacerbate hypertriglyceridemia (HTG).

The signs, symptoms, and complications of chylomicronemia include eruptive xanthomas, lipemia retinalis, hepatosplenomegaly, and acute pancreatitis with onset as early as in infancy. Acute pancreatitis can be fatal and recurrent episodes of abdominal pain may lead to dietary fat intolerance and failure to thrive.

The main goal of treatment is to prevent acute pancreatitis by reducing plasma TG levels to at least less than 500-1,000 mg/dL. However, current TG-lowering medications are generally ineffective for PCM. The only other treatment options are modulation of secondary/environmental factors. Most patients need strict dietary fat restriction, which is often difficult to maintain and likely affects their quality of life.

Timely diagnosis is critical for the best prognosis with currently available management, but PCM is often misdiagnosed and undertreated. The aim of this review is firstly to summarize the pathogenesis, signs, symptoms, diagnosis, and management of PCM, and secondly to propose simple diagnostic criteria that can be readily translated into general clinical practice to improve the diagnostic rate of PCM. In fact, these criteria are currently used to define eligibility to receive social support from the Japanese government for PCM as a rare and intractable disease.

Nevertheless, further research to unravel the molecular pathogenesis and develop effective therapeutic modalities is warranted. Nationwide registry research on PCM is currently ongoing in Japan with the aim of better understanding the disease burden as well as the unmet needs of this life-threatening disease with poor therapeutic options.

Key words: **Chylomicronemia, Triglyceride, Pancreatitis, Diagnostic criteria, Treatment guide**

1. Definition of Chylomicronemia

Chylomicrons (CMs) are intestine-derived lipoproteins that transport dietary fat to peripheral tissues[1]. CMs are usually quickly cleared from plasma after an overnight fast. The hallmark of chylomicronemia is persistent elevation of CMs in the fasting state (>12h). Plasma triglyceride (TG) levels

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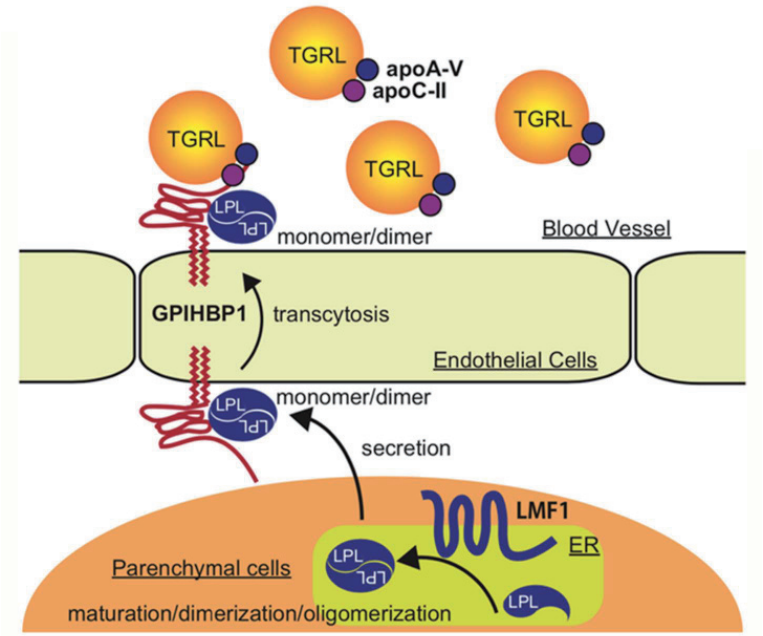

Fig. 1. Molecular basis of primary chylomicronemia

Lipoprotein lipase (LPL) hydrolyzes triglycerides (TGs) in TG-rich lipoproteins (TGRLs), such as very low-density lipoproteins (VLDLs) and chylomicrons (CMs) to liberate free fatty acids (FFAs), which are utilized by peripheral tissues (e.g., muscle, heart, and adipose tissues). Activity of LPL is regulated by a quaternary structure (monomer/dimer/oligomer) as well as by multiple LPL-pathway proteins[210-212]. LMF1 is required for the synthesis of LPL in parenchymal cells of these peripheral tissues. GPIHBP1 is a transmembrane protein that tethers LPL on the endothelial cell surface to provide a platform for TG hydrolysis. GPIHBP1 captures LPL in the subendothelial (interstitial) space of peripheral tissues, transports LPL from the subendothelial surface to the luminal surface of endothelial cells by transcytosis, and anchors LPL on the luminal surface facing the bloodstream to facilitate lipolysis. For the hydrolytic activity of LPL, two apolipoproteins, apoC-II and apoA-V, are required. ApoC-II is necessary for the enzymatic activity of LPL. ApoA-V primarily enhances the interaction between TGRL and LPL by forming TGRL-apoA-V-GPIHBP1-LPL complex via its dual binding affinity to TGRL and GPIHBP1. Defects in LPL pathway proteins (LPL, LMF1, GPIHBP1, apoC-II, apoA-V) due to genetic mutations or autoantibodies cause primary chylomicronemia (PCM). LPL activity can be measured after releasing LPL from the luminal surface into the circulation by i.v. injection with heparin.
Abbreviations: apoA-V, apolipoprotein A-V; apoC-II, apolipoprotein C-II; GPIHBP-1, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; LMF1, lipase maturation factor 1.

in chylomicronemia typically range from 1,000 to 15,000 mg/dL or higher[2]. As CMs start to accumulate in plasma when TG levels increase to more than 500 - 1,000 mg/dL[1], it is practical to screen and suspect chylomicronemia if plasma TGs >1,000 mg/dL[2, 3].

2. Metabolism of Chylomicrons

CMs are produced by the intestine after a meal and secreted into the circulation[1]. Their synthesis requires apoB-48 protein, which is transcribed from the edited mRNA of *APOB*, and microsomal triglyceride transfer protein (MTTP), which incorporates dietary TGs into CMs. More than 90% of lipids in CMs are TGs (derived from dietary fatty acids and TGs), which are hydrolyzed by lipoprotein lipase (LPL) on the endothelial cell surface of peripheral tissues (muscle, heart, adipose tissue, etc.) to liberate free fatty acids (FFAs). FFAs are used as an energy source in peripheral tissues, or stored as TGs in adipose tissues, or re-esterified and secreted as very low-density lipoprotein (VLDL)-TG by the liver. CMs are converted to CM remnants after TG hydrolysis by LPL and then cleared from plasma through endocytosis mainly by the liver.

3. Molecular Basis of Chylomicronemia

Plasma levels of CMs are affected by primary factors as well as secondary factors[2, 4, 5]. Primary factors consist of defects in the proteins that metabolize CMs, such as LPL and its related proteins (apolipoprotein(apo)C-II, apoA-V, glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1 (GPIHBP1), lipase maturation factor 1 (LMF1)) **(Fig. 1)**. Secondary factors include conditions that impair CM metabolism, such as poor control of diabetes, excessive alcohol intake, and pregnancy. In primary chylomicronemia (PCM), chylomicronemia usually persists even after

management of secondary factors. PCM is caused by defects in LPL pathway genes (*LPL*, *APOC2*, *APOA5*, *GPIHBP1*, *LMF1*) due to genetic mutations or presence of autoantibodies against LPL pathway proteins (GPIHBP1, LPL, and apoC-II)[6-9].

4. Complications of Chylomicronemia

Chylomicronemia is a risk factor for acute pancreatitis[10]. Although the underlying mechanisms are not fully understood, the widely accepted hypothesis is that an excess of FFAs derived from lipolysis of chylomicron-TG by pancreatic lipase damages pancreatic acinar cells or endothelial cells of pancreatic capillaries, leading to activation of inflammatory processes[11]. In addition, high levels of plasma CM may increase the viscosity of pancreatic microcirculation and impair pancreatic blood flow, further exacerbating inflammation. Genetic predisposition may also contribute to the pathogenesis[12].

Based on this hypothesis, it is generally believed that chylomicronemia per se induces pancreatitis and, therefore, reducing plasma CM levels should lower the risk of pancreatitis[10]. The widely accepted treatment goal is to reduce plasma TG levels to at least less than 1,000 mg/dL[2, 4, 5, 12-14].

5. Primary Factors of Chylomicronemia

Five genes (*LPL*, *LMF1*, *GPIHBP1*, *APOC2*, *APOA5*) have been identified as the causative genes of monogenic chylomicronemia **(Fig. 1)**[4, 5]. All of them are required for the normal function of LPL. Homozygous, compound heterozygous, or double heterozygous loss-of-function mutations of these LPL pathway genes usually cause monogenic chylomicronemia with an autosomal recessive mode of inheritance[15]. Heterozygous mutations or pathological variants in HTG-susceptible genes, including those for hepatic lipase (HL) and apolipoprotein E, may also predispose to chylomicronemia[3, 5, 16-18].

Loss-of-function mutations in LPL-pathway genes have been identified in only less than 30-40% of patients suspected of monogenic chylomicronemia[19, 20]. In some cases, autoantibodies against LPL pathway proteins can cause PCM. Additional genetic factors or unknown causes may also underlie PCM.

•***LPL*** (LPL deficiency, OMIM: 238600): *LPL* is the most common causative gene of monogenic chylomicronemia. More than 220 pathogenic variants in *LPL* have been described (missense, nonsense, splicing variants, insertion/deletion of nucleotide(s), deletion/duplication/insertion/rearrangement of exon(s))[2, 4, 15, 20-22]. A list of mutations in *LPL* has been comprehensively summarized in exon-intron diagrams by Rabacchi C *et al.* and Rodrigues R *et al.*[20, 22]. LPL activity is usually tested in post-heparin plasma taken 10-15 min after iv. heparin injection (10-60 IU/kg body weight)[4, 23].

•***LMF1*** (LMF1 deficiency, OMIM: 246650): *LMF1* encodes LMF1, a transmembrane chaperone protein of parenchymal cells (muscle, adipose tissues, etc.). LMF1 is localized to the endoplasmic reticulum and is required for proper synthesis and secretion of LPL and HL. In addition to nonsense mutations that were originally reported, several other mutations, including missense loss-of-function mutations, have been identified in *LMF1*[24-29].

•***GPIHBP1*** (GPIHBP1 deficiency, OMIM: 615947): *GPIHBP1* encodes GPIHBP1, a transmembrane protein that tethers LPL on the endothelial cell surface to provide a platform for TG hydrolysis[30, 31]. GPIHBP1 captures LPL in the subendothelial (interstitial) space of peripheral tissues (skeletal muscles, heart, adipose tissues, etc.), transports LPL from the subendothelial surface to the luminal surface of endothelial cells by transcytosis, and anchors LPL on the luminal surface facing the bloodstream to facilitate lipolysis. So far, at least 23 pathogenic mutations in *GPIHBP1* have been reported in severe HTG patients, including those causing total GPIHBP1 deficiency[21, 32-36]. Mutations in *GPIHBP1* are comprehensively summarized in the exon-intron diagram by Rabacchi *et al.*[35]. GPIHBP1 deficiency may be differentiated from LPL deficiency in that LPL activity or protein in post-heparin plasma is not totally lacking in GPIHBP1 deficiency[37].

•***APOC2*** (apoC-II deficiency, OMIM: 207750): *APOC2* encodes apoC-II, a co-factor required for LPL activity. *APOC2* is the second most common causative gene of monogenic chylomicronemia. At least 24 mutations have been reported worldwide[2, 4, 5, 38-41], and are comprehensively summarized in the exon-intron diagram by Wolska *et al.*[41]. In some cases, plasma levels of apoC-II have been severely decreased but are detected with apparently normal electrophoretic patterns (so-called hypoapoC-II)[42-45]. In apoC-II deficiency, symptoms often develop at an older age (13-60 years) than in LPL deficiency[1, 4]. As apoC-II deficient patients tend to be subjected to strict fat restriction at an older age, they may have poorer dietary adherence and more frequent episodes of acute pancreatitis in adulthood than LPL deficient patients, often accompanied by high VLDL levels[2].

•***APOA5*** (apoA-V deficiency, OMIM: 144650): *APOA5* encodes apoA-V, a co-factor of LPL that enhances interaction between LPL and TG-rich lipoproteins (TGRLs)[46, 47]. ApoA-V has dual binding

affinity for both TGRL and GPIHBP1, thereby forming the TGRL-apoA-V-GPIHBP1-LPL complex to facilitate lipolysis[31, 48, 49]. So far, at least 21 mutations in *APOA5* have been reported, which are comprehensively summarized in exon-intron diagrams by Albers *et al.*[50-53]. In most cases, severe HTG develops later in life due to the combinatorial effects of primary (genetic) and secondary factors (aging, diabetes, pregnancy, HIV therapy, etc.)[53]. The underlying molecular mechanisms of apoA-V deficient HTG in terms of gene-environmental interactions has only begun to be elucidated[54, 55].

•**Autoantibodies against LPL pathway proteins**: Autoimmune chylomicronemia due to autoantibodies against LPL pathway proteins (GPIHBP1, LPL, apoC-II) has been reported[6-9]. Autoimmune chylomicronemia may be complicated by other autoimmune diseases and be ameliorated by steroid or immune-suppressive therapy.

6. Secondary Factors of Chylomicronemia

The following factors have been reported to induce chylomicronemia[3-5, 13, 35, 56-61]. Among them, excess alcohol consumption and diabetes mellitus are the two most common factors associated with severe HTG[18, 62, 63].

Pregnancy is another important factor that can induce chylomicronemia. Hormonal changes during pregnancy result in hyperlipidemia even in healthy subjects, as a physiological response to ensure nutrient supply to the fetus[64-66]. Plasma TG levels progressively increase in healthy subjects by 2- to 4-fold[67], and markedly increase in subjects with PCM[68-74]. Pregnancy increases TGRL (VLDL) production and decreases TGRL clearance[75-78].

•**Lifestyle-related factors**: Dietary factors such as excessive alcohol intake, high-fat diet, high-carbohydrate diet rich in fructose and other simple sugars. Less exercise and excessive intake of total calories, particularly in subjects who are overweight, have metabolic syndrome, or diabetes mellitus.

•**Pathophysiological conditions**: Pregnancy, obesity, metabolic syndrome, anorexia nervosa, glucose intolerance, diabetes mellitus with insulin resistance or insulin deficiency, endocrine diseases such as hypothyroidism, acromegaly, Cushing's syndrome, Nelson's syndrome, glycogen storage diseases, amyloidosis, renal disease (nephrotic syndrome, proteinuria, uremia, glomerulonephritis, etc.), liver disease, autoimmune disorders, lipodystrophies, Weber-Christian disease, multiple myeloma, paraproteinemia, and lymphoproliferative disorders, etc.

•**Medications**: Glucocorticoids, oral estrogens (contraceptives, postmenopausal replacement therapies), clomiphene, tamoxifen, exogenous testosterone; retinoids such as isotretinoin, bexarotene; immunosuppressants and anticancer drugs such as sirolimus, cyclosporine A, tacrolimus, capecitabine, cyclophosphamide, asparaginase; antihypertensives such as thiazides, loop diuretics, non-selective β -blockers; bile acid-sequestrants; antiviral drugs such as entecavir, ritonavir and other antiretroviral protease inhibitors; second-generation antipsychotics (atypical antipsychotics), such as dozapine, clozapine, olanzapine, risperidone, quetiapine; antidepressants such as mirtazapine, venlafaxine; selective serotonin reuptake inhibitors (sertraline, etc.); anticonvulsants, such as valproate; anesthetic drugs, such as propofol.

7. Classification of Chylomicronemia

Chylomicronemia was formerly classified as type 1 and 5 hyperlipoproteinemia (HLP) in the Fredrickson classification (WHO classification)[5, 79], where increased plasma lipoproteins are CM for type 1 and CM+VLDL for type 5 HLP. However, differentiation of type 1 and type 5 HLP is often difficult because of considerable overlaps in phenotypes and genetic backgrounds[3, 5, 17].

Differentiation of monogenic from polygenic chylomicronemia is also difficult[80]. Even when monogenic chylomicronemia is suspected, causative mutations have been identified in less than 30-40%[19, 20].

For practical reasons, we prefer to use the term PCM, which is defined as a condition with persistent elevation of TG >1,000 mg/dL even after management of secondary factors. The term familial chylomicronemia syndrome (FCS) is not used here, as monogenic chylomicronemia is typically autosomal recessive, and most cases are sporadic, without a family history. The term "familial" may confuse both patients and doctors, and may lead to underdiagnosis[3, 81].

8. Prevalence of Chylomicronemia

The prevalence of severe HTG (TG >10 mmol/L (885 mg/dL)) is estimated at ~1 in 600 in North America[5]. In a population of 440,240 subjects in the US, severe HTG (886-2,000 mg/dL) and very severe HTG (>2,000 mg/dL) were observed in 0.15% and 0.014%, respectively[36].

The monogenic type of chylomicronemia is very rare and its frequency is estimated at 1 to 2 per million in the general population[1, 4, 5]. The most common causative gene is *LPL*, followed by other LPL pathway

genes (*APOC2*, *GPIHBP1*, *APOA5*, and *LMF1*)[5, 15, 53].

Severe HTG is more often due to polygenic causes[3, 82]. Dron *et al.* reported that the etiology of severe HTG (TG >10 mmol/L (885 mg/dL)) is monogenic in 1.1%, polygenic in 46%, and genetically unidentified in the rest of cases[83]. Another study identified monogenic causes in 0.96% of patients with very severe HTG (TG >20 mmol/L (1770 mg/dL)) recorded at least once during regular medical care[22].

9. Prevalence of HTG-Induced Acute Pancreatitis

Regardless of the underlying etiology of HTG, the risk of acute pancreatitis increases as TG levels increase, particularly when they exceed 1,000 - 2,000 mg/dL[84].

HTG is the third leading cause (5-38%) of acute pancreatitis after alcohol and gallstones[1, 12, 85-87]. HTG is the leading cause (25~50%) of acute pancreatitis during pregnancy[12, 74, 88], which is most often seen in the third trimester (19%, 26%, 53% in the 1st, 2nd, and 3rd trimester, and 2% in postpartum period)[89]. The frequency of HTG-induced acute pancreatitis in pregnancy is estimated as 1 in 1000-12,000 pregnancies[14, 73, 74].

Risk of acute pancreatitis increases by ~4% for every 100 mg/dL increase in plasma TG[56, 84, 87, 90, 91]. According to the 2010 Endocrine Society guidelines, HTG can be classified into mild HTG (150-199 mg/dL), moderate HTG (200-999 mg/dL), severe HTG (sHTG, 1000-1999 mg/dL), or very severe HTG (vsHTG, >2000 mg/dL). The prevalence of pancreatitis in sHTG and vsHTG is about 10% and 20%, respectively[5, 13, 14, 87, 92].

Clinically, it remains difficult to predict if a HTG patient will develop acute pancreatitis or not. Some patients do not develop acute pancreatitis even at TG levels higher than 30,000 mg/dL[1, 2]. Conversely, patients can develop acute pancreatitis at TG levels of 5-10 mmol/L (442-885 mg/dL)[93]. The underlying etiology of monogenic chylomicronemia seems to confer a potent risk of acute pancreatitis[53, 94-96]. Compared to normolipidemic individuals, the risk of acute pancreatitis increased by 16-fold, 56-fold, and 361-fold in HTG (5-9 mmol/L (442-796 mg/dL)) without LPL deficiency, HTG (>9 mmol/L (796 mg/dL)) without LPL deficiency, and HTG (>9 mmol/L (796 mg/dL)) with LPL deficiency (genetically-confirmed), respectively[94]. Greater cumulative exposure of HTG to the pancreas due to genetic causes may impose higher pancreatitis risk[53, 94-97](See **sections 12 and 16(B)** for other suggested risk factors of acute pancreatitis among HTG subjects).

10. Signs, Symptoms, and Complications of Chylomicronemia

Depending on the severity of the mutation, signs, symptoms, and complications of chylomicronemia may manifest as early as in infancy, in childhood, or later in life[4, 95].

•**Abdominal pain, fat intolerance, failure to thrive**: Abdominal pain affects ~60% of monogenic chylomicronemia patients and can be mild to incapacitating[4, 95, 96]. Recurrent episodes of abdominal pain may lead to dietary fat intolerance and failure to thrive. Body weight may be lower because of restricted food intake.

•**Pancreatitis**: Acute pancreatitis can be severe, recurrent, and life-threatening[1, 4, 95]. Acute pancreatitis may lead to chronic pancreatitis and diabetes. Irrespective of its etiology, severe HTG should be carefully monitored for the possible complications of pancreatitis. Compared to polygenic chylomicronemia, monogenic chylomicronemia is associated with a higher risk of acute pancreatitis and tends to manifest severe phenotypes[86, 94, 95]. According to a survey of lipidologists, ~67% of monogenic patients were hospitalized for acute pancreatitis vs. ~14% of polygenic patients[95, 96]. It should be noted that high levels of plasma TG may interfere with assays of plasma pancreatic enzymes (lipase, amylase), resulting in falsely low levels[2, 98-100]. HTG-induced acute pancreatitis should not be misdiagnosed due to apparently low serum levels of pancreatic enzymes.

•**Lipemic plasma**: Lipemic plasma (milky-looking plasma) is characterized by a creamy CM layer floating above the bottom layer, after leaving serum standing overnight in a refrigerator (the "refrigerator" test)[1]. In type 5 HLP, the bottom layer contains VLDLs and has a lactescent appearance. In type 1 HLP, the bottom layer is clear without apparent VLDL accumulation. Type 1 HLP is more frequently observed than type 5 in monogenic chylomicronemia[19]. (See reference by Yuan G *et al.* for a photograph of lipemic plasma[56].)

