表1 新生児マススクリーニング対象となる有機酸代謝異常症（2次対象含む）（次頁）

疾患名	遺伝子	日本における頻度	遺伝子診断
メチルマロン酸血症	*MUT*, *MMMA*, *MMMB*, *MMADHC*, *LMBRD1*, *MMACHC*	11万人に1人	オーファンネット* 一部研究室（東北大学）
プロピオン酸血症	*PCCA*, *PCCB*	4.5万人に1人	オーファンネット
イソ吉草血症	*IVD*	65万人に1人	研究室（東北大学）
複合カルボキシラーゼ欠損症	*HLCS*, *BTD*	65万人に1人	オーファンネット*
HMG-CoAリアーゼ欠損症	*HMGCL*	−	研究室（岐阜大学）
メチルクロトニルグリシン尿症	*MCCA*, *MCCB*	15万人に1人	
グルタル酸血症1型	*GCDH*	28万人に1人	
グルタル酸血症2型	*ETFDH*, *ETFA*, *ETFB*	33万人に1人	研究室（島根大学）
β-ケトチオラーゼ欠損症	*ACAT1*	−	オーファンネット

上記疾患は全て常染色体劣性遺伝．1疾患に複数の遺伝子が存在するが，そのうちのどれかの遺伝子の異常によって生じる．メチルマロン酸血症の多くは*MUT*遺伝子異常である．cblF（*LMBRD1*），cblC（*MMACHC*）の異常，一部のcblD（*MMADHC*）の異常ではホモシスチン尿を伴う．

日本における頻度：1997～2012年のタンデムマス・スクリーニングパイロット研究で約195万人の解析によった[1]．

"−"：上記195万人のスクリーニングで同定されていないことを示す．HMG-CoAリアーゼ欠損症は日本で9症例，β-ケトチオラーゼ欠損症は日本で8家系11例が過去に報告されている．

"オーファンネット"：NPO法人オーファンネットジャパンで依頼可能．

＊：解析が可能な遺伝子が限られていることを示す．

る症例もある．

c）慢性進行型

乳幼児期から神経症状や発達遅滞，退行が現れ，徐々に進行する．特に感染などを契機に症状の悪化がみられる．

その他の臨床像としては，発作時の特異的な汗臭い体臭，尿臭（イソ吉草血症など），皮膚粘膜移行部の難治性湿疹（マルチプルカルボキシラーゼ欠損症）や尿路結石（原発性高シュウ酸尿症など），黒色尿（アルカプトン尿症），溶血性貧血（5-オキソプロリン尿症など）などをきたすものがある．奇形は一般に少ないが，多発性嚢胞腎（グルタル酸血症2型）など疾患特異的にみられるものがある．　重篤な発作の後遺症として退行や筋緊張低下，ジストニア，ジスキネジア，舞踏病様症状，小脳失調症状などの症状を呈することもある．

頻度

おもな疾患の日本におけるタンデムマス・スクリーニングパイロット研究での頻度[2]は表1に示した．マススクリーニング対象となっていない疾患の頻度は一般に低い．

治療，予後

疾患によって異なるので，成書を参照のこと．原則は急性期の治療として，①蛋白摂取をやめ，早期十分量のブドウ糖投与，②高アンモニア血症に対する血液浄化療法，③カルニチン，ビタミンカクテル療法，④状態安定すれば早期に蛋白摂取開始（48時間以内）．

慢性期治療として，①食事療法　蛋白制限（特殊ミルク使用），②カルニチン投与，③シックデイの早期受診，早期ブドウ糖輸液，である．

プロピオン酸血症，メチルマロン酸血症では，重篤なアシドーシス発作が何度も反復する場合などは生体肝移植が考慮される場合がある．

遺伝

遺伝形式：多くは常染色体劣性遺伝を示す

同胞再発率：常染色体劣性遺伝の疾患では25％

遺伝学的検査

多くの疾患で遺伝子診断が行われている．遺伝子検査は新生児マススクリーニング1次対象疾患においては保険点数が設定されているが，コマーシャルラボでは行われていない．2014年現在，新生児マススクリーニング対象疾患の現状は表1の通りである．NPO法人オーファンネットジャパンを通して解析が依頼できる疾患もあるが，多くの疾患は依然研究者レベルで行われているのが実情である．

遺伝カウンセリングのポイント

①疾患によって予後も異なり，遺伝カウンセリングの内容も異なってくる．したがって正確な発端者の診断が重要である．表1に示した疾患は全て常染色体劣性遺伝であるが，有機酸代謝異常症のなかにはX連鎖遺伝形式のものも存在する．

②正確な遺伝カウンセリングにおいては両親が保因者かどうかの判定も重要であり，まれに一方が*de novo*変異と考えられ，次子の罹患の可能性がほとんどない場合もありうる．そのため両親の遺伝子解析がなされているほうがよい．

③タンデムマスによる新生児マススクリーニングの対象疾患であっても，メチルクロトニルグリシン尿症のように臨床症状をきたしにくい疾患も存在する．必要以上に家族に心配をさせないよう，基本的な生活指導でのフォローを行う．

④疾患によって，また遺伝子変異によって重症度が異なるため，個別の家系においての検討が必要となる．p.Y435C変異をもつ軽症プロピオン酸血症のように，生化学的にはプロピオン酸血症であっても，臨床像をほとんど示さないことがわかってきているものも存在する．また同じ遺伝子変異をもっていても乳幼児期発症型の次子が新生児発症する可能性もあり，病型を遺伝子変異から推定することは難しい場合が多い．