•**Eruptive xanthomas**: Eruptive xanthomas affect 10-50% of the monogenic type[95, 96]. They appear when plasma TG levels increase to more than 2,000 mg/dL as yellow papules on the skin of the trunk, buttocks, and extremities (extensor surfaces of the arms and knees) as a result of TG uptake by macrophages (see references by Nayak KR *et al.* and Yuan G *et al.* for photographs)[2, 4, 56, 101]. Along with reduction in plasma TG levels, they gradually

Table 1. Diagnostic criteria for primary chylomicronemia

A. Entry Criterion:
A1 and A2 with exclusion of differential diagnosis in E
A1) Plasma TG level ≧1,000 mg/dL (after fasting for 12 hours or longer)
A2) Presence of chylomicrons in serum (from appearance of supernatant cream layer after allowing serum to stand for 24 hours or longer at 4℃, ultracentrifugation, or electrophoresis (agarose gel, polyacrylamide gel, or HPLC))
B. Clinical manifestations (major (B1-B4) and minor (B5, B6))
B1) Recurrent episodes of abdominal pain and/or acute pancreatitis
B2) Eruptive xanthomas
B3) Lipemia retinalis
B4) Hepatomegaly and/or splenomegaly
B5) Dyspnea
B6) Neurological symptoms (cognitive impairment, memory impairment, depression, etc.)
C. Laboratory findings
C1) LPL activity and/or protein in post heparin plasma, adipose tissue, or macrophages is absent or markedly decreased (＜10% of normal subjects)
C2) Plasma apoC-II is absent or markedly decreased (＜10% of normal subjects)
C3) Plasma apoA-V is absent or markedly decreased (＜10% of normal subjects)
C4) Autoantibodies against LPL, heparin, apoC-II, or GPIHBP1.
D. Genetic test
Identification of causative mutation(s) in *LPL*, *APOC2*, *GPIHBP1*, *LMF1*, or *APOA5*
E. Differential diagnosis
Type 3 hyperlipidemia, familial combined hyperlipidemia (FCHL), and secondary hyperlipidemia due to following: excess alcohol intake, nephrotic syndrome, anorexia nervosa, pregnancy, diabetes mellitus, lipodystrophies, Weber-Christian disease, hypothyroidism, acromegaly, Cushing's syndrome, Nelson's syndrome, multiple myeloma, systemic lupus erythematosis, malignant lymphoma, sarcoidosis, etc.; medications such as estrogens, steroids, diuretics, β-blockers, antipsychotics including selective serotonin reuptake inhibitors (SSRIs), retinoids such as isotretinoin, antiretroviral protease inhibitors, immunosuppressants, etc.
<Diagnosis>
Definite: Entry criterion (A) associated with at least one item from C or D
Probable: Entry criterion (A) associated with at least one item from B1-B4
Possible: Entry criterion (A) with or without item(s) from B5-B6

disappear over several weeks to a few months[2].

•Lipemia retinalis: Lipemia retinalis affects ~40% of the monogenic type[95, 96] and is characterized by retinal blood vessels with a milky appearance (a pale pink color) on fundoscopy (see references by Kumar J *et al.* and Yuan G *et al.* for photographs)[56, 102]. Vision is not impaired. It is usually visible when plasma TG levels increase to more than 4,000 mg/dL[2].

•Hepatomegaly and splenomegaly: Hepatomegaly and splenomegaly affect 10-50% of the monogenic type[95, 96] as a result of TG uptake by macrophages and other cell types in these tissues[1, 4]. Both conditions are reversible and rapidly improve within a week, along with reduction in plasma TG levels[2].

•Other symptoms (fatigue, dyspnea, and neurological symptoms): Other clinical symptoms include fatigue, dyspnea, and neurological symptoms[1] such as memory impairment (transient memory loss), cognitive impairment, mild dementia, cloudy thought, brain fog, neurosis, irritability, anxiety, and depression[4, 95, 103-107]. Neurological symptoms affect ~8% of the monogenic type[95]. Although little is known about the underlying mechanisms of these symptoms, large surveillance studies among chylomicronemia patients have shown that they dominantly and adversely affect patients' quality of life and increase the burden of the disease[104-107].

11. Diagnosis of Chylomicronemia

Undertreatment and underdiagnosis of chylomicronemia are one of the major risks for acute pancreatitis[84, 87]. In order to achieve early diagnosis and treatment for chylomicronemia, simple diagnostic criteria that can be readily translated into general practice are required.

Based on TG levels that lead to suspicion of chylomicronemia (TG ＞1,000 mg/dL), clinical manifestations and the available data on diagnostic tests, here we propose diagnostic criteria for PCM

(Table 1).

It should be noted that PCM is genetically confirmed in less than 30-40% of patients suspected of monogenic chylomicronemia[19, 20]. Therefore, we have set three categories (definite, probable, and possible) so that PCM patients will not be missed even without a genetic diagnosis.

To achieve timely diagnosis and improve the diagnostic rate of PCM, screening of plasma TG levels in the following settings will be helpful. Clinicians across multiple disciplines, such as primary care physicians, gastroenterologists, gynecologists, and other doctors who have occasionally encountered severe HTG patients, should consult lipidologists concerning further diagnostic tests for chylomicronemia.

•**Health checkup or opportunistic blood test**: All patients who have TG levels of more than 1,000 mg/dL in universal lipid screening[108] or a routine clinic visit should be suspected of chylomicronemia[96, 109].

•**Acute abdomen (including pancreatitis)**: Those who have acute abdomen or are suspected of pancreatitis should have their plasma TG levels measured[96]. Plasma TG should be measured as early as possible after the onset of abdominal pain, as TG levels rapidly decrease within 24-48 hours of onset[110].

•**Pregnancy**: Many cases of monogenic chylomicronemia have been discovered in the third trimester of pregnancy[111-118]. HTG-induced acute pancreatitis in pregnancy can be lethal to both mother and fetus[119]. Gestational HTG may also increase the risk of hyperviscosity syndrome[120], pre-eclampsia[121], fetal macrosomia, and fetal pancreatitis-related complications (in-utero fetal death, preterm labor, and prematurity)[66]. Pregnant women who are suspected of pancreatitis should be tested for plasma TG. Pregnant women at high-risk for HTG-induced acute pancreatitis may benefit from plasma TG screening and monitoring on a weekly basis[122]. Such patients include: those with HTG or pancreatitis prior to or during pregnancy; high predisposition for HTG-induced acute pancreatitis due to diabetes mellitus, obesity, hypertension, hypothyroidism, renal disease, liver disease, family history of HTG, alcohol consumption, and medications that cause HTG; HTG with abdominal pain or other symptoms typical to chylomicronemia[84, 87, 122](See **sections 12 and 16(B)** for suggested risk factors of acute pancreatitis among HTG patients).

•**Family members of chylomicronemia patients**: Evaluation of plasma TG levels in family members is beneficial for early diagnosis and management of possible complications[96].

12. Features for Suspecting Monogenic Chylomicronemia

Clinical features that lead to suspicion of monogenic chylomicronemia have been suggested by previous studies and in expert opinions, but further validation in various cohorts is required[2-5, 15, 18, 53, 80, 96, 109, 123, 124]. These features may be useful not only for indicating the likelihood of monogenic chylomicronemia but also for predicting a higher risk of pancreatitis[53, 86, 94-96]:

- Intractable, severe HTG (TG >10 mmol/L or 1,000 mg/dL)
- Fasting severe HTG on multiple occasions
- Very severe HTG
- No history of normal to mild plasma TG levels (<200 mg/dL)
- Severe HTG with no secondary factors (except for pregnancy and oral estrogens)
- Severe HTG with pregnancy
- No response (TG decrease <20%) to hypolipidemic agents
- Severe HTG with type 1 rather than type 5 HLP
- History of recurrent abdominal pain or acute pancreatitis
- Younger age at onset
- Lower body mass index (BMI)
- Eruptive xanthomas
- Lipemia retinalis
- Hepatosplenomegaly
- Consanguinity

On the other hand, the polygenic type of chylomicronemia is more frequently associated with secondary/environmental factors, such as high-alcohol intake, diabetes mellitus, hypertension, and obesity[2, 18, 96].

13. Treatment of Chylomicronemia

The treatment goal of chylomicronemia is to lower plasma TG levels enough to reduce the risk of pancreatitis. Data from large healthcare databases suggest that sustained HTG (>500 mg/dL) increases the risk of pancreatitis (hazard ratio 1.79 [CI 95%: 1.10-1.28])[125] and lowering TG from >500 mg/dL to less than 200 mg/dL can reduce the incidence of acute pancreatitis from 1.1 to 0.4 per 100 person-year (adjusted OR 0.45 [CI 95%: 0.34-0.60])[126]. Due to the rareness of the disease, there have been no randomized control trials (RCTs) to determine treatment TG targets for prevention of pancreatitis. Mainly based on clinical experience, the opinion of

experts is to recommend maintaining plasma TG levels below 500-1,000 mg/dL to prevent pancreatitis[2, 4, 5, 12-14].

A) Control of Secondary Factors

Comorbid conditions that aggravate chylomicronemia should be thoroughly evaluated in order to rule them out. If any are present, they should be managed adequately. Bodyweight reduction, reduced calorie intake, and increased energy expenditure through regular physical exercise may help reduce plasma TG levels, particularly in overweight subjects. Regular physical exercise may also help in the non-obese[93, 127]. Bodyweight should be carefully controlled as rebound weight gain might elicit pancreatitis[13].

B) Dietary Therapy

Strict dietary control is currently the primary treatment modality for chylomicronemia, although it is often insufficient and difficult to maintain in the long term[128, 129]. Children and adolescents should be carefully monitored to ensure proper growth and development. Adjustment of social life might be a challenge throughout life[104-107].

•**Fat restriction**: The mainstay of dietary treatment is a low-fat diet. Restriction of total dietary fat to <15-20 g per day (<10-15 % of total energy intake) is usually required to reduce plasma CMs and prevent pancreatitis[128, 129]. Under fat restriction, adequate intake of essential fatty acids (EFA; 2-4% of daily calories) and fat-soluble vitamins (A, D, E, and K) should be ensured to avoid deficiency. Signs and symptoms typical of EFA deficiency include: inadequate growth in pediatric patients, dry or dull hair, dry or scaly skin, skin lesions, particularly raised bumps on the skin, soft and brittle nails, and impaired wound healing[129]. Food sources of EFAs include soybeans, tofu, flaxseeds, walnuts, and chia seeds for alpha-linolenic acid (ALA) and whole grains for linoleic acid (LA).

•**Medium-chain triglycerides (MCTs)**: In a very-low-fat diet, MCTs containing fatty acids of ≦ 10 carbon atoms in length may be used to provide sufficient calories in meals or infant formula[4, 36, 128, 129]. MCTs are absorbed directly into the circulation via the CM-independent pathway. MCTs may help reduce plasma TG levels[130]. In order to avoid possible adverse effects (diarrhea, abdominal pain, etc.), MCTs should be introduced slowly. The safety of long-term MCTs is not established and patients should be carefully monitored for possible complications such as hepatotoxicity. MCTs should not be confused with coconut oil, which contains lauric acid (C12) and other long-chain fatty acids[129].

•**Carbohydrate restriction**: Restriction of carbohydrates, particularly fructose and other simple and refined carbohydrates, is advisable for patients with increased VLDL levels such as those with diabetes mellitus, metabolic syndrome, and obesity. As both CMs and VLDLs are substrates for LPL, reduced production of VLDLs due to carbohydrate restriction enhances the catabolism of CMs by LPL[131]. In cases where carbohydrate intake needs to be adequate, such as in pregnancy-associated HTG, carbohydrate iv may be a better therapeutic choice, as oral carbohydrate intake may produce a greater rise in plasma TG than carbohydrate iv[122, 132].

•**Alcohol restriction**: Alcohol intake should be restricted[4, 128, 129].

C) Lipid-Lowering Medications

Current lipid-lowering medications (fibrates, n-3 polyunsaturated fatty acids (PUFAs), niacin, etc.) generally have little to no TG-lowering effects in patients with PCM, as they lower plasma TGs mainly by enhancing the LPL pathway and reducing VLDL levels. Treatment with n-3 PUFA or fish oil may be useful for lowering TG and preventing pancreatitis as suggested in patients with *APOA5* mutations[21]. However, the effect of n-3 PUFAs needs to be monitored carefully, as their effectiveness has only been suggested by small studies without controls[3, 5]. Fish oil supplements may increase the production of chylomicrons and are contraindicated according to an expert opinion[4]. In patients with autoantibodies against LPL pathway proteins (GPIHBP1, LPL, apoC-II), immune-suppressive agents may ameliorate HTG as well as the comorbid autoimmune diseases[7].

14. Treatment of HTG-Induced Acute Pancreatitis

The clinical course of HTG-induced acute pancreatitis may be more severe than acute pancreatitis due to other causes in terms of complications and mortality rates[12, 14, 133, 134], but more controlled studies are required to produce firm evidence. Meta analysis of acute pancreatitis is difficult due to the heterogeneity of scoring systems for its severity[86].

A) Standard Care for Acute Pancreatitis

Treatment of HTG-induced acute pancreatitis is based on standard care, including cessation of oral food intake, admission to hospital, intravenous hydration, hypocaloric parenteral nutrition avoiding excess calories and glucose infusions, pain management, prophylactic antibiotics, and protease inhibitors[12, 130, 135]. Any precipitating factors should be treated appropriately (e.g., insulin treatment for

diabetes). Patients should be carefully monitored for development of pancreatic complications (necrosis, abscesses, etc.).

B) Specific Therapy for HTG-Induced Acute Pancreatitis

When patients can tolerate, oral TG-lowering medications (fibrates, n-3 PUFAs, niacin, etc.) may be administered[12, 130, 135]. MCTs may help reduce plasma TG levels as well as the risk of pancreatitis[130]. With a few exceptions, current TG-lowering medications are not based on the etiology of chylomicronemia. In apoC-II deficiency, infusion of normal human plasma containing apoC-II can greatly reduce plasma TG levels, and plasmapheresis has been suggested as a treatment of choice for pancreatitis due to apoC-II deficiency[4, 58].

C) Management of Chronic Pancreatitis

As acute pancreatitis can lead to chronic complications, patients with a history of it are better monitored for complications such as chronic pancreatitis, pancreatic pseudocysts, pancreatic insufficiency, steatorrhea, and insulin-dependent diabetes mellitus[4, 86]. Although chronic complications are not invariably associated with HTG-induced acute pancreatitis[136], they are not uncommon despite modern medical care[95].

D) Other Therapeutic Options for HTG-Induced Acute Pancreatitis

•**Insulin (should be individualized)**: Insulin therapy is advised in patients with diabetes mellitus. Insulin stimulates LPL activity, thereby reducing plasma TG levels. Administration of insulin or insulin plus glucose may be considered in non-diabetic patients in the case of severe HTG-induced acute pancreatitis[14, 137-139]. Detailed protocols for insulin/glucose administration have been summarized elsewhere[137, 139].

•**Heparin (not usually recommended)**: Heparin infusion has been used as a therapeutic option but is not usually recommended as a monotherapy in treatment guides by experts[12, 14]. Heparin transiently increases plasma LPL levels by releasing LPL from the endothelial cell surface, which temporarily reduces plasma TG levels. However, heparin can also deplete LPL, causing a rebound increase in plasma TGs[140]. Heparin may increase the risk of pancreatic hemorrhage when pancreatic necrosis is present[66].

•**Heparin plus insulin (should be individualized)**: Combination of heparin and insulin may be a therapeutic option for severe HTG-induced acute pancreatitis[14]. Although heparin infusion alone is usually not advised, a recent study has suggested that combination of heparin and insulin may be effective[14]. Evaluation in RCTs is awaited.

•**Apheresis for HTG-induced acute pancreatitis (should be individualized)**: In the acute setting, apheresis (lipoprotein apheresis (LA), plasmapheresis, or plasma exchange (PEX), etc.)[141, 142] can rapidly reduce plasma TG levels (40-80%) by directly removing TGRLs, as reported in case reports, case series, and multi-center studies[12, 14, 36, 57]. However, it is not proven whether rapid TG reduction by apheresis leads to better clinical outcomes than other therapeutic modalities in terms of pancreatic complications and mortality[59]. Plasmapheresis is costly, has only a transient TG- lowering effect (usually for a day), and may have adverse reactions (e.g., allergic reactions, anaphylactic shock, infusion-related infections, thromboses, etc.)[14]. A recent systematic review and case-control studies indicated that while plasmapheresis decreased plasma TG, it did not conclusively affect the morbidity or mortality of acute pancreatitis[14, 86]. A recent RCT, the first one in HTG-induced acute pancreatitis, has demonstrated that although plasma apheresis lowers plasma TG more efficiently than insulin plus heparin, it is costly and does not lead to better clinical outcomes[143]. In the guideline of the American Society for Apheresis (ASFA), plasmapheresis is a category III indication with Grade 2C recommendation ("optimum role of apheresis therapy is not established. Decision making should be individualized"; "Weak recommendation, low-quality or very low-quality evidence due to observational studies or case series")[144], and generally not recommended by experts in treatment guides for chylomicronemia[4, 5]. Plasmapheresis may be a therapeutic option for: 1) severe HTG-induced acute pancreatitis with persistent TG elevation past the first 48-72h with no other therapeutic choice[57, 59, 86, 120]; 2) HTG-induced acute pancreatitis in pregnancy or postpartum with no other therapeutic choice[14, 36, 74, 120, 145-149]; or 3) severe HTG-induced acute pancreatitis with high levels of serum lipase, hypocalcemia, lactic acidosis, worsening inflammation or organ dysfunction[149, 150]. However, such advice is experience-based, not evidence-based.

•**Prophylactic apheresis to prevent HTG-induced acute pancreatitis (should be individualized)**: Prophylactic apheresis may be a therapeutic choice for preventing severe recurrent HTG-induced acute pancreatitis but evidence for it is limited to several case reports of HTG-induced acute pancreatitis[12, 14, 57, 151-154] and gestational HTG-induced acute pancreatitis[155, 156].

15. Treatment of HTG and HTG-induced Acute Pancreatitis in Pregnancy

There are currently no formal guidelines for gestational HTG and HTG-induced acute pancreatitis due to the rarity of these conditions and insufficient evidence. The treatment approach for gestational HTG and HTG-induced acute pancreatitis is well summarized by Wong *et al.* [66].

•**Dietary therapy (restriction of dietary fat, MCTs, n-3 PUFA)**: There have been reports of successful management of HTG and prevention of HTG-induced acute pancreatitis during pregnancy through early intervention with a low-fat or very-low fat diet, MCTs, and n-3 fatty acids[4, 66, 113, 122, 149, 157-162]. For pregnant women at high-risk of pregnancy-associated pancreatitis, extreme fat restriction to <2 g/day may be required during the 2nd and 3rd trimesters for successful delivery[1, 4, 122, 159]. Topical application of sunflower oil or corn oil in pregnancy with an extra-low-fat diet may help prevent EFA deficiency[122, 129, 159]. In pregnancy-induced HTG, carbohydrate may need to be restricted, but an adequate amount should be taken. Carbohydrate iv may be a better therapeutic choice during carbohydrate restriction, as carbohydrate per os may produce a greater rise in plasma TG than carbohydrate iv[122, 132]. The risk of MCTs to the fetus is thought to be low[66]. The safety of maternal n-3 fatty acid supplementation (DHA 2.2 g and EPA 1.1 g/day) for the mother and the fetus has been confirmed through a RCT[66].

•**TG-lowering medications (some are contraindicated in Japan)**: There have been several reports on the use of niacin, or fibrates (gemfibrozil and fenofibrate) for pregnancy-associated HTG [66,120,122,159,163-166]. However, the safety of niacin or fibrate use during pregnancy has not been established, and the use of fibrates during pregnancy is contraindicated in Japan.

•**Admission to hospital**: For gestational HTG, admission to hospital may be advised in the following cases: suspected pancreatitis, persistent abdominal pain, steep increase in plasma TG in the 3rd trimester, or TG >40 mmol/L (3540 mg/dL)[66, 122, 159]. Gestational acute pancreatitis is managed through standard care, which has been extensively reviewed by Papadakis EP *et al.*[73].

•**Other therapeutic options**: When uncontrollable, further management may include: insulin, insulin pus glucose, insulin plus heparin, or plasmapheresis[36, 66, 119, 120, 137-139, 149, 156, 161]. In a treatment guide for gestational HTG, the use of insulin is recommended only for hyperglycemic pregnant women, and the use of heparin is not recommended due to the paucity of clinical evidence [66].

16. Unanswered Questions

A) Molecular Basis and New Therapeutic Modalities

Unraveling the molecular basis of chylomicronemia may lead to the development of new therapeutic modalities[167].

Emerging therapeutic targets for chylomicronemia include: a microsomal triglyceride transfer protein (MTTP) inhibitor (lomitapide)[168-170]; an *APOB* antisense oligonucleotide (ASO) inhibitor (mipomersen)[171-173]; *APOC3* ASO inhibitors, e.g., volanesorsen[174], which has been approved by the EMA for genetically confirmed chylomicronemia at high-risk for pancreatitis[93]; diacylglycerol O-acyltransferase 1 (DGAT1) inhibitors (AZD7687, LCQ908 (Pradigastat))[175-177]; angiopoietin-like protein 3 (ANGPTL3) inhibitors, e.g., *ANGPTL3* ASOs (IONIS-ANGPTL3-LRx)[178] and ANGPTL3 antibody (evinacumab)[179-182].

For these new therapies, potential adverse effects need to be carefully evaluated, including fatty liver associated diseases for lomitapide and mipomersen[168-170, 172] as a consequence of their inhibition of VLDL secretion; thrombocytopenia for volanesorsen[174]; gastrointestinal adverse effects (diarrhea, nausea, etc.) for DGAT inhibitors[175-177], consistent with the fact that homozygous loss-of-function mutations of DGAT1 cause a congenital diarrheal disorder (OMIM: 615863)[183].

Other agents under development include CAT-2003, a niacin-eicosapentaenoic acid conjugate that blocks sterol regulatory element-binding protein (SREBP). Inhibition of SREBP-1c has ameliorated environment-induced severe HTG in mouse models of hyperlipidemia, including apoA-V deficient mice, by blocking secretion of large-sized VLDL particles[54, 55].

Orlistat, an inhibitor of intestinal lipase, may help reduce TG levels in PCM[21, 184, 185] but may have adverse effects such as oily stools and fat-soluble vitamin insufficiency[128].

Treatment that targets a specific genetic cause of PCM is not available. A gene therapy for LPL (alipogene tiparvovec) was approved by the EMA in 2012, but is costly and has been withdrawn from the market[94, 186].

B) Risk and Management of CM-Related Complications

Not all patients with severe HTG manifest pancreatitis. Suggested risk factors of acute pancreatitis among HTG patients include underlying genetic

etiology of monogenic type, underdiagnosis and undertreatment, younger age, higher baseline TG levels, prior history of acute pancreatitis, male, alcohol use, obesity, diabetes, hypertension, renal disease, liver disease, and hypothyroidism[84, 87, 94, 95]. Further elucidation and validation of the risk factors and genetic predisposition for HTG-induced acute pancreatitis is awaited[187-191]. Understanding the molecular basis of HTG-induced acute pancreatitis is necessary for developing diagnostic markers as well as effective therapeutic modalities.

There has been controversy as to the atherogenicity of HTG, including chylomicronemia[136, 192, 193]. Although it remains uncertain whether HTG is a causal factor or a mere marker of atherosclerosis[3, 91, 194-196], recent mendelian randomization studies have indicated an association between risk of cardiovascular diseases and variants in HTG-related genes, including causative genes of chylomicronemia (*APOA5*, *LPL*, etc.)[197-199]. Chylomicronemia, particularly when it is polygenic, may be associated with higher risk of cardiovascular diseases[53, 96, 200], which warrants further studies.

C) Genotype-Phenotype Relationship of PCM

The genetic etiology of chylomicronemia may influence the risk of complications such as pancreatitis and atherosclerotic diseases[86, 94-96]. The benefit, risk, and cost-effectiveness of genetic testing for chylomicronemia should be carefully evaluated[15, 109, 201-203]. Some expert reviews, which include the Consensus Panel report of the European Atherosclerosis Society, do not recommend routine genetic testing for severe HTG[3, 204].

D) Underdiagnosis and Undertreatment

Underdiagnosis of chylomicronemia is one of the major risks for pancreatitis[84, 87]. A web-based patient survey reported that patients with chylomicronemia typically visit 5 physicians (range, 1-30) on average before receiving a final diagnosis of chylomicronemia[106, 107]. Owing to the variety of symptoms and complications, patients with chylomicronemia may visit not only lipidologists and endocrinologists but also other diverse specialists, such as primary care physicians, pediatricians, obstetricians, emergency physicians, gastroenterologists, pancreatologists, and psychologists. Simple diagnostic criteria as well as cooperation among different medical specialists will be necessary to achieve timely diagnosis and treatment.

E) Unmet Needs and Burden of Disease

Due to the rarity of the disease, the clinical experience of each doctor is limited. Large registry studies[205, 206] as well as patient-oriented observational studies[104-107] from the patient's perspective are useful for understanding the unmet needs and burden of the disease from the physical, psychological, social, and financial viewpoints[104-107].

A recent web-based patient survey revealed physical, emotional, and cognitive symptoms that are relevant to patient's quality of life but have not been recognized by physicians[207, 208], including abdominal pain (41%), fatigue (23%), feeling sad/down/blue/depressed (18%), difficulty in concentrating (16%), impaired judgment (11%), brain fog (8%), forgetfulness (8%), and recent memory loss (5%)[106, 107]. This survey also revealed actual handicaps felt at school, in society, and work, and family-related issues[106, 107].

Self-monitoring of plasma TG may be an unmet need that could help patients with the long-term management of the disease. It may enable patients to individualize their low-fat diets, hopefully leading to fewer episodes of acute pancreatitis[209].

F) Support for Patients

The mainstay of the current treatment for chylomicronemia is dietary interventions. Supporting information and materials for patients on diets will help develop recipes and menu plans that would be more enjoyable and sustainable. Information and support for patients can be found at FCS Foundation (www.livingwithfcs.org; www.facebook.com/livingwithfcs), FCS Focus (fcsfocus.com), LPLD Alliance (UK) (www.lpldalliance.org), the National Organization for Rare Disorders (NORD) (https://rarediseases.org), and the Japan Intractable Diseases Information Center (https://www.nanbyou.or.jp/entry/4883). Supportive care from other healthcare professionals, such as medical social workers and mental health professionals, will be necessary to reduce the burden of the disease as well as to improve the quality of life of patients with chylomicronemia[105-107].

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Conflicts of Interest

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Cerebrotendinous Xanthomatosis: Molecular Pathogenesis, Clinical Spectrum, Diagnosis, and Disease-Modifying Treatments

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Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive lipid storage disorder caused by mutations in the *CYP27A1* gene, which encodes the mitochondrial enzyme sterol 27-hydroxylase. Decreased sterol 27-hydroxylase activity results in impaired bile acid synthesis, leading to reduced production of bile acids, especially chenodeoxycholic acid (CDCA), as well as elevated serum cholestanol and urine bile alcohols. The accumulation of cholestanol and cholesterol mainly in the brain, lenses, and tendons results in the characteristic clinical manifestations of CTX. Clinical presentation is characterized by systemic symptoms including neonatal jaundice or cholestasis, refractory diarrhea, juvenile cataracts, tendon xanthomas, osteoporosis, coronary heart disease, and a broad range of neuropsychiatric manifestations. The combinations of symptoms vary from patient to patient and the presenting symptoms, especially in the early disease phase, may be nonspecific, which leads to a substantial diagnostic delay or underdiagnosis. Replacement of CDCA has been approved as a first-line treatment for CTX, and can lead to biochemical and clinical improvements. However, the effect of CDCA treatment is limited once significant neuropsychiatric manifestations are established. The age at diagnosis and initiation of CDCA treatment correlate with the prognosis of patients with CTX. Therefore, early diagnosis and subsequent treatment initiation are essential.

Key words: **Cerebrotendinous xanthomatosis, CTX, CYP27A1, Cholestanol, Chenodeoxycholic acid**

Introduction

Cerebrotendinous xanthomatosis (CTX: OMIM#213700), first described by van Bogaert *et al.* in 1937, is a rare autosomal-recessive lipid storage disease caused by deficiency of the mitochondrial cytochrome P 450 enzyme, sterol 27-hydroxylase (CYP27A1, EC 1.14.15.15) due to mutations in the *CYP27A1* gene[1]. Clinical presentation is characterized by neonatal jaundice or cholestasis, refractory diarrhea, juvenile cataracts, tendon xanthomas, osteoporosis, coronary heart disease, and progressive neuropsychiatric disturbances including mental retardation or dementia, psychiatric symptoms, pyramidal and cerebellar signs, progressive myelopathy, peripheral neuropathy, extrapyramidal manifestations, and seizures[2-9]. CTX is associated with considerable variability in clinical manifestations among patients and even within the same family[2]. The broad and diverse clinical symptoms cause a substantial diagnostic delay[2-4, 9]. Replacement treatment with chenodeoxycholic acid (CDCA) in the early stage of the disease has been reported to improve or even prevent clinical symptoms of CTX[10, 11]; however, after significant neurological pathology is established, the effect of the treatment is limited and deterioration of clinical manifestations may continue[3, 8, 12, 13]. Therefore, it is crucial to treat CTX patients at the initial stage of the disease. In this article, we provide the current understanding of the underlying pathomechanisms, clinical manifestations, diagnosis, and treatment of CTX.

Pathophysiology

CTX is caused by mutations in the *CYP27A1* gene encoding sterol 27-hydroxylase, a key enzyme in the bile acid synthesis pathway. A schematic

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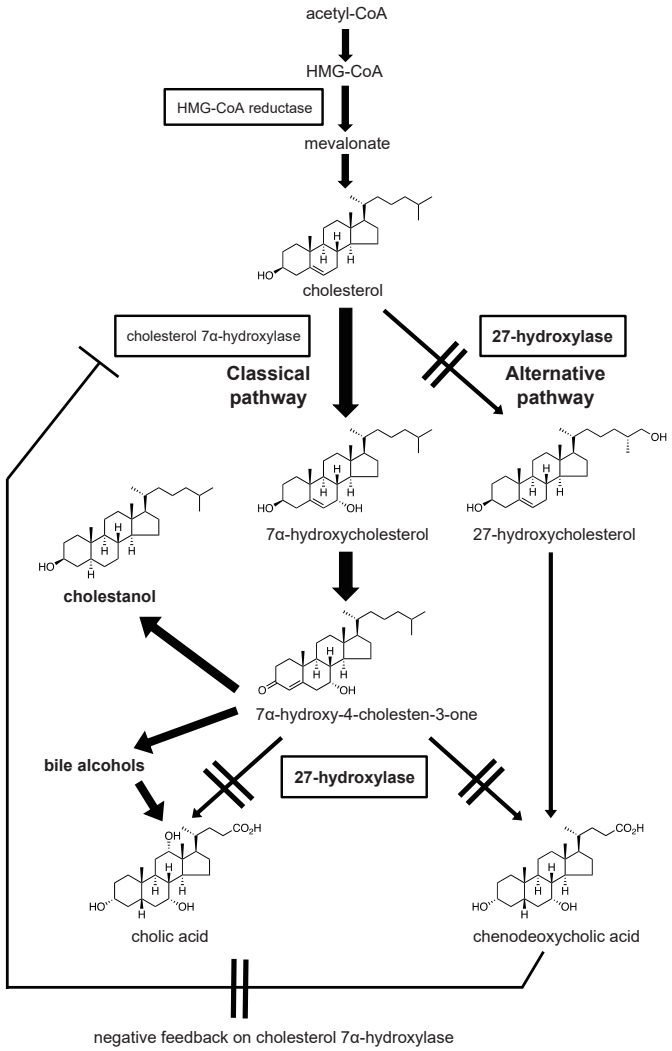

Fig. 1. Impaired bile acid synthesis in cerebrotendinous xanthomatosis (CTX)

In CTX, mutations in the *CYP27A1* gene lead to sterol 27-hydroxylase deficiency, resulting in reduced production of chenodeoxycholic acid and upregulation of the rate-limiting enzyme in the bile acid synthesis pathway, cholesterol 7α-hydroxylase. Increased levels of serum cholestanol and urinary bile alcohols are biological markers in CTX. HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA.

representation of the bile acid synthesis pathway is shown in **Fig. 1**. The classical pathway is initiated by 7α-hydroxylation of cholesterol, catalyzed by the rate-limiting enzyme cholesterol 7α-hydroxylase. The alternative pathway is initiated by 27-hydroxylation of cholesterol, which is catalyzed by sterol 27-hydroxylase. Decreased activity of sterol 27-hydroxylase leads to impaired bile acid synthesis in both the classical and alternative pathways[14], resulting in reduced production of bile acids, especially CDCA, and to a lesser extent cholic acid[15]. The absence of a negative feedback effect of CDCA on cholesterol 7α-hydroxylase accelerates these metabolic abnormalities, leading to increased levels of the bile acid intermediate 7α-hydroxy-4-cholesten-3-one as a precursor for cholestanol and bile alcohols[16]. Elevated serum cholestanol and urine bile alcohols are the biochemical diagnostic hallmarks in CTX. Consequently, increased cholesterol metabolites, such as cholestanol, accumulate mainly in the brain, lenses, and tendons, leading to the characteristic clinical manifestations of CTX. Elevated levels of cholestanol have been found in the serum and tissues, including those of the central nervous system, tendon xanthomas, and atheromatous lesions, in CTX patients. Although the cholestanol-to-cholesterol ratios of various tissues were higher than that of serum, cholesterol was more abundant than cholestanol in both serum and tissues[17]. Cholestanol is widely used as a diagnostic marker but the usefulness of 7α-hydroxy-4-cholesten-3-one

quantification in both the diagnosis and monitoring of CTX has also been reported[18]. It has also been shown that quantification of a panel of plasma ketosterol bile acid precursors (7α-hydroxy-4-cholesten-3-one, 7α,12α-dihydroxy-4-cholesten-3-one, and 7α,12α-dihydroxy-5β-cholestan-3-one) provides a more sensitive biochemical approach when compared with measurement of cholestanol[19].

In 1968, Menkes *et al.* discovered accumulation of cholestanol and cholesterol in the cerebrum and cerebellum of patients with CTX[20]. Although the mechanism by which cholestanol accumulates in the brain remains unclear, one possible explanation is that the bile acid precursor 7α-hydroxy-4-cholesten-3-one, which passes through the blood-brain barrier (BBB) more efficiently than cholestanol, can be converted to cholestanol by neurons, astrocytes, microglia, and human monocyte-derived macrophages[21, 22]. Another possible explanation is impairment of the BBB. Increased levels of cholestanol and apolipoprotein B were observed in the cerebrospinal fluid of patients with CTX, indicating disrupted function of the BBB[23]. It has also been proposed that large plasma bile alcohol glucuronides play a role in the abnormal BBB permeability in CTX, leading to increased transport of cholestanol and cholesterol in the brain[24].

Although the major pathway for production of cholestanol in CTX has been clarified, little is known about its metabolism. Under normal conditions, the 7α-hydroxy-4-cholesten-3-one-dependent pathway accounts for only about 30% of cholestanol biosynthesis in the brain, and cerebral cholestanol is mainly formed from cholesterol[25]. Using *Cyp27a1* and *Cyp46a1* knockout mice, Mast *et al.* demonstrated that CYP46A1 plays an important role in cholestanol removal from the brain and that CYP27A1 deficiency results in a preferential increase in cholestanol in the cerebellum[25].

CTX patients develop premature atherosclerosis and xanthomas despite normal serum cholesterol concentrations. However, abundant deposits of cholesterol are detected in addition to cholestanol in the respective lesions in CTX[17]. Although the mechanism leading to premature arteriosclerosis and tendon xanthomas in CTX remains unclear, reduced capacity for reverse cholesterol transport has been proposed as a possible cause[26-31]. Sterol 27-hydroxylase, which is expressed in macrophages, endothelial cells, and tenocytes as well as in the liver, seems to contribute to the transport of peripheral cholesterol to the liver by transforming intracellular cholesterol into 27-hydroxycholesterol, which has a higher capacity for passing through lipophilic membranes compared with cholesterol[26-28]. In addition, 27-hydroxycholesterol is an endogenous ligand for liver X receptor (LXR). LXR activation induces upregulation of ATP-binding cassette transporter A1 (ABCA1) expression, leading to increased cholesterol efflux[29-31]. Fu *et al.* demonstrated that upregulation of ABCA1 in response to cholesterol loading was impaired in primary fibroblasts derived from a CTX patient[29]. In addition, since 27-hydroxycholesterol was found to be the major oxysterol in human atherosclerotic lesions[28], extrahepatic sterol 27-hydroxylase is thought to be an anti-atherosclerotic enzyme. Absence of the two above defense mechanisms may contribute to premature atherosclerosis and xanthoma formation in CTX.

Epidemiology

CTX patients have been reported worldwide but prevalence of the disease is considered to be underestimated[32]. Based on the carrier frequency of the pathogenic *CYP27A1* c.1183C>T (p.R395C) mutation in 115 control subjects, the prevalence of CTX in the USA among Caucasians of European ancestry was estimated to be 3-5:100,000 individuals[32]. Pilo-de-la-Fuente *et al.* estimated a minimum prevalence of 1/1,8000,000 individuals in Spain[3]. Estimates of the incidence of CTX vary among locations. A recent genetic epidemiological study based on the Exome Aggregation Consortium (ExAC) cohort, a large cohort of over 60,000 unrelated subjects, evaluated the allele frequency of 57 known and 29 predicted CTX-causing variants and estimated the incidence of CTX to be 1:134,970-1:461,358 in Europeans, 1:263,222-1:468,624 in Africans, 1:71,677-1:148,914 in Americans, 1:64,247-1:64,712 in East Asians, and 1:36,072-1:75,601 in South Asians[33]. Prevalence among Jews of Moroccan origin and the Druze sect in Israel has been reported to be particularly high[34, 35].

Molecular Genetics

In 1991, human sterol 27-hydroxylase cDNA was isolated from a liver cDNA library. The *CYP27A1* gene consists of nine exons and eight introns and spans 18.6 kb of DNA on chromosome 2q33-qter[36, 37]. Sterol 27-hydroxylase consists of a 33-residue mitochondrial signal sequence followed by a mature protein of 498 amino acids containing putative binding sites for heme and adrenodoxin[1]. Cali *et al.* first identified two *CYP27A1* missense mutations, p.R395C and p.R479C, in patients with CTX and demonstrated that a loss-of-function mechanism is responsible for CTX[1].

CYP27A1 is the only gene known to be

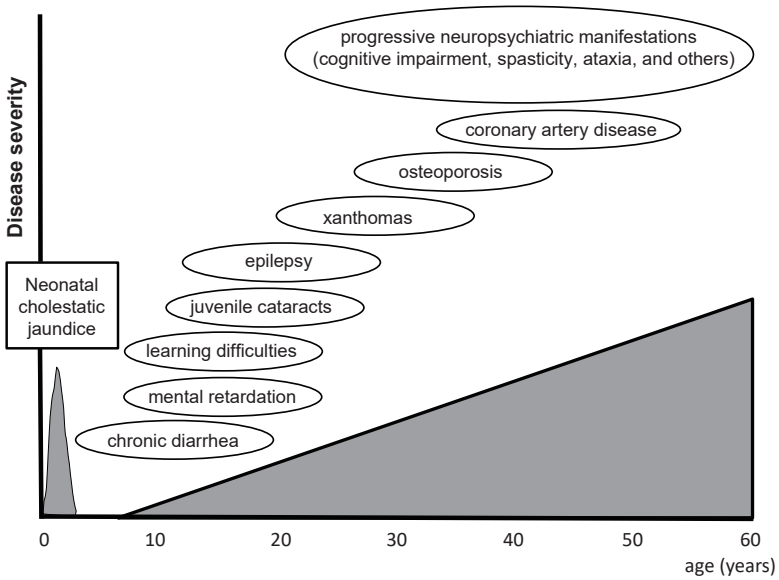

Fig. 2. Representative clinical course of classical form CTX
Figure shows typical ages of onset of CTX-related symptoms.

associated with CTX. Therefore, the diagnostic gold standard is genetic analysis of the *CYP27A1* gene[4, 38]. The diagnosis is confirmed by the presence of biallelic pathogenic *CYP27A1* mutations[4, 38]. To date, over 99 pathogenic mutations, including missense mutations, nonsense mutations, splice-site mutations, and insertion/deletion mutations, have been reported worldwide[6]. A relatively high frequency of *CYP27A1* mutations in particular ethnic groups has been reported: c.1016C>T (p.T339M), c.1183C>T (p.R395C), and c.1263+1G>A in the Netherlands[13], c.646G>C (p.A216P), c.1183C>T (p.R395C), c.1184+1G>A, c.1263+1G>A, and a 1.9 kb deletion including exons 7-9 in Italy[38], c.1183C >T (p.R395C) in northwestern Spain and c.1213C>T (p.R405W) in southern Spain[3], c.1214G>A (p.R405Q), c.1421G>A (p.R474Q), c.435G>T (p.G145=), and c.1420C>T (p.R474W) in Japan[9], which seems to be reasonable considering the allele frequency reported in the ExAC[33]. The allele frequencies of these variants in six global populations according to the ExAC database (version 0.3) are shown in **Supplementary Table 1**. Although no genotype-phenotype correlation has been reported[2, 3, 13], our nationwide survey revealed possible associations between c.1421G>A (p.R474Q) and classical form CTX, c.1241G>A (p.R405Q) and spinal form CTX, and c.435G>T (p.G145=) and non-neurological form CTX despite considerable phenotypic variation among patients with the same genotype[9].

Clinical Features

Clinical Phenotypes

Clinical presentation of CTX is characterized by diverse systemic and neuropsychiatric manifestations and combinations of symptoms vary from patient to patient. Systemic symptoms include neonatal jaundice or cholestasis, chronic diarrhea, juvenile cataracts, xanthomas, osteoporosis, and coronary heart disease. The neurological and psychiatric manifestations of CTX vary widely. Intellectual disability as well as pyramidal and cerebellar signs are the most frequent and are cardinal clinical features[2-4, 7, 9]. In addition, CTX patients can present with extrapyramidal manifestations, peripheral neuropathy, epilepsy, and psychiatric disturbances. Autonomic involvement has also been reported[39].

A representative clinical course of classical form CTX, the most common form of this condition, is shown in **Fig. 2**. Patients with classical form CTX develop neuropsychiatric symptoms attributed to the cerebrum, cerebellum, and/or brainstem, in combination with various systemic manifestations. The concept of spinal form CTX, also called spinal xanthomatosis, was proposed by Virrips *et al.* in 1999[40]. Patients exhibit clinical symptoms and signs related to involvement of the corticospinal tracts and dorsal columns of the spinal cord, without intellectual impairment, cerebellar signs, or peripheral neuropathy, at the time of presentation of the spinal cord syndrome[40]. Although most patients with spinal form

CTX also exhibit various systemic and neurological symptoms, spinal form CTX without other neurological manifestations has been reported[41-46]. Spinal form CTX has a relatively mild clinical course compared with classical form CTX[40].

We have proposed non-neurological form CTX[9] as another clinical phenotype. Although patients with the non-neurological form may develop neurological symptoms later in life, two genetically confirmed CTX patients in their fifties showed no evidence of neurological manifestations ≥ 20 years after disease onset. Therefore, we regarded the non-neurological form as a distinct clinical phenotype of CTX[9].

All CTX patients exhibit increased serum cholestanol levels at the time of diagnosis[2-4, 9]. While a significant relationship between serum cholestanol and clinical phenotype or disability was not detected[3], Sekijima *et al.* showed that classical form patients had significantly higher levels of cholestanol than spinal form patients[9].

Systemic Manifestations/Neonatal Jaundice or Cholestasis

Prolonged neonatal jaundice or cholestasis could be the earliest clinical presentation of CTX[47]. Laboratory findings have revealed conjugated hyperbilirubinemia with raised transaminases and alkaline phosphatase, whereas levels of γ-glutamyl transferase were normal or minimally elevated[47-50], which is the characteristic feature of inborn errors of bile acid synthesis[51]. In one study, hepatomegaly or hepatosplenomegaly was evident[50]. Liver biopsy specimens have revealed nonspecific chronic active hepatitis with giant cell transformation, piecemeal or focal bridging necrosis, and fibrosis, in addition to intralobular cholestasis[47-50]. Cirrhosis was detected in an explanted liver[50]. In addition, retrospective cohort studies have demonstrated that about 8–16% of patients had a past medical history of neonatal cholestatic jaundice[4, 13, 47]. Furthermore, family histories have revealed fetal deaths or jaundice-related infantile deaths among siblings of affected individuals[47].

Von Bahr *et al.* described a patient with genetically confirmed CTX who had fatal cholestatic liver damage[48]. Recently, Gong *et al.* reported on eight patients who presented with neonatal cholestasis. Among their cohort, this was fatal in four and one underwent liver transplantation. Although neonatal cholestasis associated with CTX has been generally assessed as transient and self-limiting with patient survival, a substantial proportion of patients could experience a more severe clinical course than previously recognized[50]. The mechanism by which mutations in the *CYP27A1* gene lead to cholestasis may involve nuclear receptors such as farnesoid X receptor (FXR). CDCA is a potent stimulator of FXR[52]. Marked reduction of CDCA in CTX leads to decreased activation of FXR, which results in reduced expression of the bile salt export pump, causing a decrease in canalicular bile salt transportation[48, 52].

Systemic Manifestations/Chronic Diarrhea

Chronic unexplained diarrhea begins in infancy and continues into adulthood[2]. It may be the earliest symptom of CTX and could start within the first year of life[53]. Gastrointestinal tract investigations in patients with diarrhea did not produce any abnormal findings[54]. Also, rectal biopsy did not demonstrate any accumulation of cholestenol or cholesterol and fatty acids could not be detected in the feces[54]. Usually, diarrhea ceases immediately after starting treatment with CDCA[11]. Although the pathogenesis of diarrhea is still unclear, presence of bile alcohol in the lumen of the gut and/or intraluminal deficiency of CDCA are the most likely causes[54].

Systemic Manifestations/Ocular Manifestations

Juvenile cataracts are one of the earliest clinical signs and often precede tendon xanthomas and neurological symptoms, and are usually noted in the second decade of life. Lens nuclei from CTX patients had a greater cholestanol content compared with the senile lens nuclei used as a control[55]. Although stabilization of cataracts with CDCA treatment has been reported[11], complete resolution is unlikely[56] and operations should be considered. Early onset of cataracts is uncommon and therefore, juvenile cataracts are arguably an important cue for early diagnosis of CTX. A screening for CTX among 170 patients with idiopathic bilateral cataracts diagnosed between the ages of 2 and 21 years identified 3 cases[57].