⑤一般に発端者の遺伝子異常がわかっていれば，遺伝子解析による出生前診断は可能である．疾患によっては出生前診断の適応とならないと考えられる疾患も存在する．出生前診断により診断がついていることで，十分な管理により新生児期発症を防ぐ，もしくは軽症化することができる可能性もある．

（深尾敏幸）

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23 脂肪酸代謝異常症

疾患の概要

病態

β酸化系は，炭水化物等からのエネルギー供給が低下したときに作動するエネルギー産生経路である．脂肪酸代謝異常症は，ミトコンドリアβ酸化系(以下，β酸化系)にかかわる酵素異常によって起こる．したがって臨床症状は，基本的にエネルギー産生不全である[1,2]．

診断は，タンデムマスによる血中アシルカルニチン分析で発見されることが多い．一部はGS/MSによる尿中有機的分析で生化学診断される．確定診断は遺伝子診断によることが多い．

a) 臨床病型

臨床病型は表1に示すように3つに大別される．

①最重症型：乳児期早期から，低血糖，肝不全，高アンモニア血症，心筋症で発症し，早期に死亡する．

②中間型：乳幼児期から，感染などを契機に低血糖，肝障害，急性脳症などの発作を起こし，乳幼児突然死のような形態で発症する．

③骨格筋型：年長児～成人期から骨格筋症状(筋緊張低下，筋肉痛，ミオパチーなど)のエピソードを繰り返すようになる．知能は正常で致死率も低い．

b) β酸化系の分類

β酸化系は表2に示すように4つに大別され，それぞれに酵素欠損症が知られている．

①カルニチン回路：長鎖脂肪酸はカルニチンと結合して細胞膜，ミトコンドリア外膜，内膜を通過して，最終的にβ酸化の基質であるアシル-CoAとして供給される．カルニチントランスポーター(OCTN2)，カルニチンパルミトイルトランスフェラーゼ-I(CPT1)と-II(CPT2)，およびカルニチン・アシルカルニチントランスロカーゼ(CACT)などがある．CPT2反応で遊離するカルニチンは再利用される．

②長鎖脂肪酸β酸化回路：内膜に結合したβ酸化酵素群によって長鎖アシル-CoAが炭素鎖C12付近まで短くされる．極長鎖アシル-CoA脱水素酵素(VLCAD)，ミトコンドリア三頭酵素(TFP)が働く．TFPはβ酸化回路の第2，第3，第4段階を代謝する三頭酵素である．

③中鎖脂肪酸β酸化回路：ミトコンドリア・マトリックスに局在するβ酸化回路である．中鎖アシル-CoAや，カルニチン回路を介さずに直接ミトコンドリアに入ってきた中鎖脂肪酸は，このβ酸化回路で代謝される．中鎖および短鎖アシル-CoA脱水素酵素(MCADおよびSCAD)，エノイル-CoAヒドラターゼ，3-ヒドロキシアシル-CoA脱水素酵

表1 脂肪酸代謝異常の臨床病型

病型	発症時期	臨床所見	死亡率
最重症型(新生児型)	新生児～乳児早期	乳児期死亡 低血糖，心筋症	+++
中間型(若年型)	乳幼児期	間欠的発作 筋緊張低下，急性脳症，突然死(SIDS様)	++
骨格筋型(遅発型)	学童～成人	時々エピソード， 全身倦怠，筋肉痛，ミオパチー，肝機能障害	±

SIDS：sudden infant death syndrome(乳幼児突然死症候群)

素(SCHAD)，および中鎖および短鎖型3-ケトチオラーゼなどがある．

④電子伝達系：電子伝達フラビン蛋白(ETF)に結合したフラビンアデニンジヌクレオチド(FAD)は，β酸化回路のアシル-CoA脱水素酵素によって還元型フラビンアデニンジヌクレオチド($FADH_2$)に還元され，さらにETF脱水素酵素(ETFDH)を介して呼吸鎖に電子が伝達され，呼吸鎖でアデノシン三リン酸(ATP)が産生される．

頻度

β酸化異常症のわが国での頻度は，タンデムマスによるマススクリーニングのパイロットスタディによると，全体で3.4万人に1人と計算されている[3]．疾患ごとの内訳は表1に示している．しかし，成人発症型のような軽症型，あるいはCPT2欠損症などのように新生児マススクリーニングで見逃されやすい疾患もあるので，実際の頻度はこれよりも高いと思われる．

治療と予後

β酸化異常症の治療は，エネルギー産生不全に陥らせないことである．最重症型のように治療の無効な症例もある．一般的な治療を以下にあげる．

a) 生活指導

長時間飢餓を避ける．特に乳児期は哺乳間隔を3～6時間以上あけないように指導する．また疲れた日(シックデイ)，感染，発熱などのときは，早めにブドウ糖輸液を受けるよう指導する．

b) カルニチン投与

一部の疾患(全身性カルニチン欠乏症など)で奏効するが，β酸化異常症に対するカルニチン投与につ

表2 主な脂肪酸代謝異常症の遺伝形式と頻度

疾患	欠損酵素(遺伝子)	染色体座位	遺伝形式	頻度
カルニチン回路				
カルニチン欠乏症	*OCTN2*	5q31.1	常染色体劣性	28万人に1人
CPT1欠損症	*CPT1*	11q13.3	常染色体劣性	39万人に1人
CPT2欠損症	*CPT2*	1q32.3	常染色体劣性	28万人に1人
CACT欠損症	*SLC25A20*	3q21.31	常染色体劣性	(3例)*
長鎖脂肪酸β酸化回路				
VLCAD欠損症	*ACADVL*	17p13.1	常染色体劣性	16万人に1人
TFP欠損症	*HADHA* *HADHB*	2p23.3 2p23.3	常染色体劣性 常染色体劣性	28万人に1人
中鎖脂肪酸β酸化回路				
MCAD欠損症	*ACADM*	1p31.1	常染色体劣性	11万人に1人
SCAD欠損症	*ACADS*	12p24.31	常染色体劣性	(4～10万人に1人)**
SCHAD欠損症	*SCHAD*	4p25	常染色体劣性	(1例)***
電子伝達系				
グルタル酸血症II型	*ETFA*	15q24.2	常染色体劣性	33万人に1人
	ETFB	19q13.41	常染色体劣性	
	ETFDH	4q32.1	常染色体劣性	