In addition to cataracts, ophthalmological manifestations include optic neuropathy with optic disc paleness, premature retinal vessel sclerosis, and cholesterol-like deposits[58]. Optic neuropathy with features suggestive of optic neuritis has also been reported[59].

Systemic Manifestations/Xanthomas

Xanthomas usually appear during the second or third decade of life. They typically occur on the Achilles tendon, but may be found on the elbow, neck, knee, and the bottom of the foot **(Fig. 3)**. The patellar and finger extensor tendons are also common sites for development of tendon xanthomas[60-64]. Xanthomas in the lung[65] and choroid plexus have also

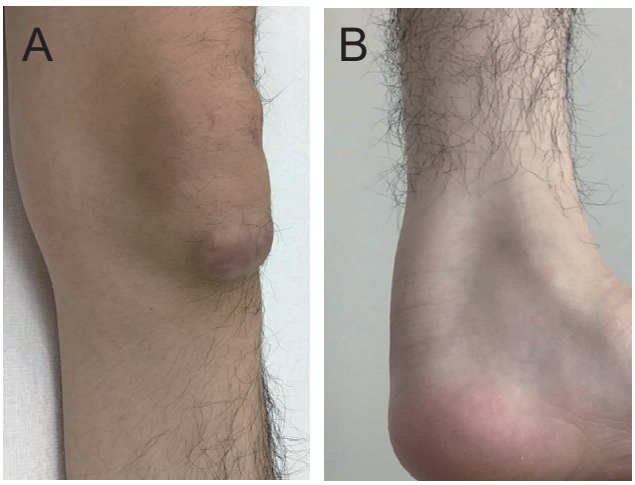

Fig. 3. Xanthomas in a patient with CTX

Figure shows xanthoma on the knee (A) and one on the Achilles tendon (B).

been reported[60, 66, 67]. It is noteworthy that presence of xanthomas is a characteristic feature of the disease, but it is not mandatory for CTX diagnosis[68]. Biopsy specimens of xanthomas show lipid crystal clefts with infiltration of foamy macrophages[64, 69]. In gallium-67 scintigraphy, there can be abnormal uptake in Achilles tendons[70], even if Achilles tendon xanthomas were not evident in a physical examination or on MRI[44]. In addition, positron emission tomography (PET) using ^{18}F-2-deoxy-2-fluoro-glucose (FDG) showed abnormally high radioactivity in the Achilles tendons and adjacent regions[5]. Although CDCA treatment does not significantly reduce tendon xanthomas[10], a decrease in size has been reported in some subjects[71, 72].

Systemic Manifestations/Skeletal System Involvement

Osteoporosis and increased bone fractures are CTX-associated systemic manifestations. However, the underlying pathogenesis of osteoporosis in this condition is still unknown. Decreased levels of serum 25-hydroxyvitamin D were detected in CTX patients[73-75]. In contrast, however, Federico *et al.* reported that levels of 25-hydroxyvitamin D were substantially within the normal range[76], indicating that a deficiency in vitamin D metabolites may not be the only factor responsible for the development of osteoporosis in CTX[74]. An alternative hypothesis for explaining the cause of osteoporosis is impairment of intestinal calcium absorption due to changes in the quantity and composition of bile acids[76]. In general, osteoporosis has been considered to occur in the later stages of the disease[4, 9]. However, teenage CTX patients could have early osteoporosis and a history of bone fracture[77]. CDCA treatment has been shown to improve bone mineral density (BMD)[74, 76].

Skeletal deformities including kyphosis, pectus excavates, pes equinovarus, and pes cavus were found in CTX patients[77] and Ginanneschi *et al.* reported that pes cavus occurrence was not significantly different in groups with and without peripheral nerve abnormalities[78].

Systemic Manifestations/Cardiovascular System Involvement

Premature atherosclerosis and cardiovascular disease have been reported as systemic manifestations in CTX patients even in their thirties[79-82]. Myocardial infarction is a cause of premature death in this condition[82]. Kuriyama *et al.* reviewed 144 cases of CTX and reported that 15 patients (10.4%) had cardiovascular disease, consisting of coronary artery disease in ten patients, ischemic changes on electrocardiogram in four, and mitral valve insufficiency in one patient[79]. Coronary artery disease was evident in 8 of 40 CTX patients (20%) in a nationwide survey on CTX in Japan[9]. In this survey, the mean age at onset of coronary artery disease was 52.5. ± 5.8 years (mean ± standard deviation (SD))[9]. Duell *et al.* reported that 3 of 43 CTX patients (7%) had premature cardiovascular disease, consisting of myocardial infarction in two patients, and angina pectoris in one patient in the USA[8]. Abdominal aortic aneurysm, coronary artery dissection, aneurysmal coronary artery disease, advanced carotid atherosclerotic lesions, and thickening of the interatrial septum compatible with lipomatous hypertrophy have also been reported in CTX [81, 83-86].

Systemic Manifestations/Pulmonary Involvement

Elevated levels of cholestanol in bronchoalveolar lavage fluid as well as in serum have been reported in CTX patients without pulmonary symptoms, or radiological and pulmonary function abnormalities. Transbronchial lung biopsy specimens have revealed foamy macrophages and small granulomas in alveolar septa[87].

Neuropsychiatric Manifestations/Intellectual disability

Among CTX patients, 48–74% present with intellectual disability[2-4, 9], which is one of the most frequent neurological symptoms. It is particularly important to take developmental delays, mental retardation, and learning difficulties beginning in childhood into consideration for early diagnosis of CTX[2-4, 7, 9, 53]. Cognitive decline, presenting in adolescence or early adulthood, is also frequently observed[2, 3, 9]. Although a neuropsychological profile

of patients with CTX remains undetermined, a fronto-temporal dementia phenotype exhibiting behavioral and personality changes[88], extensive cerebral cortex symptoms including left-right disorientation, constructional apraxia, and temporal and spatial disorientation in addition to frontal lobe dysfunction[89], and a corticobasal syndrome phenotype[90] have been reported.

Neuropsychiatric Manifestations/Pyramidal and Cerebellar Signs

Pyramidal and/or cerebellar signs typically emerge in the third or fourth decade and lead to gait disturbance in CTX patients[2, 4, 9]. Pyramidal and cerebellar signs have been detected in 64–92% and 36–83% of patients with CTX, respectively[2-4, 9]. Pyramidal signs such as spasticity, hyperreflexia, and extensor plantar response can be cardinal clinical signs especially in patients with spinal form CTX[40-46]. Owing to dorsal column involvement, simultaneous occurrence of impaired position and vibration sensation in the lower extremities can lead to spastic-ataxic gait in this form[41, 45]. Mignarri *et al.* have reported the usefulness of transcranial magnetic stimulation in detecting corticospinal tract damage[91]. Cerebellar signs include nystagmus, ataxic dysarthria, as well as limb and truncal ataxia[69, 92-94]. Pyramidal signs frequently coexist with cerebellar signs[2, 3].

Neuropsychiatric Manifestations/Extrapyramidal Manifestations

CTX patients can present with a wide range of movement disorders including parkinsonism[90, 95, 96], dystonia[97-99], myoclonus[98, 100, 101], and postural tremor[100, 102]. When movement disorders are diagnosed, patients have a tendency to present with other CTX-associated systemic and neuropsychiatric manifestations[103]. Parkinsonism usually occurs later in life[7, 95, 103] and is the most frequently reported type of movement disorder in CTX, followed by dystonia, myoclonus, and postural tremor[103]. Parkinsonism seems to be a treatment-resistant feature in CTX[13], with CDCA treatment seemingly having no effect. In addition, CTX patients may develop parkinsonism during treatment with CDCA[103]. The effect of L-dopa is controversial[90, 95, 103-105]. In addition to the characteristic brain MRI findings of CTX, signal hyperintensities on T2-weighted images in the substantia nigra, globus pallidus, and striatum [90, 95, 96, 103] have been described and functional dopaminergic imaging has demonstrated a pre-synaptic dopaminergic deficit in CTX patients presenting with parkinsonism[90, 95, 96, 104, 105]. Although movement disorders are considered a late disease manifestation, Zubarioglu *et al.* reported that all six patients who were diagnosed before 18 years of age had intention tremor[77].

Neuropsychiatric Manifestations/Peripheral Nervous System Involvement

Peripheral neuropathy is an established clinical feature of CTX; however, it is still being debated whether the underlying pathogenesis of CTX-related polyneuropathy is demyelinating or axonal in origin. Based on the presence of onion bulbs, which are generally considered a hallmark of chronic demyelination, the pathological process has been interpreted as demyelinating[106, 107]. On the other hand, Verrips *et al.* reported that axonal degeneration was the predominant process on the basis of nerve conduction velocity (NCV) studies and sural nerve biopsy specimens showing features of axonal degeneration[108]. In addition to axonal polyneuropathy and demyelination polyneuropathy, a mixed type of neuropathy has been reported, indicating that CTX could exhibit any type of neuropathy[109]. CTX-related polyneuropathy seems to be predominantly motor neuropathy[78, 109]. Although neurophysiologically confirmed neuropathy frequently occurs in CTX, signs and symptoms related to polyneuropathy are often absent or difficult to appreciate because central nervous system involvement may dominate the clinical picture[4, 78, 109]. The disease severity of polyneuropathy varies greatly among patients, ranging from asymptomatic presentations to severe polyneuropathy[78, 109, 110]. Thickening of the nerve roots and trunks of the lumbosacral plexus or cauda equina has been reported[90, 111].

Neuropsychiatric Manifestations/Muscle Involvement

Controversy exists regarding whether muscle involvement is a characteristic feature in CTX. Federico *et al.* noted mild myopathic changes[112], while Verrips *et al.* reported that muscle biopsies demonstrated neurogenic changes without any definite myopathic characteristics[108]. The results for mitochondrial respiratory chain enzymatic activity are also controversial[108, 113]. Abnormal findings from ultrastructural studies of muscles include changes in the mitochondria and membranous system, and an increased amount of lipid droplets, lipofuscin, and glycogen; however, the significance of these findings remains to be determined[39, 108, 112].

Neuropsychiatric Manifestations/Epilepsy

In CTX, 10–33% of patients have epileptic seizures[2-4, 7, 9]. Epilepsy can develop at any stage in life and is often seen in the early phase of the disease[7].

Epilepsy could be a diagnostic cue in some cases[114-116]. A CTX patient presenting with infantile spasms has also been reported, but this is a rare case[117]. Electroencephalographic abnormalities are frequently observed in cases of CTX even without clinical signs of seizures[11, 118]. In addition to slow background activity composed of theta and delta waves, bursts of high voltage slow activity are frequently demonstrated. Spike and sharp wave complexes can also be detected[10, 11, 118]. CDCA treatment leads to improvement or normalization of electroencephalographic findings[10, 11, 60, 118], and epilepsy in CTX seems to respond well to anti-epileptic agents[12, 114-116, 119]. CDCA treatment could lead to improved seizure control[12, 60, 120], even in patients with drug-resistant epilepsy[121].

Neuropsychiatric Manifestations/Behavioral manifestations

Psychiatric and behavioral manifestations include personality changes with irritability and aggressivity, depression, delusional syndrome, catatonia, psychosis, attention-deficit hyperactivity disorder, oppositional-defiant disorder, and autism spectrum disorder[13, 122]. Behavioral disorders and affective/mood disorders associated with learning difficulties or mental retardation appearing during childhood or adolescence should lead to biochemical investigations to exclude CTX.

Radiological, Pathological, and Neurophysiological Examinations

Neuroimaging

The most distinctive neuroradiological findings are signal hyperintensities on T2-weighted and/or FLAIR images in the dentate nuclei and adjacent cerebellar white matter[123, 124]. Abnormal signal changes in the dentate nuclei can be more clearly detected on FLAIR images than on T2-weighted images[123]. It was found that abnormal hyperintensities on T2-weighted and/or FLAIR images could be detected in the globus pallidus, internal capsule, substantia nigra, cerebral peduncles, inferior olive, and periventricular white matter, with a tendency to spare the U-fibers and corpus callosum[125]. Supratentorial and/or infratentorial atrophy are also observed[123, 124, 126] **(Fig. 4)**. Cortical volume, rather than white matter volume, was correlated with clinical status and cortical atrophy could be detected in all neocortical regions, with a preference for the fronto-parietal cotrtex[126]. In addition, cerebellar vacuolation, which is detected as hypointense lesions on both T1-weighted and FLAIR images, has been recently indicated as a marker of a poor prognosis in CTX[127, 128], while absence of dentate nuclei signal alteration is considered an indicator of a better prognosis[128]. Furthermore, calcifications were detected in the dentate nuclei in a subgroup of patients[128] and the hot cross bun sign in the pons, a characteristic finding of multiple system atrophy, has been reported[69].

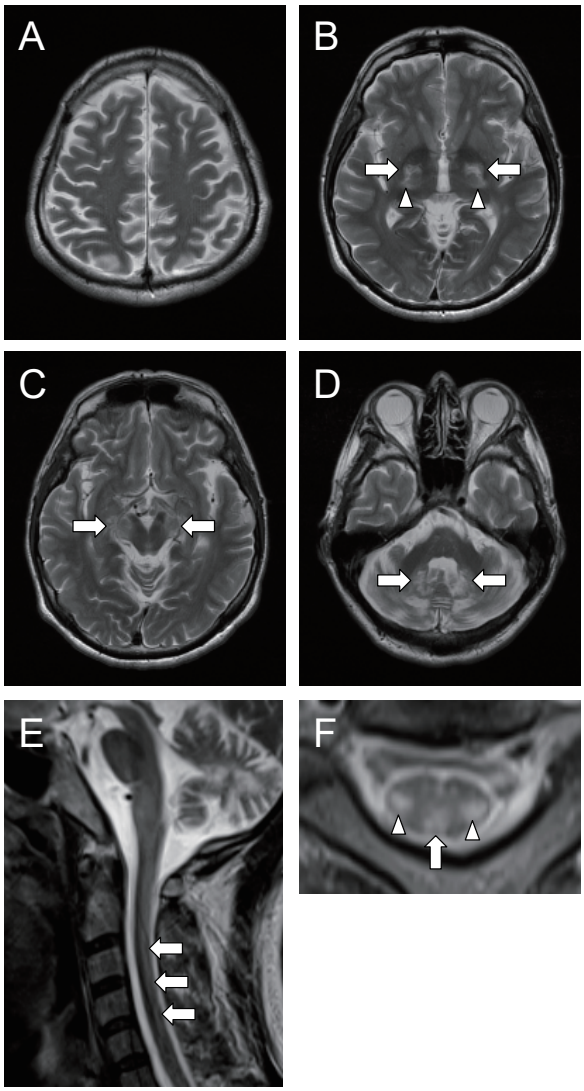

Fig. 4. Brain magnetic resonance imaging (MRI)

Axial T2-weighted images of the brain showing abnormal hyperintensities in the globus pallidus (arrows in B), internal capsules (arrowheads in B), cerebral peduncles (arrows in C), and dentate nuclei (arrows in D). Diffuse cerebral (A) and cerebellar (D) atrophy are evident. Sagittal T2-weighted image of the spinal cord exhibiting longitudinally extensive hyperintense lesions (arrows in E). Axial T2-weighted image at the C3 level showing involvement of lateral corticospinal tracts (arrowheads in F) and gracile tracts (arrow in F).

In patients with spinal cord involvement, a spinal cord MRI demonstrated longitudinally extensive

hyperintense lesions involving lateral corticospinal tracts and gracile tracts on T2-weighted images[40, 44-46]. It is noteworthy that absence of signal changes on spinal cord MRI cannot rule out the possibility of spinal form CTX[42, 43].

On magnetic resonance spectroscopy (MRS), decreases in N-acetylaspartate (NAA) intensities and increases in lactate signals point to axonal damage and brain mitochondrial dysfunction, respectively[123]. In addition to decreased NAA intensities, lipid peaks were evident on MRS using a short TE[129]. Increased levels of myo-inositol indicate gliosis and astrocytic proliferation[129, 130].

Cerebellar glucose hypometabolism in ^{18}F-2-deoxy-2-fluoro-glucose positron emission tomography (FDG-PET) and cerebellar hypoperfusion in single photon emission computed tomography (SPECT) with ^{99m}Tc-ethylcysteinate dimer (ECD) have been reported despite normal cerebellar morphology[88, 131, 132]. In addition to in the cerebellum, SPECT using ^{99m}Tc-ECD and ^{123}I-*N*-isopropyl-*p*-iodoamphetamine (^{123}I-IMP) revealed cerebral hypoperfusion, predominantly in the fronto-parietal lobes[88, 89, 132]. Gray matter atrophy patterns were correlated with hypoperfusion in SPECT using ^{99m}Tc- ECD[133].

Diffusion tensor imaging (DTI) revealed that fractional anisotropy (FA) reduction preceded structural alterations detected by voxel-based morphometry and correlated with cognitive function[133]. Widespread reductions of FA and decreased track-density were demonstrated[120, 134].

Neuropathology

At macroscopic examination, nonspecific brain and cerebellar atrophy and a yellowish soft tissue in the cerebellum, cerebrum, choroid plexus, cerebral peduncles, and globus pallidus were observed[135-138]. In the cerebral peduncles, cystic necrosis of the corticospinal tracts has been reported[139]. Microscopic examinations have revealed lipid crystal clefts, neuronal loss, demyelination, reactive astrocytosis, and foamy macrophages in the affected regions, especially in the dentate nucleus and surrounding area, as well as in the cerebrum, basal ganglia, brainstem, and, spinal cord[65, 124, 135-139]. In patients with spinal cord involvement, extensive symmetric loss of myelin and axons was detected particularly in the lateral corticospinal tracts and gracile tracts of the spinal cord[40].

Neurophysiological Examinations

In addition to NCV studies and electroencephalography, abnormalities have been found in neurophysiological examinations. The P100 peak latency of visual evoked potentials (VEPs) was delayed[109, 140, 141] and the Ⅰ to Ⅲ, Ⅲ to Ⅴ, and Ⅰ to Ⅴ interpeak latencies of brain stem evoked potentials (BAEPs) were prolonged[109, 140, 141]. Central conduction time in somatosensory evoked potentials (SSEPs)[109, 142] and motor evoked potentials (MEPs)[89, 91, 141] were increased, with lower extremity predominance.

Diagnosis

Importance of Early Diagnosis and Treatment

CTX is a treatable metabolic disorder; however, once significant neurological symptoms are established, clinical deterioration can occur despite normalization of cholestanol levels after treatment with CDCA[3]. Even with therapy, only 28% of the patients remained stable, whereas 60% continued to deteriorate and 20% died, in a cohort of 25 patients with CTX in Spain[3]. Duell *et al.* reported that clinical deterioration during follow up was observed in patients who had significant neurological symptoms when they were diagnosed at the age of 25 years or older[8]. Yahalom *et al.* and Stelten *et al.* have shown that the age of diagnosis and initiation of CDCA treatment correlates with the prognosis of patients with CTX[12, 13]. Berginer *et al.* reported two siblings with CTX who began CDCA treatment from 2 and 7 years of age, respectively, and did not develop any neurological manifestations during a 14-year follow-up period[142]. These findings strongly suggest that early diagnosis and treatment are crucial in CTX. However, retrospective cohort studies on CTX have revealed a substantial diagnostic delay of 15–25 years[2-4, 9].

Juvenile cataracts are usually the earliest clinical sign that precedes tendon xanthomas and neurological symptoms. Cruysberg *et al.* emphasized that the combination of juvenile cataracts and chronic diarrhea is noteworthy in the early diagnosis of CTX[143]. It is recommended that all patients with cataracts before the age of 30 years are screened for CTX, especially if they also have CTX-related conditions such as chronic diarrhea, tendon xanthomas, and/or neuropsychiatric symptoms[8]. Verrips *et al.* emphasized that presence of tendon xanthomas is not obligatory for a diagnosis of CTX and recommended that presence of two of the four clinical features of premature cataracts, intractable diarrhea, progressive neurological signs and symptoms, and tendon xanthomas prompt thorough biochemical screening for CTX[68]. It is also important to consider intellectual disability, usually presenting at school age, for early diagnosis of CTX[4]. In addition, because affected relatives may be asymptomatic, biochemical examination of all siblings of a patient with CTX is recommended[2, 4].

Table 1. Diagnostic criteria for cerebrotendinous xanthomatosis (Sekijima *et al.*[9])

A. Symptoms
1. Tendon xanthoma
2. Progressive neurological dysfunction[a] or mental retardation
3. Juvenile cataract
4. Juvenile coronary artery disease
5. Chronic unexplained diarrhea
6. Juvenile osteoporosis
7. Prolonged neonatal cholestasis
B. Biochemical finding
Elevated serum cholestanol level
C. Genetic testing
Pathogenic mutation in *CYP27A1* gene (homozygosity or compound heterozygosity)
D. Differential diagnosis
Increased serum cholestanol level due to following diseases should be excluded
· Familial hypercholesterolemia
· Sitosterolemia
· Obstructive biliary tract disease
· Hypothyroidism
Diagnostic category
Definite: At least one of symptom in A and B+C+D
Probable: At least one of symptom in A and B+D
Possible: At least one of symptom in A and B

[a] Representative progressive neurological dysfunction includes cognitive dysfunction, cerebellar symptoms, pyramidal symptoms, extrapyramidal symptoms, seizure, peripheral neuropathy, and sensory disturbance attributed to spinal cord.

To identify and treat CTX patients at an initial stage of the disease, Mignarri *et al.* created a suspicion index and developed a diagnostic algorithm for early diagnosis of CTX[4]. Their suspicion index comprised weighted scores assigned to indicators such as family history characteristics and common systemic and neurological symptoms. They suggested that their proposed algorithm would be useful for early diagnosis, even in patients before the onset of disabling neurological symptoms including ataxia, spasticity, and psychiatric disturbances[4].

Diagnostic Criteria

In the absence of generally accepted diagnostic criteria for CTX, we recently proposed new diagnostic criteria with emphasis on early diagnosis **(Table 1)**[9]. They include clinical symptoms, biochemical findings, genetic analysis, and differential diagnosis. We established three diagnostic categories in accordance with levels of certainty: definite, probable, and possible CTX. The diagnosis of possible CTX is made when there is at least one CTX-related clinical symptom and elevated levels of serum cholestanol (≥ 4.5 μg/mL, mean ± SD: 2.35 ± 0.73 μg/mL). Excluding other conditions with elevated levels of cholestanol is necessary for diagnosis of probable CTX. A definite diagnosis of CTX is confirmed by the presence of biallelic mutations in the *CYP27A1* gene.

Differential Diagnosis

Differential diagnosis of CTX differs substantially according to presenting symptoms. Inborn errors of bile acid metabolism including CTX lead to neonatal cholestasis or hepatitis[144, 145], which can be the first manifestation in this disease. In patients with juvenile bilateral cataracts and/or progressive mental deterioration, CTX should be considered[2, 57]. When xanthomas are evident, differential diagnosis includes familial hypercholesterolemia (FH) and sitosterolemia. FH is characterized by elevated levels of LDL cholesterol, the presence of tendon xanthomas, and premature coronary artery disease, and mutations in *LDLR*, *APOB*, and *PCSK9* have been reported to cause FH[146]. Sitosterolemia is an autosomal recessive sterol storage disorder characterized by elevated levels of LDL cholesterol and plant sterols such as sitosterol and campesterol, tendinous and tuberous xanthomas, and premature atherosclerosis. It is caused by biallelic mutations in either *ABCG5* or *ABCG8*[147]. The presence of juvenile cataracts, chronic unexplained diarrhea, and progressive neuropsychiatric manifestations can distinguish CTX from these two disorders. Other

conditions with elevated levels of cholestanol include obstructive biliary tract diseases and hypothyroidism. In patients with cerebellar ataxia, CTX patients might be misdiagnosed as spinocerebellar atrophy, multiple system atrophy, or Marinesco-Sjögren syndrome[68]. CTX should be included in the differential diagnosis of spastic paraplegia[42, 44].

Clinical Management

CDCA has been approved as first-line treatment for CTX. In a landmark study published in 1984, Berginer *et al.* demonstrated the long-term efficacy of oral CDCA treatment[10]. In addition to a decrease in serum cholestanol and elimination of abnormal urinary and biliary excretion of bile alcohols, CDCA treatment led to an improvement in electroencephalographic findings and neurological manifestations including intellectual impairment, pyramidal and cerebellar signs, and peripheral neuropathy[10, 11]. CDCA treatment is recommended at a dose of 750 mg/day for adults and 15 mg/kg/day for children in three divided oral doses[10, 11]. It has been shown to result in a gradual decline in serum cholestanol during the first 2 years[148, 149]. Assessment of cholestanol levels may be useful in monitoring patient adherence to treatment. However, it should be noted that a decreased level of cholestanol does not necessarily suggest a good prognosis[3]. In Japan, CDCA has been approved for dissolution of gallstones, but not for the treatment of CTX.

Although CDCA is a relatively safe drug, gastrointestinal manifestations and drug-induced liver damage may occur[44, 60, 150]. Huidekoper *et al.* reported an infantile patient with CTX who developed jaundice with hepatomegaly within 6 weeks after initiating CDCA administration at a dosage of 15mg/kg/day[151]. After treatment with CDCA was stopped, liver size and function rapidly normalized. CDCA supplementation was then restarted and maintained at 5 mg/kg/day with no further evidence of liver dysfunction and adequate metabolic control. Duell *et al.* reported that 9% of patients required dose adjustment for CDCA owing to moderate drug-induced liver damage[8]. These findings suggest that clinical and laboratory monitoring and dosage adjustment for CDCA are essential in the treatment of CTX, especially in infants and young children[8, 151].

CDCA was initially preferred to cholic acid because it was more effective in reducing cholesterol 7α-hydroxylase and had a stronger negative feedback effect on it[127, 152]. Cholic acid has been shown to be effective in the treatment of other genetic defects in bile acid synthesis[153]. Since CDCA is intrinsically hepatotoxic, cholic acid is considered the safer option in CTX, especially in infancy[49]. Mandia *et al.* reported potential efficacy for cholic acid in adult patients with CTX, including individuals whose CDCA treatment was discontinued due to supply difficulties[127]. Treatment with cholic acid not only significantly reduced cholestanol levels in all patients but also led to improvement or stabilization of systemic and/or neurological manifestations[127]. No adverse effects were reported in patients undergoing cholic acid treatment, suggesting that cholic acid may be a suitable alternative treatment, especially in patients with adverse effects related to CDCA, such as drug-induced liver damage[60, 127].

Treatment with ursodeoxycholic acid, which does not inhibit cholesterol 7α-hydroxylase, has been shown to be ineffective[10, 154]. When ursodeoxycholic acid was substituted for CDCA, plasma cholestanol returned to pretreatment levels[10].

The effectiveness of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors (statins) remains controversial. Lewis *et al.* reported that mevinolin normalized serum cholestanol and reduced the size of xanthomas[155], whereas Batta *et al.* found that lovastatin did not affect abnormal bile acid synthesis or reduce plasma cholestanol levels[154]. Although synergistic effects of combination therapy with CDCA and HMG-CoA reductase inhibitors on serum cholestanol or urine bile alcohols have been observed[71, 81, 149], absence of an additive effect has also been reported[148]. After switching from combined therapy of CDCA and HMG-CoA reductase inhibitors to HMG-CoA reductase inhibitor monotherapy, clinical symptoms such as xanthomas and neurological manifestations, and electroencephalographic findings were re-exacerbated with reappearance of abnormal bile alcohol excretion or elevated plasma cholestanol [71, 156]. Therefore, HMG-CoA reductase inhibitors could be beneficial when combined with CDCA, but long-term clinical benefits should be proven.

Low-density lipoprotein (LDL) is a major carrier of serum cholestanol. LDL-apheresis, usually combined with CDCA and HMG-CoA reductase inhibitors, has been performed to reduce serum cholestanol[157-160] Levels of serum cholestanol or 7α -hydroxy-4-cholesten-3-one decreased after each LDL-apheresis, but returned to their initial levels within 1–2 weeks[159, 161], suggesting that LDL-apheresis at a frequency of at least once every 2 weeks is necessary. The effects of LDL-apheresis on clinical manifestations are still controversial despite the decrease in cholestanol. In addition, the invasiveness of this procedure and its necessity for the long-term management of the disease should be taken into

account[161].

Symptomatic treatments for epilepsy[115, 120], psychiatric manifestations[122], and movement disorders such as dystonia[97, 98] and parkinsonism[90, 95] should be considered. Cataract extraction is also usually required[57].

After treatment with CDCA, improvements in neurophysiological examinations including NCV studies[78], VEP[72, 78], SSEP[72], MEP[72, 91], and EEG[10, 11] have been reported. Besides conventional MRI, DTI and tractography, MRS, and SPECT imaging might have potential as neuroimaging modalities for monitoring treatment response[120, 132-134, 162, 163].

Conclusions and Perspectives

CTX is considered a rare inherited metabolic disorder. However, it may be under- or misdiagnosed, although effective treatment is available. There is a crucial "point of no return" in CTX, after which treatment initiation can no longer prevent the progression of the disease[12]. The earlier the diagnosis is made and the sooner treatment is started, the more likely it is that the significant neurological manifestations that diminish the quality of life of patients with CTX can be improved or even prevented. Neonatal jaundice, chronic unexplained diarrhea, developmental delays, mental retardation, and learning difficulties are non-specific symptoms, but they could be diagnostic cues for pediatricians. Ophthalmologists have an opportunity to diagnose CTX, because bilateral cataracts are one of the earliest clinical symptoms and juvenile-onset bilateral cataracts could be useful as a screening marker for CTX[57]. Furthermore, it could be beneficial to screen newborns for CTX in the future[164].

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Supplementary Table 1. Allele frequencies of *CYP27A1* variants according to Exome Aggregation Consortium database (version 0.3)

variant	AFR	AMR	EAS	FIN	NFE	SAS
p.G145=	0.00000	0.00000	0.00040	0.00000	0.00000	0.00000
p.A216P	0.00000	0.00000	0.00000	0.00000	0.00004	0.00000
p.T339M	0.00000	0.00000	0.00010	0.00000	0.00002	0.00007
p.R395C	0.00010	0.00020	0.00000	0.00030	0.00020	0.00006
p.R405W	0.00000	0.00009	0.00000	0.00000	0.00000	0.00006
p.R405Q	0.00010	0.00009	0.00050	0.00000	0.00004	0.00000
p.R474W	0.00000	0.00000	0.00000	0.00000	0.00002	0.00000
p.R474Q	0.00000	0.00000	0.00010	0.00000	0.00002	0.00000
c.1184+1G>A	0.00000	0.00000	0.00000	0.00000	0.00006	0.00070
c.1263+1G>A	0.00000	0.00009	0.00010	0.00000	0.00007	0.00000

AFR: African; AMR: Admixed American; EAS: East Asian; FIN: Finnish; NFE: Non-Finnish European; SAS: South Asian.

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Review

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Current Diagnosis and Management of Abetalipoproteinemia

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Abetalipoproteinemia (ABL) is a rare autosomal recessive disorder caused by biallelic pathogenic mutations in the *MTTP* gene. Deficiency of microsomal triglyceride transfer protein (MTTP) abrogates the assembly of apolipoprotein (apo) B-containing lipoprotein in the intestine and liver, resulting in malabsorption of fat and fat-soluble vitamins and severe hypolipidemia. Patients with ABL typically manifest steatorrhea, vomiting, and failure to thrive in infancy. The deficiency of fat-soluble vitamins progressively develops into a variety of symptoms later in life, including hematological (acanthocytosis, anemia, bleeding tendency, etc.), neuromuscular (spinocerebellar ataxia, peripheral neuropathy, myopathy, etc.), and ophthalmological symptoms (e.g., retinitis pigmentosa). If left untreated, the disease can be debilitating and even lethal by the third decade of life due to the development of severe complications, such as blindness, neuromyopathy, and respiratory failure. High dose vitamin supplementation is the mainstay for treatment and may prevent, delay, or alleviate the complications and improve the prognosis, enabling some patients to live to the eighth decade of life. However, it cannot fully prevent or restore impaired function. Novel therapeutic modalities that improve quality of life and prognosis are awaited. The aim of this review is to 1) summarize the pathogenesis, clinical signs and symptoms, diagnosis, and management of ABL, and 2) propose diagnostic criteria that define eligibility to receive financial support from the Japanese government for patients with ABL as a rare and intractable disease. In addition, our diagnostic criteria and the entry criterion of low-density lipoprotein cholesterol (LDL-C) <15 mg/dL and apoB <15 mg/dL can be useful in universal or opportunistic screening for the disease. Registry research on ABL is currently ongoing to better understand the disease burden and unmet needs of this life-threatening disease with few therapeutic options.

Key words: **Abetalipoproteinemia, MTTP, Fat-soluble vitamin, Chylomicron, VLDL, Hypolipidemia**

1. Introduction

Abetalipoproteinemia (ABL; OMIM 200100) is a rare inherited disease characterized by the absence of plasma apolipoprotein (apo) B-containing lipoproteins and fat-soluble vitamins in the plasma. In 1950, Bassen and Kornzweig first described the syndrome, which is characterized by acanthocytes ("star-shaped" erythrocytes with irregular cytoplasmic projections, i.e., acantha, "thorn" in Greek), retinitis pigmentosa, and ataxia[1]. In 1960, the absence of beta-lipoprotein in the plasma of the syndrome was reported[2]. Later, in 1992, the activity of microsomal triglyceride transfer protein (MTTP) was found to be absent in the intestinal mucosa of ABL patients[3]. In 1993, mutations in the *MTTP* gene, which encodes the large subunit of MTTP, were identified in ABL patients (Fig. 1)[4, 5]. In this review, we summarize the pathogenesis, clinical signs and symptoms, diagnosis, and management of ABL. We also propose diagnostic criteria for ABL, which have been used to determine the eligibility to receive financial aid from the Japanese

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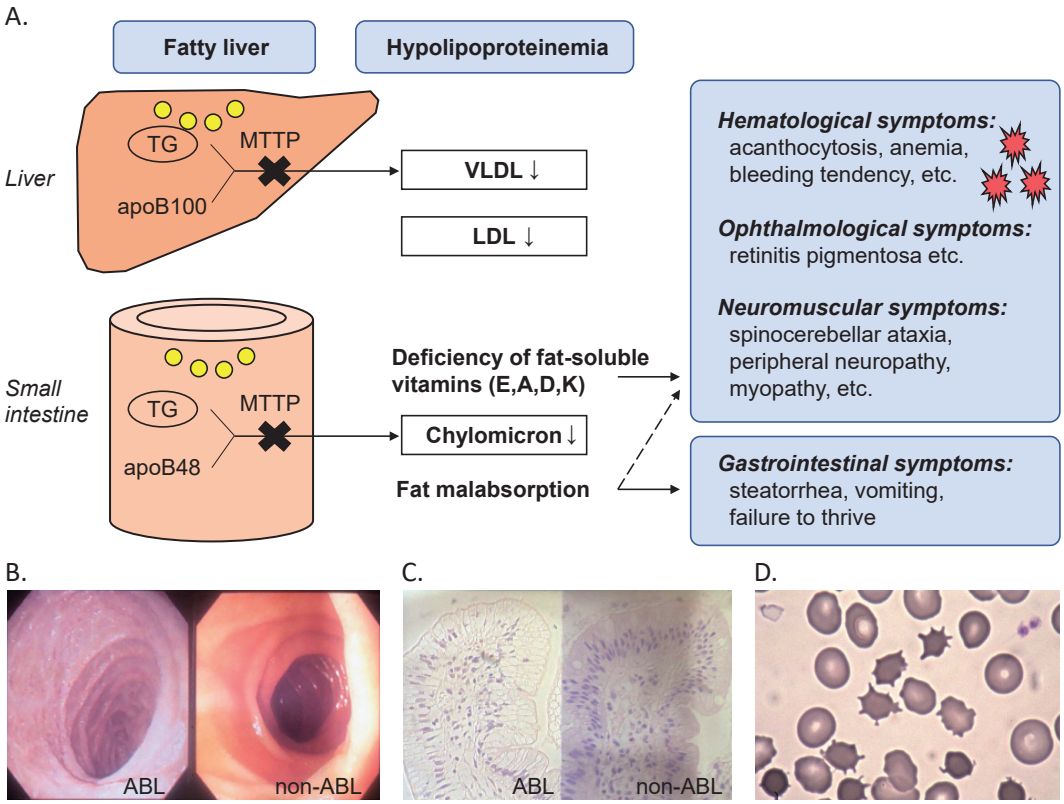

Fig. 1. Overview of abetalipoproteinemia

(A) MTTP is a prerequisite for the assembly and secretion of VLDL and CM by the liver and small intestine, respectively. Homozygous *MTTP* deficiency causes fat malabsorption, steatorrhea, vomiting, failure to thrive, hypolipoproteinemia, fatty liver, as well as symptoms related to deficiencies of fat-soluble vitamins. (B, C) Endoscopic examination and histological analysis of the duodenal mucosa of an ABL patient and a non-ABL control. Accumulation of intracellular lipids in epithelial cells (C) results in a snowy appearance (B), called snow-white duodenum, a gelee blanche, or white hoar frosting. (D) Acanthocytes of an ABL patient (Patient 1 in Ref 29). Figures 1B, 1C, and 1D are reproduced with permission from Ishibashi S and Ohashi K (The Lipid, 2014; 25: 200-203).

government for patients with ABL as a rare and intractable disease. The financial aid is provided by The Program for Designated Intractable Diseases under the Japanese Public Healthcare system. Pediatric ABL patients can be supported separately under The program of Medical Aid for Chronic Pediatric Diseases of Specified Categories.

2. Genetic and Molecular Basis

ABL is an autosomal recessive disorder caused by biallelic mutations in the *MTTP* gene. The estimated frequency of ABL is as rare as less than 1 in 1,000,000 [6]. Approximately 100 cases and at least 74 different *MTTP* mutations have been reported, including five (c.61+1G>C, c.1237-1G>A, c.1389del, p.I564T, p.N780Y) in four Japanese patients (Fig. 2)[7-35]. About one-third of patients were the progeny of consanguineous marriages[7]. The male-to-female sex ratio is reportedly 1:1 [7] or 3:2 [2], although both males and females should theoretically be equally affected. Genetic and clinical features of Japanese ABL patients are listed in Table 1. As the number of patients is limited, it is difficult to clarify the characteristics of Japanese cases of ABL.

MTTP is localized in the lumen of the endoplasmic reticulum of hepatocytes and intestinal epithelial cells. By transferring triglyceride (TG) and cholesterol ester to apoB, MTTP is essential for the formation of very low-density lipoproteins (VLDLs) and chylomicrons (CMs). A lack of MTTP abrogates the secretion of apoB-containing lipoproteins, which results in malabsorption of dietary fat and fat-soluble vitamins as well as accumulation of intracellular lipids in hepatocytes and intestinal epithelial cells. MTTP is a heterodimer of a large 97 kDa subunit containing 894 amino acids (encoded by *MTTP*) and a 55 kDa protein disulfide isomerase (PDI) subunit (encoded by *P4HB*)[36]. The *MTTP* gene consists of 18 coding exons. Crystal structure analysis reveals three structural

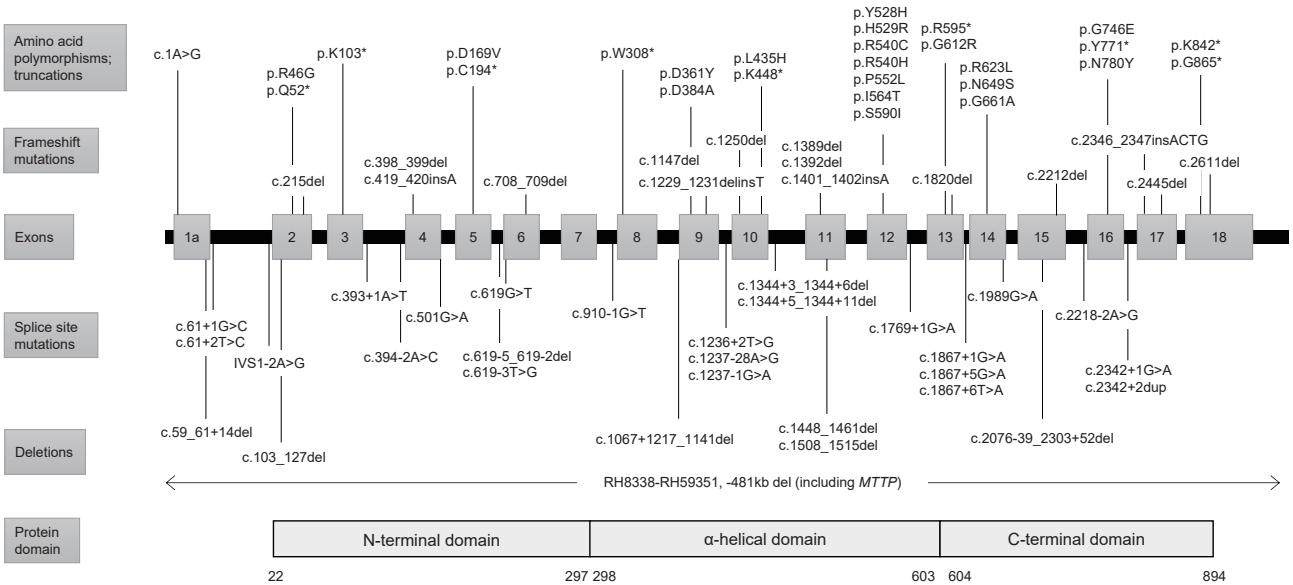

Fig. 2. Mutations in the *MTTP* gene

At least 74 *MTTP* mutations have been reported. The type of mutation may influence the severity of the disease[29]. The exon-intron structure of the *MTTP* gene encoded by exons 1a to 18 has been described[52]. Gray boxes represent exons. Lines represent the position of each mutation and polymorphism. Adapted from Zamel R, *et al.*[41], Narcisi TM *et al.*[27], and Suzuki T *et al.*[52]

domains in the large subunit of MTTP: an N-terminal β-barrel domain (amino acids 22-297), which interacts with the N-terminus of apoB; a central α-helical domain (298-603), which interacts with apoB as well as PDI; and a C-terminal domain (604-894)[7, 37-39]. The interaction between the α-helical domain and PDI is required for lipid-transfer activity, and the C-terminal domain mediates lipid-binding and lipid-transfer activity **(Fig. 2)**[37].

3. Clinical Manifestations

Gastrointestinal Symptoms (Fat Malabsorption and Failure to Thrive):

Symptoms of ABL typically develop in infancy after breastfeeding, including vomiting, steatorrhea due to fat malabsorption, and failure to thrive[2]. Patients often avoid dietary fat to relieve these gastrointestinal symptoms[2]. Endoscopic examination of the intestinal mucosa may reveal a snowy appearance, which is also called snow-white duodenum[40], a gelee blanche, or white hoar frosting **(Fig. 1B and 1C)**[7, 8].

Symptoms Related to Vitamin Deficiencies:

Chronic lipid malabsorption leads to a deficiency of fat-soluble vitamins (vitamins E, A, D, K). These vitamins require apoB-containing lipoproteins for their absorption and transport to peripheral tissues almost totally (for vitamin E and β-carotene) or partially (for vitamins A, D, and K)[7]. The resulting deficiency of these fat-soluble vitamins, particularly vitamin E and β-carotene, causes a variety of symptoms and complications, as described below.