頻度はタンデムマス・スクリーニングのパイロットスタディの結果．(195万人)
*：これまでのわが国の報告例．
**：海外の報告より引用．新生児マススクリーニングで発見されるSCAD欠損症はほとんどが無症状であり，わが国では対象としていないため，データなし．
***：後方視的に診断された症例であり，本症はマススクリーニングで発見できるとは限らない．

いては議論がある．CPT1 欠損症では不要である．

c）食事療法

長鎖脂肪酸代謝異常症に対する MCT ミルク / オイルはよく行われ理にかなっている．また高炭水化物 / 低脂肪食が推奨されるが，アミノ酸・有機酸代謝異常症のような厳格な指導は不要である．

d）その他

ビタミン（リボフラビン，CoQ10，あるいは脂質異常症治療薬のベザフィブラートの奏効例[4]も報告されている．

遺伝

遺伝形式：常染色体劣性遺伝
同胞再発率：25 %

表 1 に示すように，これまで知られているβ酸化異常症は全て常染色体劣性遺伝である．

遺伝学的検査

現在知られている疾患の遺伝子検査は全て可能である．日本人患者ではほとんどの疾患がヘテロジーナスである．遺伝子変異のホットスポットは，日本人 MCAD 欠損症の c449-4 塩基欠失（約 45 % のアレル）がある．また日本人 CPT2 欠損症患者のコモン変異として c.1249T>A が有名である．

遺伝カウンセリングのポイント

①β酸化異常症は新生児マススクリーニングの対象になったが，疾患によっては見逃される症例もある．
②常染色体劣性遺伝形式なので次子の再発率は 4 人に 1 人である．
③治療予後は，遺伝子型に規定される面があり，適切な治療や生活上の注意で発症を防ぐことの可能な症例もあるが，治療効果には限界がある例もある．
④最重症型の家族歴のある場合（乳児期早期死亡など），前子の遺伝子型がわかっていれば，出生前診断のオプションはある．妊娠 16 週頃に羊水穿刺（約 5 ～ 10 mL）して，遠心した沈渣の DNA 解析を行えば数日以内に結果が判明する．羊水上清の分析も有用な疾患もある[5]．

（山口清次）

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24 糖原病(グリコーゲン代謝異常症)

疾患の概要

病態

グリコーゲンは主に筋肉と肝臓に貯蔵され，必要に応じてグリコーゲンが分解(解糖)し利用される．解糖の目的は，筋肉と肝臓では異なり(表 1)，筋肉では筋収縮に利用するエネルギー源としてのATP供給であり，肝臓では血糖維持のためのグルコース供給という役割をしている[1]．

糖原病(グリコーゲン代謝異常症)ではグリコーゲンの利用目的が障害されるという病態から，筋型糖原病，肝型糖原病，肝筋型糖原病の主要な3病型が認められる．筋型では筋痛，筋硬直，横紋筋融解症などがATP供給不足の結果としてみられ，肝型では低血糖，肝腫大がみられる．現在糖原病は15種類の病型が報告されているが，酵素の臓器別発現の違いなどからそのなかでも様々な亜型が報告されている[2](図 1)．

主要な(高頻度病型)糖原病はI型(von Gierke病)，II型(Pompe病)，III型(Cori病)，V型(McArdle病)，VII型(Tarui病)，VIII/IX型である．

頻度

わが国での十分な疫学調査はないため，欧米あるいは我々の経験からの頻度調査のみである．それによるとI型は10万人に1人，II型は4万人に1人，III型は20万～30万人に1人，V型，VII型はまれである．最も多いのはVIII/IX型で明確な疾患頻度は不明だが，筆者らの診断実数を参考にすると，Pompe病の約2.5倍の頻度があり，少なくとも1万～1.5万人に1人程度ではないかと考えられる．

治療・予後

基本的には病態に応じた食事療法が主体である．低血糖に対しては頻回の食事摂取，あるいは腸管で分解する持続ブドウ糖放出型の糖質である，コーンスターチの利用である[3,4]．

表 1 各臓器における解糖の目的

臓器	役　割
肝臓	ブドウ糖供給，グリコーゲン貯蔵
筋肉	筋収縮のためのATP供給
脳	神経細胞へのATP供給(short term)

最近II型(Pompe病)ではレコンビナントのアルグルコシダーゼ－αを用いた酵素補充療法が開始され，乳児型では心筋障害に対して明瞭な効果をもたらし，生命予後の改善がみられている．遅発型ではその効果は様々である．V型(McArdle病)ではわが国から相次いでビタミンB6補充療法が効果があるという報告があり有用性が期待できる．しかし海外では否定的な報告もあり，その違いは遺伝子変異の違いにも起因しているかもしれない[5]．