• **Neuromuscular symptoms** develop mainly as a result of vitamin E deficiency, which is often associated with demyelination of spinocerebellar axons[2, 41, 42]. Typical symptoms include spinocerebellar ataxia, peripheral neuropathy, and myopathy[2]. Myopathy may result from both neural degeneration and an intrinsic myositis[7], which may be caused by pigment deposition due to the loss of vitamin E's anti-oxidant activity[2, 7]. The first symptom is often diminution of deep tendon reflexes as early as in the first few years or the first decade of life[7], followed by progressive abnormalities such as loss of vibratory sense, position sense, proprioception, a positive Romberg sign, spinocerebellar ataxia, dysmetria, dysarthria, wide-based spastic gait, hypesthesia, myopathy, muscular weakness, pes cavus, pes equinovarus, kyphoscoliosis, and lordosis. When left untreated, these symptoms gradually worsen and severely affect the quality of life, eventually rendering patients wheelchair-bound or bedridden. Without early treatment with vitamin E, patients may not survive past the third decade[2, 41, 43]. Mental retardation has been reported in some cases, although the evidence for causality is lacking[2, 17, 26]. There might be other

Table 1. Genetic and clinical features of Japanese patients with abetalipoproteinemia

Authors	Age	Gender	Mutation (*MTTP*)	Type	Consanguinity	Biochemical parameters (mg/dL)						
						TC	TG	LDL-C	HDL-C	cLDL-C	apoB	Vitamin E
Yang XP *et al.*[28]	29	M	c.1237-1G>A	Ho	No (Uniparental disomy)	33	0	N.D.	28	5	0	<0.1
Ohashi K *et al.*[29]	32	F	c.1389del	Ho	Yes	42	0.2	N.D.	36	6.0	0.9	<0.1
Ohashi K *et al.*[29]	27	M	c.2338A>T (p.N780Y)	Ho	Yes	34	2.6	N.D.	23	10.5	0.6	<0.1
Sakamoto O *et al.*[30]	15mo	M	c.61+1G>C c.1691T>C (p.I564T)	C. het	N.D.	46-92	10-100	N.D.	N.D.	-	<7.0	0.43

Authors	Clinical features			
	Gastrointestinal	Neuromuscular	Ophthalmological	Hematological
Yang XP *et al.*[28]	Frequent diarrhea, fat malabsorption with malnutrition, and short stature (from childhood); lipid-laden enterocytes by intestinal biopsy (29 years old).	Cerebellar and posterior spinal column dysfunction, decreased deep tendon reflexes, impaired vibratory sense and proprioception, dysmetria, ataxia, spastic gait, and positive Chaddock sign (29 years old).	Suspected loss of night vision (3 years old); descreased vision in dim light, visual field defects, and pigmentary retinal degeneration (29 years old).	Acanthocytosis
Ohashi K *et al.*[29]	Intolerance for fat-rich meals; snow-white duodenum and lipid-laden enterocytes by biopsy (32 years old).	Absent ankle and knee jerks, positive Romberg's sign (32 years old).	Fine mottling in the retina (32 years old).	Acanthocytosis (32 years old).
Ohashi K *et al.*[29]	Mild fatty liver, no history of steatorrhea	Normal	Normal	Acanthocytosis
Sakamoto O *et al.*[30]	Hepatomegaly and fatty liver, no steatorrhea.	Normal	Normal	No acanthocytosis

*Age (years or months (mo)) at molecular diagnosis; M=Males; F=Females; Ho=homozygous; C. het=compound heterozygous; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; cLDL-C, calculated LDL-C; N.D., Not described.

rare mutations due to consanguinity that could cause mental retardation[2, 17].

• **Cardiomyopathy**, supposedly due to vitamin E deficiency, may develop and can be lethal[7, 41, 43].

• **Ophthalmological symptoms** develop most likely as a consequence of deficiency of vitamin A and E. Retinitis pigmentosa is typically present by adolescence. Alterations in visual acuity, loss of night vision and color vision may appear as the first ophthalmological symptoms, followed by a gradual loss of vision, progressive scotoma, typically annular scotomas with macular sparing[2], and narrowing of the visual field, which ultimately lead to complete loss of vision. In some cases, ptosis, ophthalmoplegia, anisocoria, nystagmus, strabismus, and corneal ulcers may develop[2, 7, 41, 42].

• **Hematological abnormalities** include acanthocytosis **(Fig. 1D)**, low erythrocyte sedimentation rate (ESR), anemia, hemolysis, reticulocytosis, hyperbilirubinemia, and elevation of prothrombin time international normalized ratio (PT-INR)[41]. Acanthocytes are often observed, in more than 50% of the erythrocyte population, likely due to abnormal composition and distribution of lipids in the bilayer leaflets of the cell membrane[2, 44]. Low ESR is due to impaired rouleaux formation[7]. Anemia may be observed due to malabsorption of iron, folate, vitamin B12, and other nutrients secondary to fat malabsorption[2, 41]. Loss of vitamin E's anti-oxidant activity may cause autohemolysis, by accelerating hydroperoxidation of fatty acids[2]. Decreases in the levels of vitamin K-dependent coagulation factors (II,

Ⅶ, Ⅸ, Ⅹ) may result in bleeding tendency with elevated PT-INR[2, 41].

• **Abnormal bone metabolism and skeletal deformities** may be observed due to Vitamin D deficiency, as documented in some cases[41, 45, 46].

• **Hypothyroidism** may be observed in ABL patients, although the causality remains uncertain[39].

• **Fatty liver** may develop due to impaired secretion of VLDL. Steatohepatitis and liver cirrhosis may develop, requiring liver transplantation in some cases[9, 47].Causality needs to be carefully assessed as supplementation of medium-chain triglycerides (MCTs) may cause liver cirrhosis[2].

4. Diagnosis

ABL is typically suspected in infants who have steatorrhea, vomiting, and failure to thrive. However, the severity of the disease varies depending on the type of mutation in *MTTP*, and the diagnosis of ABL may be delayed until adulthood[2, 29]. ABL patients may be found opportunistically at health examinations in adulthood because of extremely low plasma cholesterol levels[29]. For early diagnosis and treatment of ABL, simple diagnostic criteria are warranted. Clinicians across multiple disciplines, including pediatricians, primary care physicians, neurologists, ophthalmologists and gastroenterologists, should consult lipidologists regarding further diagnostic tests when they suspect ABL.

Typical Levels of Plasma Lipids and Lipoproteins:

Plasma levels of total cholesterol (TC) in ABL patients are typically less than half normal, ranging from 20 to 50 mg/dL, with most of TC derived from high-density lipoprotein (HDL). Plasma levels of HDL are typically decreased by ~50%. The decrease in HDL may result in part from absence of phospholipid transfer from VLDL to HDL during the lipolysis of VLDL-TG. Catabolism of HDL, particularly apoE-containing HDL, may be increased, contributing to the apparently normal delivery of cholesterol to peripheral tissues in the absence of apoB-containing lipoproteins in ABL patients[7]. Plasma TG levels in ABL are typically less than 10 mg/dL[7] and do not increase after a dietary fat load[2, 7, 48]. Although the levels of TC and TG are variable in ABL patients, plasma levels of low-density lipoprotein (LDL) and apoB are consistently absent or extremely low. We searched PubMed for all previously reported cases and found that ABL patients have LDL-C <15 mg/dL and/or apoB <15 mg/dL (typically apoB <5 mg/dL)[7, 9, 28, 29], except for three cases of the mild-moderate phenotype[34]. Therefore, patients who have such levels of hypolipidemia should be suspected of having ABL.

Diagnostic Criteria:

A definitive diagnosis of ABL requires genetic testing of *MTTP*. Clinical diagnosis of ABL based on diagnostic criteria would help identify suspected cases for early diagnosis and treatment. Based on lipid levels of ABL and the clinical manifestations described above, we propose diagnostic criteria for ABL **(Table 2)**. Our criteria have been used to define the eligibility of ABL patients to receive financial support from the Japanese government as a rare and intractable disease. The entry criterion (LDL-C <15 mg/dL and/or apoB <15 mg/dL) of the criteria will also be useful for identifying suspected cases at health checkups or opportunistic blood testing (i.e., universal or opportunistic screening) for further referral to lipidology specialty clinics.

Differential Diagnosis:

Hypocholesterolemia in combination with fat malabsorption may result from the following diseases.

• **Familial hypobetalipoproteinemia 1(FHBL1; OMIM 615558)** is caused by mutations in *APOB* (mostly nonsense or frameshift) with an autosomal dominant mode of inheritance. The homozygous type of FHBL1 (Ho-FHBL1) presents with similar biochemical and clinical characteristics to ABL. Ho-FHBL1 can be differentiated from ABL only by family history. As FHBL1 is an autosomal dominant disorder, obligate heterozygote parents of Ho-FHBL1 patients have <50% of normal plasma levels of LDL-C and apoB. On the other hand, obligate heterozygote parents of ABL patients have normal plasma lipid levels. The estimated frequency of Ho-FHBL1 is as rare as less than 1 in 1,000,000, and that of heterozygote FHBL1 is 1 in 1,000 to 3,000 [42, 49].

• **Chylomicron retention disease (CMRD; OMIM 246700),** also referred to as Anderson disease, is a rare autosomal recessive disorder caused by biallelic mutations in the *SAR1B* gene encoding Sar1b (secretion-associated and Ras-related GTPase 1B). The deficiency of Sar1b, which is a prerequisite for the secretion of CMs, causes severe hypocholesterolemia as well as steatorrhea, vomiting, and failure to thrive[50]. As VLDL secretion is preserved, CMRD can be differentiated from ABL and FHBL1 by plasma lipid levels: In CMRD, plasma levels of total cholesterol, LDL-C, and HDL-cholesterol (HDL-C) are more than 50% decreased, whereas the plasma TG level is normal.

Table 2. Diagnostic criteria for ABL in Japan

A. Entry criterion
- Plasma LDL-C level ＜15 mg/dL AND/OR plasma apoB level ＜15 mg/dL.

B. Clinical manifestations
1. Gastrointestinal: fat-malabsorption related symptoms (steatorrhea, chronic diarrhea, vomiting, failure to thrive, etc.).
2. Neuromuscular: ataxia, spastic paralysis, hypoesthesia due to peripheral neuropathy, diminution of deep tendon reflexes, etc.
3. Ophthalmological: retinitis pigmentosa, loss of night vision, constriction of visual field, decreased visual acuity, etc.

C. Laboratory findings
1. Acanthocytosis

D. Differential diagnosis
Familial hypobetalipoproteinemia 1 (FHBL1)(OMIM 615558), chylomicron retention disease (Anderson disease) (OMIM 246700), hyperthyroidism.
*ABL and homozygous FHBL (Ho-FHBL) can not be distinguished only from the clinical manifestations and laboratory findings of a proband. Family history is helpful. As FHBL1 is an autosomal dominant disorder, obligate heterozygote parents of Ho-FHBL1 patients have ＜50% of normal LDL-C and apoB plasma levels. On the other hand, obligate heterozygote parents of ABL patients have normal plasma lipid levels. Plasma levels of lipids, apoB, and fat-soluble vitamin of other family members may be helpful.

E. Genetic test
Pathogenic mutations in the *MTTP* gene

<Diagnosis>

Definite ABL:
Entry criterion (A) is associated with at least one item of B or C AND exclusion of differential diagnosis (D) AND genetic diagnosis (E).

Probable ABL:
Entry criterion (A) is associated with at least two items of B or C AND exclusion of differential diagnosis (D).

5. Assessment, Treatment, and Management

The current strategy and recommendations for the treatment and management of ABL, which are adapted and modified from reviews by Hegele *et al.* and others, are summarized below[2, 6, 7, 39, 41, 42].

Assessment:

The recommended assessments for ABL patients include[2, 6, 7, 39, 41, 42]:

- **Evaluation of growth** at every visit.
- **Annual blood analysis** including lipid profiles (TC, TG, LDL-C, HDL-C, apoB, apoA-I), liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), total and direct bilirubin, alkaline phosphatase, albumin), fat-soluble vitamins (Vitamin A (retinol), β-carotene, 25-OH vitamin D, vitamin E, vitamin K), other micronutrients (vitamin B12, iron, folate), complete blood count, PT-INR, reticulocyte count, ESR, calcium, phosphate, uric acid, and thyroid stimulating hormone (TSH).
- **Ophthalmological and neurological evaluation** every 6-12 months.
- **Hepatic ultrasonography, bone mineral density measurements, echocardiography** every 3 years.

Treatment and Management:

For the treatment of ABL patients, the standard of care includes[2, 6, 7, 39, 41, 42]:

- **Restriction of fat intake** is necessary to prevent steatorrhea. Total fat intake should be restricted to less than 30% of the total energy intake, or less than 15 to 20 g per day, or even less than 5 g per day in children[2, 6, 7, 39, 42]. Increased fat in the stool may induce oxalate urolithiasis by binding dietary calcium and increasing dietary oxalate absorption. This might be prevented by providing sufficient dietary calcium, fluid intake, and reducing dietary oxalate[2].
- **Adequate calorie intake** is essential to avoid growth retardation. It should be noted that fat malabsorption may lead to malabsorption of carbohydrates proteins, and other nutrients[7]. A fat-restricted diet may mitigate such secondary malabsorption.
- **Medium-chain triglyceride (MCT) administration** can help correct malnutrition, particularly in infants, though not absolutely necessary. MCTs are absorbed and then transported in the circulation not by CMs but by albumin. Since hepatic fibrosis is a potential adverse effect of MCTs, liver enzymes should be monitored in infants who are administered MCTs, and long-term administration is better avoided[2, 7].

• **Oral essential fatty acid supplementation.** The daily requirement for essential fatty acids, e.g., up to 1 teaspoon per day of oil rich in polyunsaturated fatty acids (e.g., soybean or olive oil) is recommended[7, 39, 42].

• **High dose oral vitamin E supplementation** (100-300 IU/kg/day[6, 7, 39, 42]; 1,000-2,000 mg/day (infant), 5,000-10,000 mg/day (older children and adults)[2]; 2,400-12,000 IU/day[41]; 1IU=1mg tocopheryl acetate) delays or prevents progression of neurological complications[2, 6]. Even with such high dose vitamin E supplementation, serum vitamin E levels increase to at most 30% of the lower limit of normal serum levels of vitamin E[7, 41]. However, serum vitamin E levels may not correlate with tissue vitamin E levels[7, 39, 41]. Better methods of monitoring tissue vitamin E concentrations are awaited. Vitamin E may be administered via alternative routes (intravenous, intramuscular, etc.). However, oral supplementation is favored due to: 1) feasibility for life-long supplementation, 2) no apparent inferiority in increasing tissue vitamin E levels compared to other methods, 3) no apparent toxicity (Other routes of supplementation may induce fatty liver and other complications[42]). It should be noted that absorption of large doses of vitamin E may induce or exacerbate vitamin K deficiency[6, 7, 41]

• **High dose oral vitamin A supplementation** (100-400 IU/kg/day[39, 41, 42]) and vitamin E supplementation can prevent or arrest ophthalmological complications[2, 6, 7, 39].

• **Supplementation of vitamin D** (800-1,200 IU/day[39, 42]) should be considered in cases of vitamin D deficiency.

• **Supplementation of vitamin K** (5-35 mg/week[39, 41, 42]) should be considered in cases of vitamin K deficiency with hypothrombinemia and prolonged PT-INR. Supplementation of vitamin K will normalize its blood levels[2, 41].

• **Supplementation of iron, folate, or vitamin B12** may be necessary in the case of anemia[2, 6, 41, 42].

• **Multidisciplinary care for neurological complications** involving neurologists, physiatrists, physical therapists, occupational therapists, and speech therapists[39].

Particular caution should be taken to avoid vitamin A toxicity[2, 39, 41], which can be seen even in those who have a normal plasma vitamin A concentration[39]. To avoid toxicity, it is recommended that the target vitamin A concentration goal should be set at the lower limit of normal levels[41], and the dose of vitamin A supplementation should be titrated by monitoring blood concentrations of vitamin A and β-carotene[39, 41, 42]. Women who are pregnant or planning to conceive should receive 50% of the dose of vitamin A supplementation to avoid vitamin A toxicity with careful monitoring of the blood concentrations of vitamin A and β-carotene[39, 42]. Supplementation of vitamin A should be continued in pregnancy as its deficiency could induce lethal complications in pregnant women[39, 41].

6. Burden of Disease and Unmet Needs

If left untreated, ABL patients start manifesting systemic complications related to fat-soluble vitamin deficiencies as early as in the first decade of life, gradually developing into lethal conditions in the third decade[7, 41]. Early diagnosis and adequate supplementation of vitamin E, A, and other fat-soluble vitamins may prevent, delay, or alleviate the complications and improve the prognosis, enabling some patients to live to the eighth decade of life[7, 39]. Successful pregnancies in ABL patients have been reported [2, 7, 41]. This review and our simple diagnostic criteria aim to contribute to the early diagnosis and treatment of ABL by facilitating cooperation among various medical specialists.

However, the growth potential of patients may not be fully restored by dietary therapy[39, 42]. High dose vitamin therapy is insufficient for most patients, and even ineffective for some, to recover from vitamin deficiencies and their complications[42]. Deficiency of other lipids or nutrients, such as essential fatty acids, could also contribute to the pathogenesis of ABL. Therefore, a good understanding of its pathogenesis and keeping abreast of novel therapeutic developments are necessary. Gene therapies that correct *MTTP* deficiency in the liver and small intestine may be promising therapeutic candidates[51].

More studies are needed to unravel the pathogenesis, genotype-phenotype relationship, burden of disease, and unmet needs. Considering the paucity of patients, a nation-wide registry for a long enough period to evaluate the prognosis would help clarify these issues. To this end, a registry study for rare and intractable lipid disorders including ABL (the PROLIPID study) is ongoing in Japan.

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（資料 5）PROLIPID 研究の登録患者数およびその内訳（令和 3 年 3 月末時点）

疾患名	N	（疑い症例）
① FH ホモ接合体	17	0
② FH ヘテロ	789	12
③ 家族性 III 型高脂血症	18	
④ 高カイロミクロン血症	47	
⑤ シトステロール血症	2	
⑥ 脳腱黄色腫症	2	
⑦ LCAT 欠損症	1	
⑧ タンジール病	0	
⑨ アポ A1 欠損症	0	
⑩ 無βリポタンパク血症・低βリポタンパク血症	0	
合計	876	12
未回答	89	

（資料 6）「高コレステロール患者のつどい」（難治性家族性高コレステロール血症患者会との共催）記録

6－1.「第２回　高コレステロール患者のつどい」のご案内状

私達は、難治性家族性高コレステロール血症と診断され、継続的な治療を受けている、あるいは必要であると診断された患者で構成する患者団体で、専門の諸先生にご支援等も頂いております。（当会ホームページ　アドレス「http://ldl-apheresis.com」をご参照ください）

患者会会員は定期的に顧問の先生方より新しい治療薬等に関する情報提供等戴いていますが、多くの患者様は予防や治療に関する情報も少なく、日常生活や治療について不安を感じていらっしゃる方も多いのではないでしょうか。この度国立循環器病研究センター様他のご共催を得て「患者のつどい」を企画致しましたのでご案内申し上げます。当「つどい」が皆様の治療等に対する一助となればと考えております。

プログラムは食事療法等の留意点や最新の医療情報等を学ぶ機会とし、専門の諸先生方を囲みグループディスカッションも計画しております。治療方法その他日頃疑問に感じておられる事等がございましたら是非この機会をご利用ください。最新の治療や食事療法等を勉強することにより、気持ちが前向きになり大いに勇気づけられるのではないでしょうか。多くの皆様のご参加をお待ち致します、

尚　当案内状及び「患者つどい」へのご参加は、患者会へのご入会等をご案内するものではございませんのでご理解の程　宜しくお願い申し上げます。

難治性家族性高コレステロール血症患者会　代表　栗山　幸生

記

日時　：２０１８年9月２４日（月・祝）（世界ＦＨ　Ｄａｙ）
　　１３：３０～１６：００（受付開始１３：００）
会場　：国立循環器病研究センター　研究所新館２階　講堂
　　大阪府吹田市藤白台５丁目７番１号
参加費：無料
内容　：◎【講演】
　　a『開会ご挨拶及び病気に対する私の思い』　　患者会代表
　　d『知って得するコレステロールを下げる食事』
　　～普段の食事で気を付けられること～　　小瀬　千晶先生
　　（国立循環器病研究センター　臨床栄養部　管理栄養士）
　　e『最新のコレステロール治療』　　斯波　真理子先生
　　（国立循環器病研究センター研究所　病態代謝部部長）
　◎【グループ討議、質疑応答】
　　『グループ単位での意見交換』（各グループに医師等が参加します）
　　『質疑応答』　　進行：小倉　正恒先生
　　（国立循環器病研究センター研究所　病態代謝部室長）

主催：難治性家族性高コレステロール血症患者会
共催：国立循環器病研究センター　病態代謝部、動脈硬化・糖尿部内科、臨床栄養部
　　厚生労働省　難治性疾患政策事業　原発性高脂血症に関する調査研究班

6－2「第 2 回高コレステロール血症患者の集い」の風景

（難治性家族性高コレステロール血症患者会・原発性高脂血症調査研究班　共催）

日時：2018 年 9 月 24 日（日）13 時から 16 時

場所：国立循環器病研究センター　研究所新館　講堂

１．患者会代表による挨拶・講演の後、世界家族性高コレステロール血症基金の代表である Katherine Wilemon 氏から　ビデオレターでメッセージをいただき、和訳した内容を紹介した（下写真)。

２．国立循環器病研究センターの管理栄養士である古瀬千晶様から「知って得するコレステロールを下げる食事～普段の食事で気を付けられること～」というタイトルで講演いただいた（下写真）。

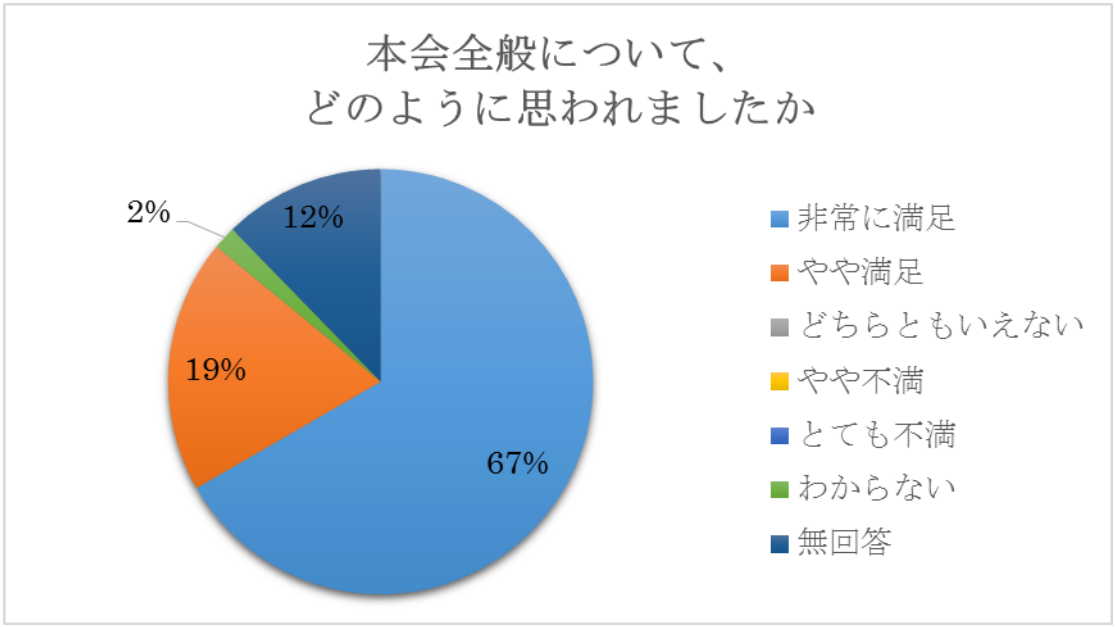
３．本研究班班長および患者会顧問医師代表である　斯波真理子から「最新のコレステロール治療」というタイトルで講演がなされた（左写真)。

４．グループ討議として各テーブルに医療従事者を配置し、患者が日常で困っていることや抱えている疑問を相談する時間を設け、またこれらの疑問を共有するために質問内容が公開され、当日出席した医療従事者が回答も共有した（右写真）。