遺伝

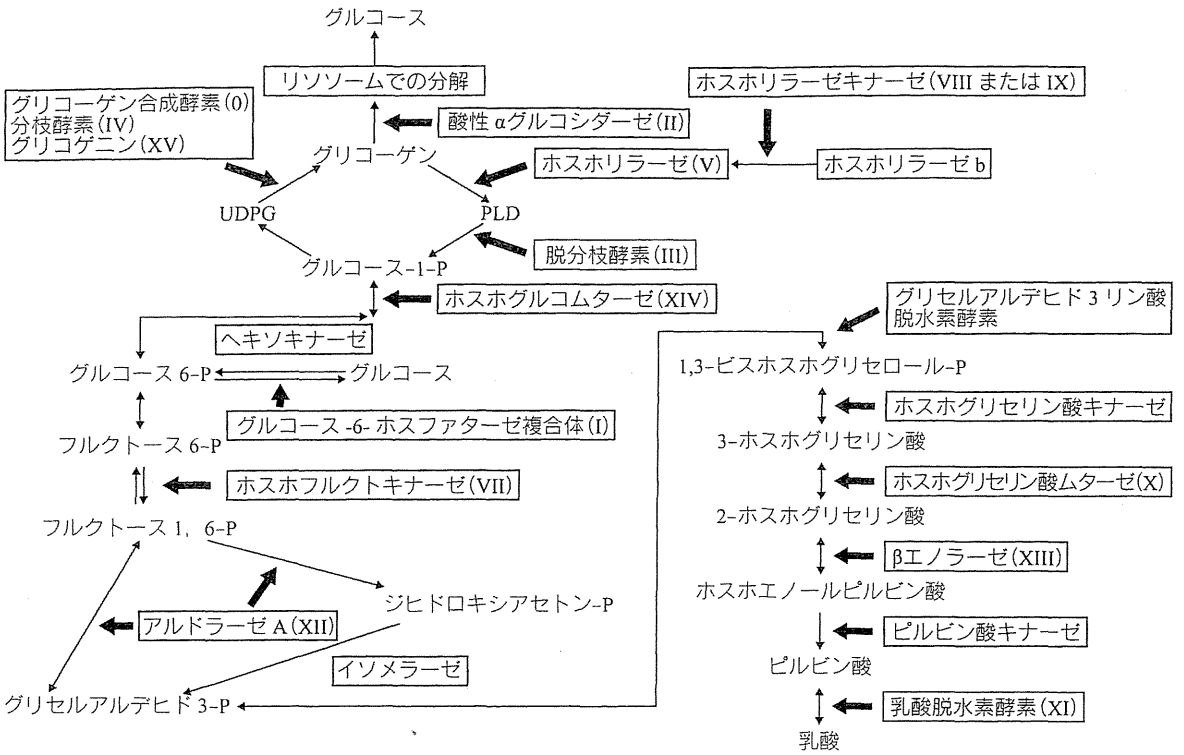
a)VIII/IX型，ホスホグリセリン酸キナーゼ欠損症
- **遺伝形式**：X連鎖劣性遺伝
- **同胞再発率**：男児で50％，女児で0％

b)その他の糖原病
- **遺伝形式**：常染色体劣性遺伝
- **同胞再発率**：25％

本症での遺伝形式はVIII/IX型，ホスホグリセリン酸キナーゼ欠損症がX連鎖性劣性遺伝，他の糖原病は常染色体劣性遺伝である．同胞発生率，一卵性双生児における発症一致率については不明である．

遺伝学的検査

本症の遺伝子検査ではI型(von Giercke病)とV型(McArdle病)を除き，日本人における好発遺伝子変異はない．I型ではIa型において日本人の約



図解 解糖経路と酵素

〔杉江秀夫，他：筋型グリコーゲン代謝異常症．杉江秀夫(編)，代謝性ミオパチー．診断と治療社，2014；31-83. より〕

90％でc.727G>Tが認められ，有用である．I型を疑った場合はまずこの好発変異の検索を行うことで，肝生検を行わないでも診断が可能となった．V型ではp.F710delが日本人では約50％に認められている．

遺伝カウンセリングのポイント

病型を確定診断すれば常染色体劣性遺伝，X連鎖劣性遺伝のいずれかの遺伝形式であるので，発症リスクなどについてのカウンセリングが可能である．

(杉江秀夫)

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27 金属代謝異常症

A Wilson 病

疾患の概要

病態

ATP7B 遺伝子の異常に基づき，肝臓からの銅の排泄障害を主たる病因とする銅蓄積性疾患である．肝臓をはじめ，中枢神経，角膜，腎臓などに銅が過剰に蓄積する．本症の 3 主徴は，肝硬変，錐体外路症状および Kayser-Fleischer 角膜輪である．しかし，本症は多彩な症状がみられる疾患である．肝障害は肝硬変のみならず，脂肪肝，急性あるいは慢性肝炎の状態も呈する．さらに，溶血を伴い急速に肝不全が進行する劇症肝炎型の症例もみられる．また，肝症状と神経症状のほかに，精神症状，血尿などの腎障害や白内障などが出現する症例もある．

頻度

わが国における発症頻度は 3.5 ～ 4.5 万人に 1 人と推察される[1]．発症年齢は 3 ～ 50 歳代と幅広く分布しており，発症のピークは 10 ～ 11 歳である[1]．

治療・予後

銅キレート薬〔D-ペニシラミン(トタルカプターゼ®)または塩酸トリエンチン(メタライトン®)〕あるいは亜鉛薬〔酢酸亜鉛(ノベルジン®)〕内服による薬物療法が確立されている．また，低銅食療法も併用する．早期に発見・診断し治療を開始すれば，各症状・所見の改善・消失が期待できる．

遺伝

- **遺伝形式**：常染色体劣性遺伝
- **同胞再発率**：25 %

遺伝学的検査

ATP7B 遺伝子の構造解析により，両方のアレルに変異が同定されれば Wilson 病と診断を確定できる．しかし本症症例の 10 ～ 15 % に変異が同定できない症例が存在する[2]．遺伝子検査が陰性(変異が同定されない)の場合でも Wilson 病であることを否定はできない．この点は注意が必要である．

遺伝カウンセリングのポイント

Wilson 病と診断された症例に同胞がいる場合は，家族内検索は必須と考えられる．同胞の発症率は 25 % である．本症の発症年齢は多岐にわたるため，発端者より年長の同胞も検索する必要がある(図 1)[3]．発症前に診断し治療を開始すれば，発症を予防することが可能である．

B Menkes 病

疾患の概要

病態

ATP7A 遺伝子の異常に基づく腸管からの銅吸収障害と細胞レベルでの銅輸送障害による銅欠乏性疾患である．中枢神経，結合織など様々な組織内の銅要求酵素に銅が供給されず，それらの活性低下により症状が出現する．臨床症状と経過により古典型(重症型)，軽症型および occipital horn 症候群(極軽症型)に分類される．古典型は，新生児期より低体温，哺乳力低下，嗜眠傾向などがみられる．青白い皮膚，水平の眉毛，小顎，弓のような上口唇などが顔貌の特徴である．最も特徴的なのは毛髪(kinky hair)であり，色が淡くねじれ，折れやすい．知的障害とけいれんは必発である．易感染性や，膀胱憩

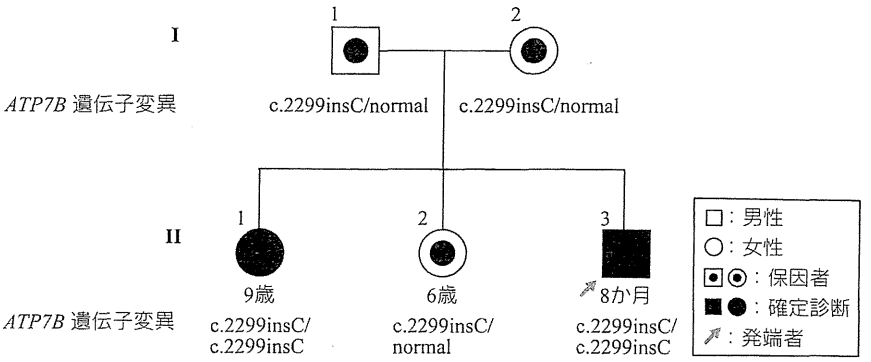

図1 Wilson 病の 1 家系

8 か月の男児(II-3)が低セルロプラスミン血症にて発見され，遺伝子診断にて Wilson 病と確定診断された．その後，遺伝子診断による家族内検索が行われ，無症状であった 9 歳の姉(II-1)が Wilson 病と診断された．両親(I-1, 2)と 6 歳の姉(II-2)は保因者であることが判明した．

〔渡辺温子，他：マススクリーニングにて発見され，ATP7B 遺伝子解析により診断できた Wilson 病 8 ヵ月男児例．日小児会誌．1998；102：688-691. より〕

室などの結合織異常もみられる．

頻度

わが国における発症頻度は，男児の約 14 万人に 1 人と考えられている[4]．古典型は，生後 3 ～ 5 か月頃に発見・診断される例が多い．

治療・予後

診断後，直ちに銅の非経口投与を行う．硫酸銅，酢酸銅の経静脈的投与，あるいはヒスチジン銅の皮下投与が用いられている．しかし，生後 1 か月以内などの極早期に治療を開始した例を除き中枢神経障害には治療効果はなく，また結合織異常への治療効果も認められない．古典型の予後は，生命予後を含めて極めて不良である．

遺伝

遺伝形式：X 染色体劣性遺伝

同胞再発率：男児の 50 %，女児は 0 %

遺伝学的検査

原因遺伝子 *ATP7A* の構造解析は，本症の確定診断法としても有用である．しかし，Menkes 病であっても *ATP7A* 遺伝子に変異が同定されない症例は存在する．遺伝子検査陰性例の評価と診断は慎重に行う必要がある．

遺伝カウンセリングのポイント

発端者において *ATP7A* 遺伝子の変異が同定・確認されれば，家族内検索において同胞が男児の場合は患者か健常か，女児の場合は保因者か健常かを，また母親が保因者であるか否かを正確に判定することができる．Menkes 病患者においては *de novo* 変異の場合もあり，母親が保因者ではない家系もみられる．また発端者の同胞女児が保因者の場合は，将来その女児が Menkes 病患者を出産する可能性がある．古典型の Menkes 病は(少なくとも現時点では)致死的な疾患であるため，これらの情報を正確に保護者に説明する必要がある．

C 腸性肢端皮膚炎

疾患の概要

病態

SLC39A4(*ZIP4*)遺伝子の異常に基づき，腸管からの亜鉛吸収障害を病因とする亜鉛欠乏性疾患である．症状は皮膚症状が中心であり，四肢末端および開口部(口囲，鼻孔，眼囲，耳孔，耳介，肛囲，外

陰)に，丘疹，小水疱，膿疱を伴う紅斑，びらん，あるいは結痂をきたす．さらに，鑷幹，爪変形，爪囲炎，脱毛(全頭，眉毛，睫毛，うぶ毛)なども生じる．皮膚症状以外では，下痢，発育不全，免疫能低下，精神症状(不機嫌やうつ傾向など)などを呈する．発症年齢は乳児期から学童期までであるが，人口乳栄養ならば生後数日から数週間，母乳栄養なら離乳期での発症が多い．