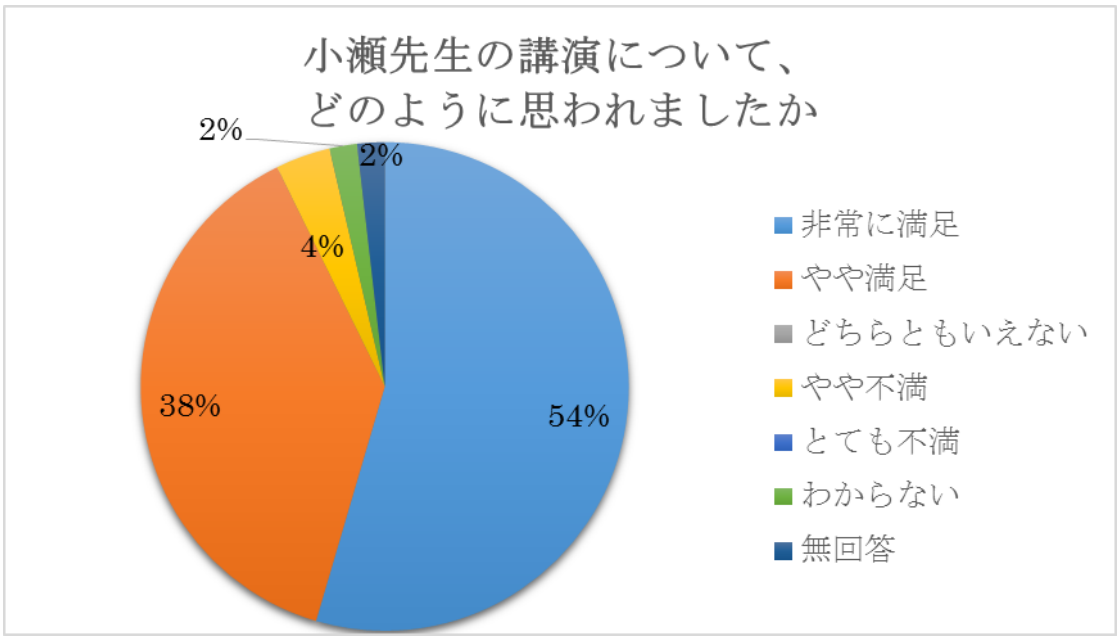
資料 6－3：「第 2 回高コレステロール血症患者の集い」のアンケート結果

（難治性家族性高コレステロール血症患者会・原発性高脂血症調査研究班　共催）
日時：2018 年 9 月 24 日（日）13 時から 16 時
場所：国立循環器病研究センター　研究所新館　講堂

１．本会全般について、どのように思われましたか

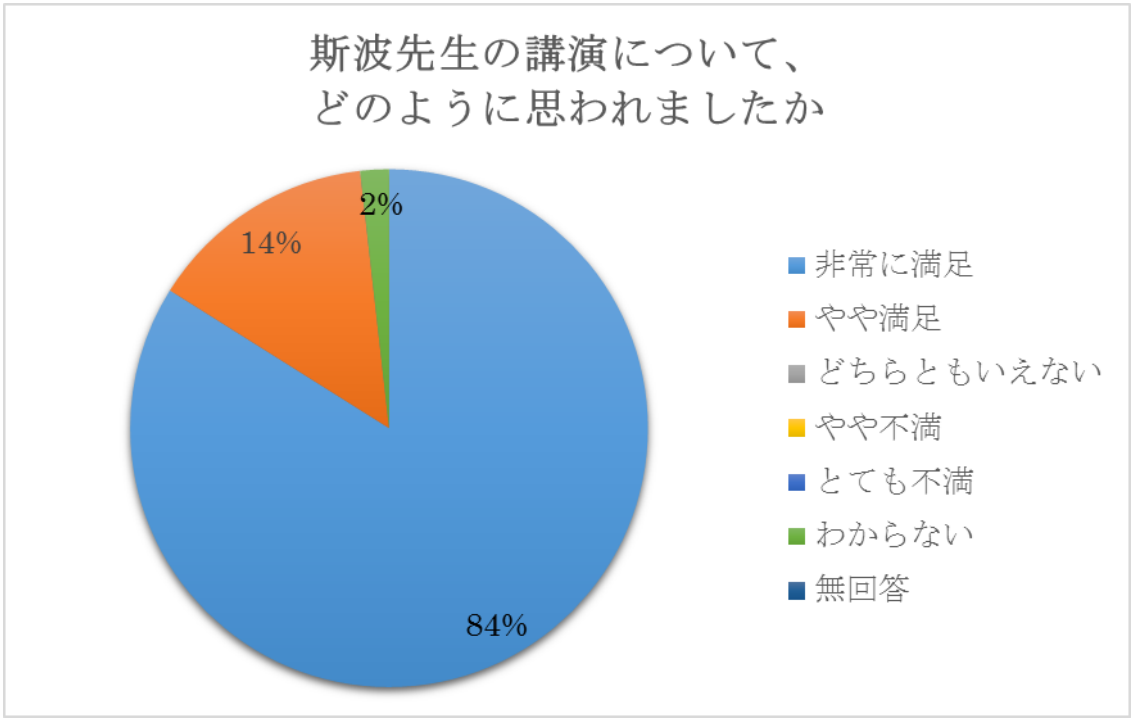


２．本会の各プログラムについて、どのように思われましたか。
２－１．講演「知って得するコレステロールを下げる食事」　小瀬千晶先生



コメント
・わかりやすく、勉強になった。
・手計法はイメージがしやすく、よかった。
・卵の量が意外でした。
・いかに食べ過ぎているかがわかりました。
・思っていた以上に野菜を多くとらなければいけないことがわかった。
・時間が短く、早口で聞き取りにくかった。
・レジュメが手元にあると良かった。
・もう少し具体例が欲しかった。

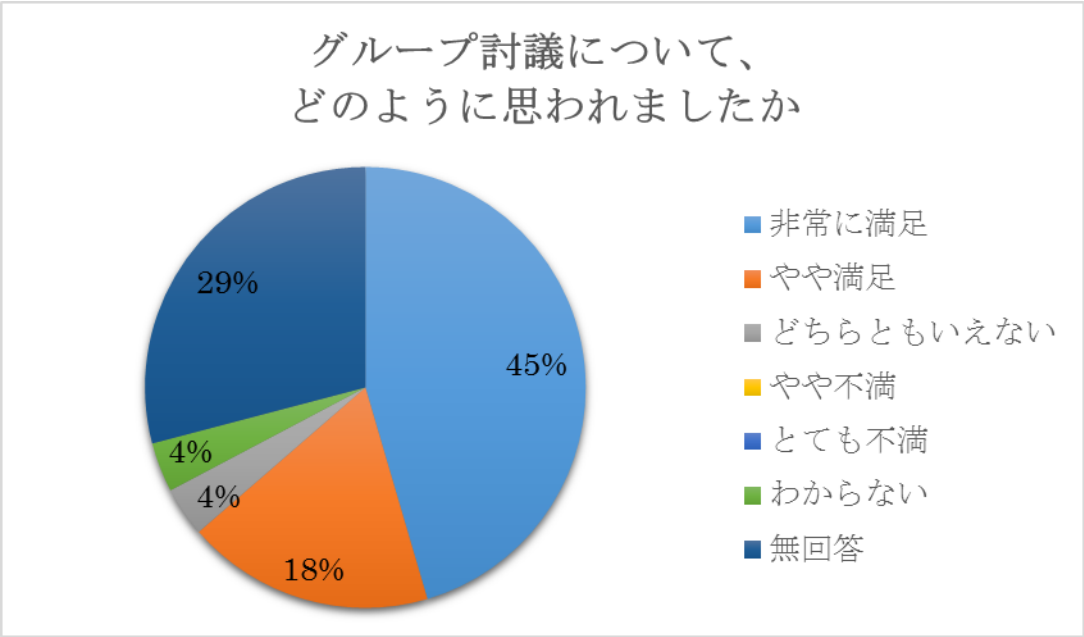
２－２．講演「最新のコレステロール治療」　斯波　真理子先生



コメント
・端的でわかりやすかった。

・最新の治療について聞けたのが良かったです。
・患者の分類別の治療法がわかりやすかった。
・根拠がきけてよかった。
・病気を前向きに考えていこうと思います。
・薬も大事だが、基本は食事と運動であることが再確認できた。
・食事療法を頑張りたくなりました。
・新しい治療法の話をもう少し詳しく聞きたかった。

２－３．グループ討議

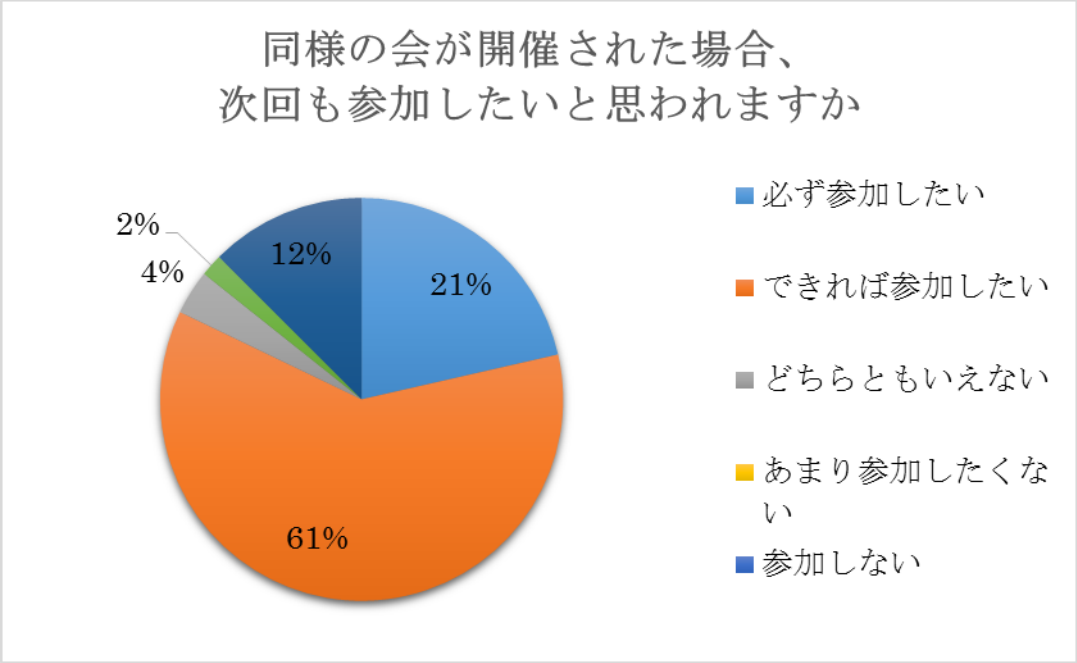


コメント
・いろいろな方がいて、病気の怖さを考えさせられた。
・いろいろな立場の方の話を具体的にきけてよかった。
・スタッフの先生方の話が分かりやすくよかった。アットホームでした。
・気軽に質問できました。
・アフェレーシス経験者の話を聞くことができてよかった。
・次回は質問を考えてきたいと思います。
・個人差がある内容なので、あまり参考にならなかった。
・時間が少ない。各テーブルのスタッフも少なく、全員の疑問に答えられていない。

３－１．運営についての要望
・レジュメ等を配布し、わかりやすくしてほしい。
・患者間の共有時間がもっとあるとよい。
・カメラのフラッシュが不快だった。

３－２．次回取り上げてほしい話題
・成長期の子供の食事内容について
・食事療法で食べて良い品、あまりとらないほうがよい品について
・食事療法、運動療法について
・油の使い方が知りたい
・適度な運動を継続するための話をききたい。
・今の不安や、よかったことなど他の患者さんの話がききたい。
・薬剤師、理学療法士など多足種の視点で講演をききたい。
・最新の治療法、知見の話（酸化 LDL など）をききたい。

４．同様の会が開催された場合、次回も参加したいと思われますか。



●感想
・多数の意思、関係者の方々にご臨席賜り心より感謝申し上げます。
・多くの方と情報共有をすることができて、充実した時間でした
・いろいろな医師の声がきけてよかった。
＊有効回答数＝56

6－4．第３回高コレステロール血症患者の集い　案内状

若くても、食事制限・運動しても

脳梗塞、心筋梗塞が

高コレステロール血症って？
共に学びませんか！

【高コレステロール血症　患者のつどい】のご案内
（参加無料）

・日時：９月１６日（月・祝）１３：３０～１６：００（受付　１３：００～）

・場所：国立循環器病研究センター

（最寄駅　ＪＲ京都線　岸辺駅　改札口を右側に徒歩　５分）

エントランス棟３階　講堂

・講演：①『家族性高コレステロール血症の光と影』

患者会会員

②『レムナントコレステロールってなに？』

国立循環器病研究センター研究所 病態代謝部 上級研究員　松木 恒太先生

③『高コレステロールを下げる最新の治療』

国立循環器病研究センター研究所 病態代謝部 部長　斯波 真理子先生

・グループ交流・相談会

グループ毎に医師が同席してご相談等にのります

【お問合せ/お申込み】（８月末締め切り）

下記の住所、またはメールアドレス宛にご連絡ください

住所：大阪府四條畷市南野1-11-25　栗山　幸生 方

難治性家族性高コレステロール血症患者会

メールアドレス：ldl.apheresis@gmail.com

（お申込みの方は、ご出席予定者のお名前をご記入ください）

※お席に限りはございますが、会場に直接ご来場いただいても結構です。

◆主催：難治性家族性高コレステロール血症患者会

共催：国立循環器病研究センター研究所

病態代謝部、糖尿病・脂質代謝内科

厚生労働省　難治性疾患政策研究事業

原発性高脂血症に関する調査研究班

◎「当日地震、台風等の警報が発令時は中止とします」

難治性家族性高コレステロール血症患者会代表　栗山　幸生

6-5：「第 3 回高コレステロール血症患者の集い」の風景

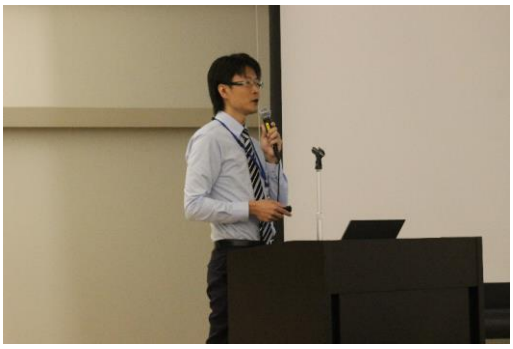
（難治性家族性高コレステロール血症患者会・原発性高脂血症調査研究班　共催）

日時：令和元年 9 月 16 日（月祝）13 時から 16 時

場所：国立循環器病研究センター　エントランス棟 3 階　講堂

患者およびその家族、班員を含む医師・医療従事者、製薬企業からの参加者合計 122 名が参加した（昨年は 106 名）。
患者会代表の挨拶に続いて、まず FH ホモ接合体の患者会員が自身の闘病生活と未来の医療に対する期待について講演した。

次に松木恒太医師（研究協力者）が患者会から要望があった「レムナントコレステロール」についての講演を実施した（右写真）。



その後、本研究班班長および患者会顧問医師代表である　斯波真理子から「高コレステロールを下げる最新の治療」というタイトルで講演がなされた（左写真）。

４．グループ討議として各テーブルに医療従事者を配置し、患者が日常で困っていることや抱えている疑問を相談する時間を設けた（右写真）。

またこれらの疑問を共有するために質問内容が公開され、当日出席した医療従事者が回答も共有した
（左写真）。

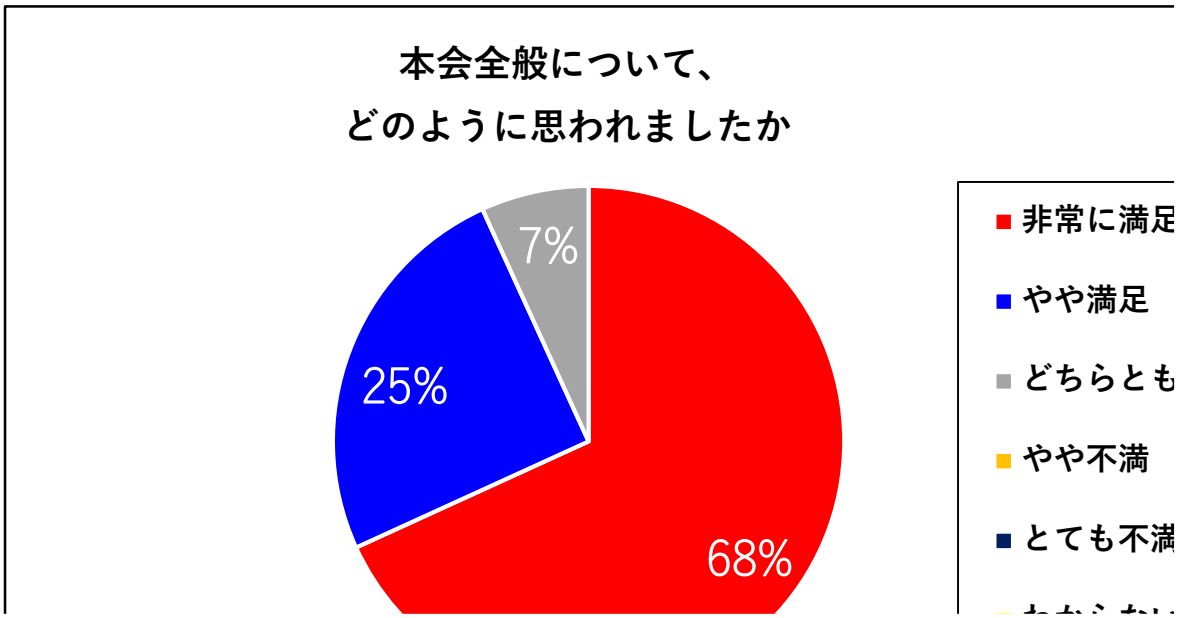
6-6.「第３回　高コレステロール血症患者の集い」のアンケート結果

難治性家族性高コレステロール血症患者会・国立循環器病研究センター研究所　病態代謝部・厚生労働省　原発性高脂血症に関する調査研究班　　共催

日時：2019 年 9 月 16 日（月・祝）　13:30～16:00

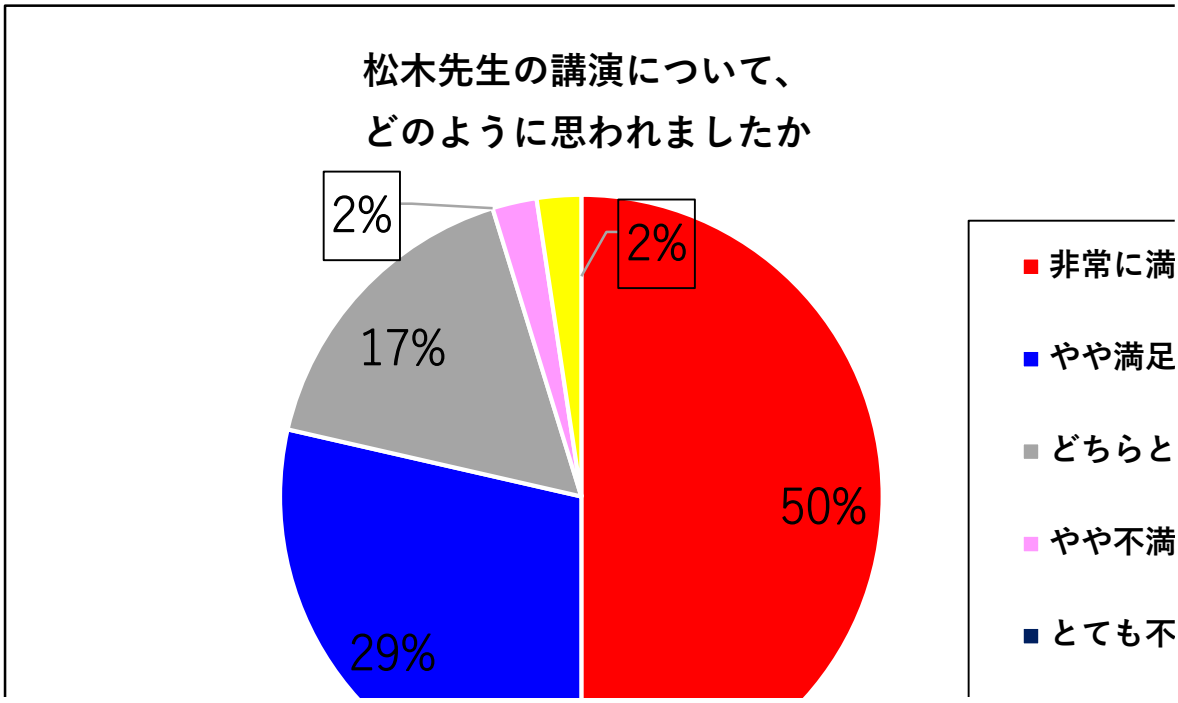
場所：国立循環器病研究センター　エントランス棟３階　講堂

１．本会全般について、どのように思われましたか。



２．本会の各プログラムについて、どのように思われましたか。

２－１．講演「レムナントコレステロールってなに？」　　松木　恒太先生

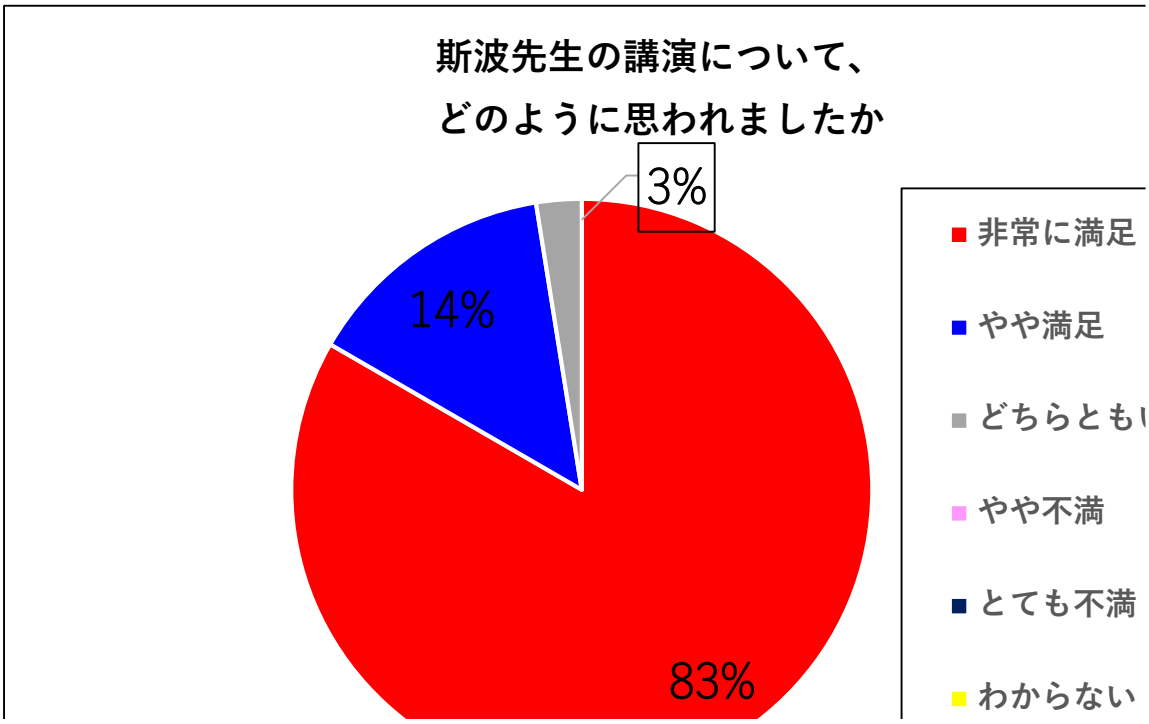


コメント

・ちょっとわかりにくい部分がありました。
・少し難しい。
・説明が解りやすかったです。
・少し難しかった。
・レムナントに関して理解が出来た。
・はじめてのレムナントという言葉が難しかった。