頻度

まれな疾患であり，世界的には50万人に1人と考えられている[5]．わが国では10年間(2001～2010年)で4家系の報告がある[5]．

治療・予後

亜鉛薬の経口投与を行う．投与量は，亜鉛として乳児期3 mg/kg/日，幼児期30～50 mg/日，学童期以降50～150 mg/日と大量投与が必要である．症状は亜鉛投与にて速やかに改善するが，再発を繰り返すため治療は生涯にわたり必要である．

遺伝

- **遺伝形式**：常染色体劣性遺伝
- **同胞再発率**：25 %

遺伝学的検査

本症の確定診断は，*SLC39A4*遺伝子解析による遺伝子診断で行う．

遺伝カウンセリングのポイント

発端者が発見・診断された場合，次子が同様の疾患である可能性が25 %である．次子が生まれた場合には，早期に遺伝子診断を行い，早期発見と治療開始につなげることが重要である．

(清水教一)

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ORIGINAL ARTICLE

The first case in Asia of 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency (HSD10 disease) with atypical presentation

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2-Methyl-3-hydroxybutyryl-CoA dehydrogenase (2M3HBD) deficiency (HSD10 disease) is a rare inborn error of metabolism, and <30 cases have been reported worldwide. This disorder is typically characterized by progressive neurodegenerative disease from 6 to 18 months of age. Here, we report the first patient with this disorder in Asia, with atypical clinical presentation. A 6-year-old boy, who had been well, presented with severe ketoacidosis following a 5-day history of gastroenteritis. Urinary organic acid analysis showed elevated excretion of 2-methyl-3-hydroxybutyrate and tiglylglycine. He was tentatively diagnosed with β-ketothiolase (T2) deficiency. However, repeated enzyme assays using lymphocytes showed normal T2 activity and no T2 mutation was found. Instead, a hemizygous c.460G>A (p.A154T) mutation was identified in the *HSD17B10* gene. This mutation was not found in 258 alleles from Japanese subjects (controls). A normal level of the HSD17B10 protein was found by immunoblot analysis but no 2M3HBD enzyme activity was detected in enzyme assays using the patient's fibroblasts. These data confirmed that this patient was affected with HSD10 disease. He has had no neurological regression until now. His fibroblasts showed punctate and fragmented mitochondrial organization by MitoTracker staining and had relatively low respiratory chain complex IV activity to those of other complexes.
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INTRODUCTION

HSD10 disease, originally described as 2-methyl-3-hydroxybutyryl-CoA dehydrogenase (2M3HBD) deficiency,[1] is a rare X-linked recessive disorder caused by a mutation in the *HSD17B10* gene.[2–5] This gene encodes a multifunctional protein that has 17β-hydroxysteroid dehydrogenase activity as well as 2M3HBD activity,[3–5] and which is also an essential component of mitochondrial RNase P, being required for tRNA processing in mitochondria.[6]

This disorder was first identified in a patient with progressive infantile neurodegeneration whose urinary organic acid profile was suspected to be due to β-ketothiolase (mitochondrial acetoacetyl-CoA thiolase; T2) deficiency in isoleucine catabolism.[1] However, the clinical presentation of that patient was different from that of typical T2 deficiency, which is characterized by intermittent ketoacidosis and no clinical symptoms between crises, and typically normal development.[7,8] Fewer than 30 patients have been reported to date.[1,2,5,9–21] Typically, HSD10 disease is characterized by a progressive neurodegenerative course from 6 to 18 months of age, in conjunction with retinopathy and cardiomyopathy, leading to death at the age of 2–4 years or later.[5] However, clinical heterogeneity is noted in this disorder.[5] An atypical milder presentation was reported in three families.[13,14,17]

Here, we describe a 6-year-old Japanese boy with the HSD10 disease, who had no neurodegeneration and developed severe ketoacidosis at the age of 6 years. This is believed to be the first report of HSD10 disease in Asia.

MATERIALS AND METHODS

Case presentation

We report the case of a boy who had been well and achieved normal development until 6 years of age when he presented with severe ketoacidosis following

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a 5-day period of appetite loss and vomiting due to gastroenteritis. Physical examination at admission showed a height of 108 cm, body weight of 18.3 kg (2 kg loss), heart rate of 128 per min and respiratory rate of 32 per min. Unconsciousness was not noted. Laboratory testing showed blood gas pH 7.01, pCO_2 9.2 mm Hg, HCO_3^- 2.8 mEq l^{-1}, blood glucose 5.9 mmol l^{-1}, white blood cell count 16 180 μl^{-1}, hemoglobin 14.3 g dl^{-1}, blood urea nitrogen 14.5 mg dl^{-1}, aspartate aminotransferase 29 IU l^{-1}, alanine aminotransferase 17 IU l^{-1}, lactate dehydrogenase 238 IU l^{-1}, ammonia 65 $\mu g\, dl^{-1}$ and lactate 2.4 mmol l^{-1}.

After bolus infusion of 20 ml kg^{-1} 5% glucose and electrolytes, blood total ketone body level was 14 mmol l^{-1} and free fatty acid was 0.97 mmol l^{-1}. He responded to intravenous fluid infusion (including 5% glucose), and blood gas showed pH 7.48 and HCO_3^- 23.7 mmol l^{-1} on day 2 of hospitalization. He became well and started oral food intake on that day. He was discharged from the hospital on day 7 of hospitalization. Semiquantitative urinary organic acid analysis in the acute phase showed elevated excretion of 2-methyl-3-hydroxybutyrate and tiglylglycine, as well as ketones. He was tentatively diagnosed with T2 deficiency. One month later, he developed an episode of abdominal pain and lethargy in which hypoglycemia (1.4 mmol l^{-1}) and mild metabolic acidosis (blood pH 7.29, pCO_2 36.4 mm Hg, HCO_3^- 17.5 mmol l^{-1} and lactate 5.5 mmol l^{-1}) were noted. He responded quickly to intravenous infusion of electrolytes and glucose. Urinary organic acid analysis at the acute phase of this episode showed elevated concentrations of 2-methyl-3-hydroxybutyrate but not of tiglylglycine and 2-methylacetoacetate (Table 1). Blood acylcarnitine analysis using tandem mass spectrometry showed elevated C5:1 carnitine but not C5-OH carnitine (Table 1). After this episode, he did not experience another metabolic event until now (6.5 years of age).

His mother claimed that his gross motor development was slow and he could walk alone after the age of 1 year and 6 months. He also had some clumsiness with fine motor skills. His growth was normal. His height and weight were 111.5 cm (−1.2 s.d.) and 22.2 kg (0 s.d.), respectively. His neurological development was slightly below normal with a verbal IQ of 112, performance IQ of 64 and a full scale IQ of 88 (Wechsler Intelligence Scale for Children). Cerebral magnetic resonance imaging and magnetic resonance spectroscopy yielded normal findings at the age of 6.5 years. No abnormal findings were identified in echocardiography and ophthalmological examinations at the age of 7 years.

Enzyme assay and immunoblot analysis

Peripheral blood mononuclear cells were isolated from heparinized blood by gradient centrifugation in Ficoll–Paque medium (GE Healthcare, Uppsala, Sweden). The fibroblasts were cultured in Eagle's minimum essential medium containing 10% fetal calf serum. Acetoacetyl-CoA thiolase and succinyl-CoA:3-ketoacid CoA transferase were assayed in lymphocytes and fibroblasts, as described previously.[22] 2M3HBD activity in fibroblasts was measured as described previously.[1] Immunoblot analysis for 2M3HBD was done using anti-rat 2M3HBD antibody, which was originally made by us (TH) and anti-human glyceraldehyde 3-phosphate dehydrogenase antibody (sc-25778; Santa Cruz Biotechnology, Santa Cruz, CA, USA) as a reference. We used fibroblasts from an HSD10-deficient patient,[16] as a positive disease control.

Mutation analysis

This study was approved by the Ethical Committee of the Graduate School of Medicine, Gifu University, Gifu, Japan. Genomic DNA was purified from the fibroblasts with Sepa Gene kits (Sanko Junyaku, Tokyo, Japan). Mutation screening was performed at the genomic level by PCR and direct sequencing, using primer sets for fragments including each exon and its intron boundaries. Primers and PCR conditions for *ACAT1* gene were as previously described.[23] For *HSD17B10*, we amplified each genomic region with the primer pairs shown in Supplementary Table S1.

Screening of A154T mutation in the Japanese population

The presence of A145T mutations was screened using TaqMan triplet genotyping in 92 Japanese men and 83 women, according to the manufacturer's protocol (Life Technologies, Carlsbad, CA, USA).

Mitochondrial morphology

Fibroblasts from HSD10 patients and control fibroblasts were cultured in Dulbecco's modified Eagle's medium (Life Technologies) supplemented with 10% fetal calf serum at 37 °C and 5% CO_2. The mitochondria in living fibroblasts were stained with 100 nM MitoTracker Red CMRXRos (Life Technologies) for 30 min at 37 °C. Fluorescent images were captured and analyzed with an LSM710 laser scanning confocal microscope equipped with an incubation system (Carl Zeiss, Oberkochen, Germany).

Respiratory chain enzyme analysis

An *in vitro* respiratory chain enzyme activity assay[24] and blue native polyacrylamide gel electrophoresis[25,26] were used to quantify the activity and amount of respiratory chain enzyme complexes. The diagnostic criteria of Bernier *et al.*[26,27] were used to judge the activity.

Structural analysis of the A154 mutation

The crystal structure of human HSD17B10 complexed with NAD^+ (PDB ID: 2O23, deposited in the RCSB protein databank; www.rcsb.org)[28] was used for

Table 1 Urinary organic acid and serum acylcarnitine analyzes

		This patient		*T2D (severe)*	*T2D (mild)*
	Mean (s.d.)	*Hypoglycemic*	*Asymptomatic*	*Asymptomatic*	*Symptomatic*
Urinary organic acids					
Lactic acid	37.9±28.1	7755.8	7.3	5.1	195.0
3-OH butyric acid	27.8±21.5	17116.1	3.0	5.4	6295.0
Acetoacetic acid	0.2±0.4	72.5	0.7	1.0[a]	16.7[a]
2-Me-3-OH butyric acid	4.4±4.0	296.2	132.6	130.4	121.6
2-Methylacetoacetic acids	0±0	0.0	0.7	69.4[a]	2.8[a]
Tiglylglycine	2.2±4.3	0.1	298.9	212.4	3.7
Serum acylcarnitines					
C0	31.3±8.4	13.4		67.4	79.2
C2	6.2±2.1	16.2		7.7[a]	2.1[a]
C5:1	0.012±0.005	0.63		0.72	0.079
C5OH	0.06±0.03	0.11		0.34	0.06

T2D (severe) was GK01, and T2D (mild) was GK77.
Amounts of urinary organic acids are expressed as mmol per mol Cr.
Amounts of serum acylcarnitine are expressed as nnom ml^{-1}.
[a]Values may be low because of degradation due to long storage at −30 °C.

structural analysis. The program COOT was used to analyze the structure and PyMOL Molecular Graphics System, version 1.4.1 (Schrödinger, LLC; www.pymol.org/citing), was used to make the figures.