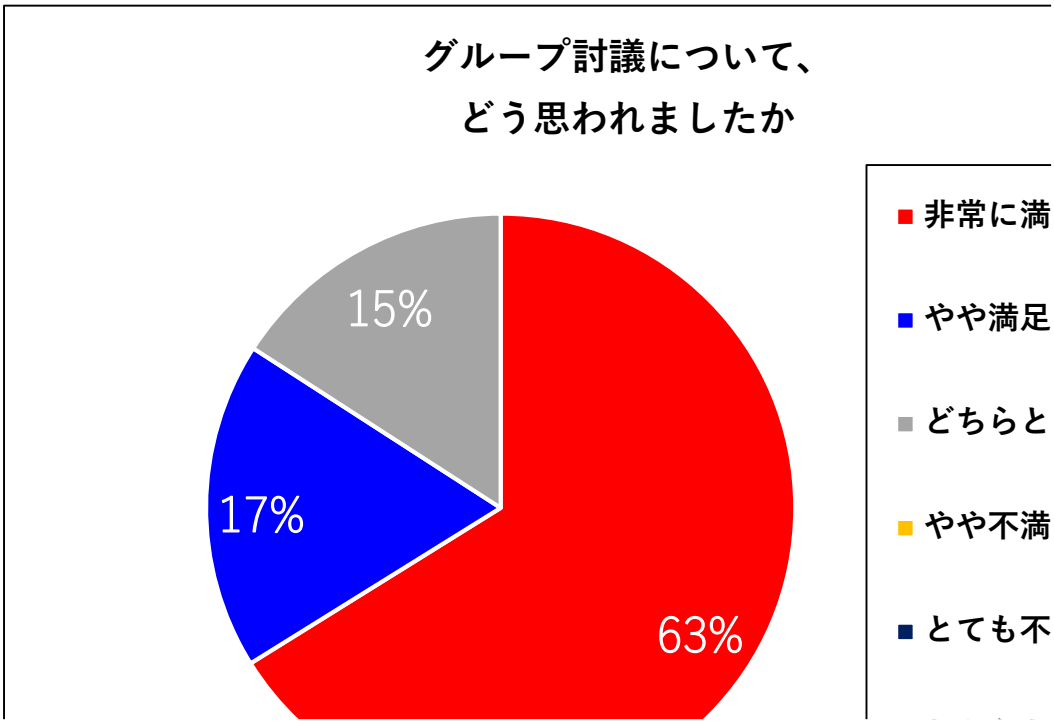
・専門用語が多いので　わかりにくい。
・むつかしかった。
・理解するのに難しすぎました。

２－２．講演「高コレステロールを下げる最新の治療」　　斯波　真理子先生



コメント
・わかりやすかった。
・もう少しくわしく知りたかった。
・説明がｇｏｏｄ。
・とてもわかりやすかったです。
・いつも言われていることばなので、改めて確認中。
・コレステロールとのつき合い方が良くわかった。
・すごい事をなさるのに驚きました。
・解り易い、希望が持てる。
・副作用の少ない、より良い薬が出来てほしいです。
・お話しが楽しくて、わかりやすかった。

２－３．グループ討議



コメント

・解りやすく、説明が聞けました。
・自分以外の患者の皆さんの事情を知ることができ、今後の考え方の参考となった。
・一つぐらいテーマがあった方が？
・近くでお話しがきけてよかった。
・時間が短いなと感じました。せっかくの機会なので・・・。

３．運営についてのご要望、次回取り上げてほしい話題等。

・各テーブルに医師がいることで、気軽に話せたことは大変良かった。しかし、同じテーブルに色んな方がいらっしゃるため、グループ討議の時間が短く感じた。参加者の属性で分けるとよかったのではないか。
・遺伝病であることについて、親としての子供等への告知などについて他の方の経験などについて伺いたい。
・患者の為にこの様な会をして頂いて、本当に有難う御座いました。
・休みにもかかわらず出席頂いた先生方、製薬会社の方　ありがとうございます。参加させて頂いて本当に良かったです。
・ディスカッションは大変良かったのですが、マイクを持って早く、小さい声で話される先生方が多く、年寄りには聞きにくかった。
・他の方の状況がわかり、先生にもていねいに回答いただけた。
・医師と栄養士が各々のテーブル席に居られるよう工夫して欲しい。

参考：有効回答数　４４件（今後のイベント実施時、「１６名」の方が案内を　希望）

（資料 7）学会承認を得た各疾患の新しい診断基準

259 レシチンコレステロールアシルトランスフェラーゼ（LCAT）欠損症の新診断基準（案）

Ａ．必須項目

１．血中 HDL コレステロール値　25 mg/dL 未満

２．コレステロールエステル比の低下（60%以下）

Ｂ．症状

１．　　蛋白尿、腎機能障害

２．　　角膜混濁

Ｃ．検査所見

血液・生化学的検査所見

(1) 貧血（ヘモグロビン値＜11 g/dl）

(2) 赤血球形態の異常（いわゆる「標的赤血球」「大小不同症」「奇形赤血球症」「口状赤血球」）

(3) 異常リポ蛋白の出現（Lp-X、大型 TG rich LDL）

眼科検査所見

コントラスト感度の正常範囲からの逸脱

Ｄ．鑑別診断

以下の疾患を鑑別する。

他の遺伝性低 HDL コレステロール血症（タンジール病、アポリポタンパク A-Ⅰ欠損症）

続発性 LCAT 欠損症（肝疾患（肝硬変・劇症肝炎）、胆道閉塞、低栄養、悪液質など蛋白合成低下を呈する病態、基礎疾患を有する自己免疫性 LCAT 欠損症）

二次性低 HDL コレステロール血症[*1]

（＊１：外科手術後、肝障害（特に肝硬変や重症肝炎、回復期を含む）、全身性炎症疾患の急性期、がん等の消耗性疾患など、過去 6 か月以内のプロブコールの内服歴、プロブコールとフィブラートの併用（プロブコール服用中止後の処方も含む））

Ｅ．遺伝学的検査

１．　　*LCAT* 遺伝子の変異

＜診断のカテゴリー＞

必須項目の 2 項目を満たした例において、以下のように判定する。

Definite：**Ｂ・Ｃ**のうち 1 項目以上を満たし，**Ｄ**の鑑別すべき疾患を除外し、**Ｅ**を満たすもの

Probable：**Ｂ・Ｃ**のうち 1 項目以上を満たし**Ｄ**の鑑別すべき疾患を除外したもの

Definite、Probable を対象とする。

260．シトステロール血症の新診断基準（案）

Ａ．症状

１．　皮膚黄色腫または腱黄色腫の存在

２．　早発性冠動脈疾患（男性 45 歳未満、女性 55 歳未満）

Ｂ．検査所見

血清シトステロール濃度１mg/dL（10μg/ml）以上

Ｃ．鑑別診断[*1]

以下の疾患を鑑別する。

家族性高コレステロール血症、脳腱黄色腫症

*1：鑑別診断が困難な場合や上記疾患とシトステロール血症の合併が否定できない場合は，*ABCG5/8* 遺伝子検査を実施する．*ABCG5/8* 遺伝子の病原性変異が確認された場合は，上記の疾患を合併していてもシトステロール血症の診断が可能である．

Ｄ．遺伝学的検査

ABCG5/8 遺伝子の変異

＜診断のカテゴリー＞

Definite：Ａ−１及びＢを満たし、Ｃの鑑別すべき疾患を除外し、Ｄを満たすもの

Probable：A-１及びＢを満たし、Ｃの鑑別すべき疾患を除外したもの
Possible：A-１、２及びＢを満たすもの
Definite、Probable を対象とする。

補足事項：
高 LDL コレステロール血症を呈したシトステロール血症では、コレステロール吸収阻害薬（エゼチミブ、コレスチミド）が著効する点が家族性高コレステロール血症と異なる。

261．タンジール病の新診断基準（案）

Ａ．必須項目
１．　血清 HDL コレステロールが 25 mg/dL 未満
２．　血中アポ A-Ⅰ濃度 20 mg/dL 未満
Ｂ．症状
１．オレンジ色の特徴的な扁桃腫大
２．肝腫大または脾腫
３．角膜混濁
４．末梢神経障害
５．心血管病変
Ｃ．　鑑別診断
以下の疾患を鑑別する。
LCAT 欠損症、アポリポ蛋白質 A-I 欠損症、二次性低 HDL コレステロール血症[*1]
（*１：外科手術後、肝障害（特に肝硬変や重症肝炎、回復期を含む）、全身性炎症疾患の急性期、がん等の消耗性疾患など、過去 6 か月以内のプロブコールの内服歴、プロブコールとフィブラートの併用（プロブコール服用中止後の処方も含む））
Ｄ．遺伝子検査
ABCA1 遺伝子変異の同定
＜診断のカテゴリー＞
Definite: 必須項目の 2 項目を全て満たす例のうち、Ｂの１項目以上を満たし、Ｃの鑑別すべき疾患を除外し、D を満たすもの
Probable: 必須項目の 2 項目を全て満たす例のうち、Ｂの２項目以上を満たし、Ｃの鑑別すべき疾患を除外したもの
Definite、Probable を対象とする。

補足事項：鑑別診断が困難な場合は，*ABCA1* 遺伝子検査を実施する．*ABCA1* 遺伝子の病原性変異が確認された場合は診断が可能である．

262．原発性高カイロミクロン血症の新診断基準（案）

Ａ．必須条件：１および２を認め、鑑別診断（下記Ｅ）が除外される。
１．血清トリグリセリド値　1,000 mg/dL以上（空腹時採血(食後 12 時間以上)）
２．カイロミクロンの証明（血清静置試験[*1]、超遠心法、電気泳動法、HPLC法による）
（*1: 血清を４℃で 24～48 時間静置した後に、血清の上清にクリーム層を認める）
Ｂ．症状 主症状：１～４、副症状：５、６

１．繰り返す腹痛かつ/または急性膵炎
２．発疹性黄色腫
３．網膜脂血症の存在
４．肝腫大かつ/または脾腫大
５．**呼吸困難**
６．神経精神症状（認知症、うつ病、記憶障害）

Ｃ．検査所見

１．LPL活性・蛋白の欠損あるいは著明な低下（正常の 10%以下）。
（ヘパリン静脈注射後血漿、脂肪組織生検検体、単球由来マクロファージ。）
２．アポリポ蛋白C-IIの欠損あるいは著明な低下（正常の 10%以下）。
３．アポリポ蛋白A5 の欠損あるいは著明な低下（正常の 10%以下）。
４．LPL、ヘパリン、アポリポ蛋白C-II、GPIHBP1 に対する自己抗体の証明。

Ｄ．遺伝学的検査

１．　リポ蛋白リパーゼ遺伝子の変異
２．　アポリポタンパクC-ＩＩ遺伝子の変異
３．　*GPIHBP1* 遺伝子の変異
４．　*LMF1* 遺伝子の変異
５．　アポリポタンパクA-V遺伝子の変異

Ｅ．鑑別診断

１．III型高脂血症
２．家族性複合型高脂血症（FCHL）
３．二次性高脂血症（アルコール多飲、ネフローゼ症候群、神経性食思不振症、　　妊娠、糖尿病、リポジストロフィー、ウェーバー・クリスチャン（Weber-　Christian）病、甲状腺機能低下症、先端巨大症、クッシング症候群、ネルソン　　症候群、薬剤（エストロゲン、ステロイド、利尿薬、βブロッカー、SSRIなど抗　　精神病薬、痙攣治療薬、HIV治療薬、免疫抑制剤など）、その他高TG血症を来す　　疾患（多発性骨髄腫、全身性エリテマトーデス（SLE）、悪性リンパ腫、サルコ　　イドーシスなど））

＜診断のカテゴリー＞

Definite（確定診断）：必須条件に、**Ｃ**あるいは**Ｄ**のいずれかの異常（疾患関連あり）が確認された場合。
Probable（臨床的診断）：必須条件に、**Ｂ**の主症状のいずれかを認める場合。
Possible（疑い例）：必須条件のみ、あるいは、必須条件に**Ｂ**の副症状を認める場合。
Definite、Probableを対象とする。

264.　無 β リポタンパク血症の新診断基準（案）

Ａ．必須項目

血中 LDL コレステロール 15 mg/dL 未満（Friedewald 式による）または血中アポリポ蛋白 B 15 mg/dL 未満

Ｂ．症状

１．消化器症状（脂肪吸収障害による脂肪便、慢性下痢、嘔吐、成長障害など）
２．神経症状（運動失調,痙性麻痺,末梢神経障害による知覚低下や腱反射消失など）
３．網膜色素変性症（夜盲,視野狭窄,視力低下など）

Ｃ．検査所見

１．有棘赤血球の存在

Ｄ．鑑別診断

以下の疾患を鑑別する。
家族性低 β リポタンパク血症,カイロミクロン停滞病（アンダーソン（Anderson）病）,甲状腺機能亢進症
※家族性低βリポタンパク血症ホモ接合体との確実な鑑別は,本人のデータのみでは困難であり遺伝子変異

の同定を要するが,以下の所見を参考に鑑別可能である.
・ホモ接合体発端者の第1度近親者のコレステロール低値
本症は常染色体潜性遺伝（**劣性遺伝**）でありホモ接合体発端者の第1度近親者のヘテロ接合体に軽度低脂血症を認めないが,家族性低 β リポタンパク血症（FHBL）1は常染色体共顕性遺伝（**共優性遺伝**）であるため,ホモ接合体発端者の第1度近親者のヘテロ接合体に低脂血症を認める.両親・兄弟の血清脂質・血中アポB濃度、脂溶性ビタミン濃度の測定も参考になる.

Ｅ．遺伝学的検査

*MTTP*遺伝子の変異

＜診断のカテゴリー＞

Definite：必須項目を満たす例で，**Ｂ・Ｃ**の計４項目のうちいずれか１項目以上を満たし、**Ｄ**の鑑別すべき疾患を除外し,**Ｅ**を満たすもの.

Probable：必須項目を満たす例で，**Ｂ・Ｃ**の計４項目のうちいずれか２項目以上を満たし,**Ｄ**の鑑別すべき疾患を除外したもの.

Definite、Probableを対象とする。

264類縁　家族性低βリポタンパク血症（FHBL）1(ホモ接合体)の診断基準（案）

Ａ．必須項目

血中LDL-コレステロール15 mg/dL未満（Friedewald式による）または血中アポリポ蛋白B 15 mg/dL未満

Ｂ．症状

１．消化器症状（脂肪吸収障害による脂肪便、慢性下痢、嘔吐、成長障害など）

２．神経症状（運動失調、痙性麻痺、末梢神経障害による知覚低下や腱反射消失など）

３．網膜色素変性症（夜盲、視野狭窄、視力低下など）

Ｃ．検査所見

１．有棘赤血球の存在

Ｄ．鑑別診断

以下の疾患を鑑別する。

無βリポタンパク血症、カイロミクロン停滞病（アンダーソン（Anderson）病)、甲状腺機能亢進症

※無βリポタンパク血症との確実な鑑別は、本人のデータのみでは困難であり遺伝子変異の同定を要するが、以下の所見を参考に鑑別可能である。

・ホモ接合体発端者の第1度近親者のコレステロール低値

家族性低β リポタンパク血症（FHBL）1は常染色体共顕性遺伝（**共優性遺伝**）であるため、ホモ接合体発端者の第1度近親者のヘテロ接合体に低脂血症を認めるが、無βリポタンパク血症は常染色体潜性遺伝（**劣性遺伝**）であり、ホモ接合体発端者の第1度近親者のヘテロ接合体に軽度低脂血症を認めない。両親・兄弟の血清脂質・血中アポB濃度、脂溶性ビタミン濃度の測定も参考になる。

Ｅ．遺伝学的検査

*APOB*遺伝子の変異

＜診断のカテゴリー＞

Definite：必須項目を満たす例で、**Ｂ・Ｃ**の計４項目のうちいずれか１項目以上を満たし、**Ｄ**の鑑別すべき疾患を除外し、**Ｅ**を満たすもの。

Probable：必須項目を満たす例で、**Ｂ・Ｃ**の計４項目のうちいずれか２項目以上を満たし、**Ｄ**の鑑別すべき疾患を除外したもの。

Definite、Probable を対象とする。

新規：アポリポタンパクA-Ⅰ欠損症　-診断基準（案）-

○概要

１．　概要

高比重リポ蛋白（high density lipoprotein: HDL）の主要構成アポ蛋白である、アポリポタンパク A-Ⅰ（アポ A-Ⅰ）の欠損、異常により生ずる病態である。アポ A-Ⅰとともにアポ C-Ⅲ、アポ A-Ⅴを欠損する場合もある。血清 HDL コレステロール、アポ A-Ⅰ濃度が著しい低値を示す。タンジール病で認められるオレンジ色の扁桃肥大や、LCAT 欠損症で認められるコレステロールエステル比の低下や腎障害は、認められない。早期に冠動脈疾患を合併する危険性があり、動脈硬化性疾患の早期診断と危険因子の管理が重要である。アポ A-1 の変異の一部にアミロイドーシスの合併が報告されているが、アミロイドーシスが主要な病態であり HDL 低値を伴わない場合は、全身性アミロイドーシス（指定難病 28）にて取り扱う。

２．　原因

血中の遊離アポ A-Ⅰが ABCA1 に結合することが、HDL 形成の第一段階である。ABCA1 は細胞内からコレステロール搬出する機能を持ち、アポ A-Ⅰと結合することでコレステロールを付加して preβ-HDL となる。本症ではアポ A-1 の欠損または機能喪失により HDL が産生されないため、血清 HDL コレステロール、アポ A-Ⅰ濃度が著しい低値となる。

３．　症状

角膜混濁

　角膜混濁がしばしば認められる

皮膚病変

　黄色腫がしばしば認められる

心血管病変

　冠動脈疾患の合併が多く認められる

血清脂質検査

　著明な低 HDL-C 血症（HDL- C＜25mg/dL）で、血清アポ A-Ⅰは 20 mg/dl 未満

　アポ A-Ⅰ含有血清 HDL の欠損、正常～低下したトリグリセライド，正常レベルの LDL-C を認める

４．　治療法

遺伝子治療などの根本的な治療はなく、合併する動脈硬化性疾患の予防・治療が中心となる。糖尿病（耐糖能異常）を合併することが多くその治療が重要であり、また高血圧、喫煙などの危険因子の管理も重要である。

５．　予後

冠動脈疾患などの動脈硬化性疾患により大きく異なる。狭心症、心筋梗塞などの発症に留意し、定期的な動脈硬化性疾患のチェックが重要である。

○要件の判定に必要な事項

１．　患者数

100 人未満（わが国では 9 例が報告されている）

２．　発病の機構

不明（アポ A－1／C－III／A－Ⅳ遺伝子変異が関与する。）

３．　効果的な治療方法

未確立（併存する動脈硬化性疾患危険因子の治療が重要である。）

４．　長期の療養

必要（遺伝子異常を背景とし、代謝異常が生涯持続するため。）

５．　診断基準

あり（研究班作成の診断基準）

６．　重症度分類

先天性代謝異常症の重症度評価で、中等症以上を対象とする。

○情報提供元

「原発性高脂血症に関する調査研究班」

研究代表者　国立循環器病研究センター研究所　病態代謝部　部長　斯波真理子

研究分担者　国立大学法人大阪大学　循環器内科　小関正博

アポリポタンパク A-Ⅰ欠損症の診断基準（案）

Ａ．必須項目

1. 血清 HDL コレステロールが 25 mg/dL 未満

2. 血中アポ A-Ⅰが 20 mg/dL 未満

Ｂ．症状

1. 角膜混濁
2. 黄色腫
3. 早発性冠動脈疾患（男性 55 歳未満、女性 65 歳未満）

Ｃ．鑑別診断

以下の疾患を除外できる。

タンジール病、LCAT 欠損症、二次性低 HDL コレステロール血症[*1]

（＊１：外科手術後、肝障害（特に肝硬変や重症肝炎、回復期を含む）、全身性炎症疾患の急性期、がん等の消耗性疾患など、過去 6 か月以内のプロブコールの内服歴、プロブコールとフィブラートの併用（プロブコール服用中止後の処方も含む））

Ｄ．遺伝子検査

APOA1 遺伝子変異の同定

＜診断のカテゴリー＞

Definite：Ａの必須項目を満たす例で、Ｂの１項目以上を満たし、Ｃの鑑別すべき疾患を除外し、Ｄを満たすもの。

Probable：Ａの必須項目を満たす例で、Ｂの１項目以上を満たし、Ｃの鑑別すべき疾患を除外したもの。

Definite、Probable を対象とする。

（資料 8）成人指定難病と小児慢性特定疾病の該当疾患の違い

表１．「難病の患者に対する医療等に関する法律」にもとづく 2015 年１月 1 日および　7 月 1 日施行の厚生労働省「指定難病」のうち原発性高脂血症該当疾患

告示番号	病名
79	家族性高コレステロール血症（ホモ接合体）
259	レシチンコレステロールアシルトランスフェラーゼ欠損症
260	シトステロール血症
261	タンジール病
262	原発性高カイロミクロン血症
263	脳腱黄色腫症
264	無βリポ蛋白血症

表２．2015 年施行「児童福祉法の一部を改正する法律」による厚生労働省　「小児慢性特定疾病」のうち原発性高脂血症該当疾患（大分類 12 脂質代謝異常）

小分類番号	病名
129	原発性高カイロミクロン血症
130	家族性高コレステロール血症
131	家族性複合型高脂血症
132	無βリポ蛋白血症
133	高比重リポタンパク（HDL）欠乏症
134	129 から 133 まで掲げるもののほか、脂質代謝異常症