RESULTS

Exclusion of the diagnosis of T2 deficiency

We first made a tentative diagnosis of T2 deficiency, based on the severe ketoacidotic event with elevated 2-methyl-3-hydroxybutyrate and tiglylglycine in urinary organic acid analysis. However, repeated enzyme assays showed normal T2 activity (Supplementary Table S2). Furthermore, no T2 mutation was identified by genomic PCR followed by direct sequencing.

Mutation analysis of HSD17B10 gene

Urinary organic acid analysis showed blockade at the T2 or 2M3HBD level in the isoleucine catabolic pathway. Therefore, we investigated the possibility of an *HSD17B10* gene mutation, although the clinical course of this patient was different from that of typical HSD10 patients. A hemizygous c.460G>A (p.A154T) mutation was identified in *HSD17B10* gene (Figure 1). His mother was a heterozygous carrier of this mutation. His maternal uncle did not have this mutation. Samples from maternal grandparents were not available for the study. TaqMan analysis showed that this mutation was not found in 258 alleles from Japanese subjects (controls).

Enzyme assay and immunoblot analysis for 2M3HBD

We used a fibroblast cell line from a Dutch patient whose mutation was c.364C>G (p.L122V) as a positive disease control. He was classified with the infantile form of HSD10 disease because he had shown motor delay and spastic diplegia since infancy.[16] The patient was able to walk but had psychomotor retardation with spasticity and minimal language development (Bwee Tien Poll-The, personal communication), and hence his clinical manifestations were milder than for the typical infantile form of the disease.

2M3HBD activity was absent from the patient's fibroblasts, as well as HSD10-deficient fibroblasts with p.L122V mutation,[16] designated as L122V fibroblasts (Table 2). However, the control samples showed 2M3HBD activity, which was in accordance with reported control values for the assay.[1] Immunoblot analysis showed that fibroblasts from our patient and the previous HSD10-deficient patient had an almost similar amount of HSD17B10 protein to the controls (Supplementary Figure S1).

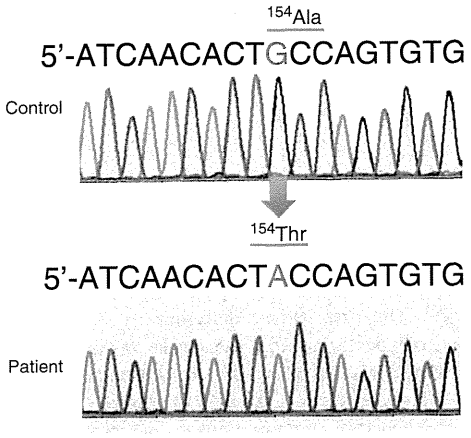

Figure 1 HSD17B10 mutation. Genomic direct sequencing of exon 5. A hemizygous c.460G>A (p.A154T) substitution was identified. A full color version of this figure is available at the *Journal of Human Genetics* journal online.

Mitochondrial staining

MitoTracker staining revealed a filamentous network-like structure of the mitochondria in control fibroblasts (Figure 2 and Supplementary Figure S2). Fibroblasts with the p.L122V and p.A154T mutations showed punctate and fragmented mitochondrial organization. This finding is the same as that previously reported in fibroblasts with R130C and D86G mutations.[17] Furthermore, mitochondria in A154T mutated cells had highly variable diameters, ranging from thin tubes to swollen bulbs.

Respiratory chain enzyme assay

Respiratory chain enzyme assay of the patient's fibroblasts showed normal activity of complexes I, II and III (98–159% relative to citrate synthase) (Supplementary Table S3). Complex IV activity was also within the normal range but significantly lower than that of other complexes (51.6% relative to citrate synthase and 44.6% relative to complex II). In blue native polyacrylamide gel electrophoresis, the band corresponding to assembled complex IV was slightly decreased too (Supplementary Figure S3). These tendencies were also detected in fibroblasts with L122V mutation.

Mutation site in the tertiary structure of human HSD17B10

HSD17B10 is a tetramer consisting of four identical subunits, each having the fold of short-chain dehydrogenase/reductase superfamily. Inspection of the human HSD17B10 structure (PDB ID: 2O23) revealed that residue Ala154 is close to the active site (Figure 3a). Ala154 is completely buried and the Cβ atom of Ala154 faces a hydrophobic (apolar) pocket created by residues such as Ile175, Val176 and Cγ of Thr195. The residue next to Ala154, Ser155, is one of the catalytic residues, and part of the catalytic triad formed by Ser155, Tyr168 and Lys172. The mutation of Ala154 to Thr154, that is, from a small, hydrophobic side chain to a larger, polar side chain results in steric clashes with residues Ile175, Val176 and Thr195 in the current conformation (Figure 3b). To avoid these steric clashes, main and side chain conformational changes are expected in the region around Ile175 and Ala/Thr154. The changes around Ile175 may also affect the catalytically competent conformation of the active site residue Lys172. In addition, the changes around Ala/Thr154 are expected to cause structural changes of the catalytic residue Ser155, which has to interact with the substrate for the reaction to occur. Therefore, all these rearrangements resulting in the non-optimal conformations of Ser155 and Lys172 may severely affect the catalytic capability of this enzyme. The substrate binding may not be affected as much because the catalytic triad is only at the beginning of the much larger substrate binding pocket[28] extending outward. Therefore, catalysis of both the steroid substrates such as allopregnanolone[21]

Table 2 2M3HBD assay using fibroblasts

	2M3HBD	*AcAcCoA thiolase*
Control fibroblasts 1	0.75±0.40	15.6
Control fibroblasts 2	0.90±0.58	28.1
L122V fibroblasts	0.19±0.08	28.0
Patient's fibroblasts	0.04±0.11	34.0

Acetoacetyl-CoA (AcAcCoA) thiolase activity was measured in the presence of potassium ion at 37 °C.

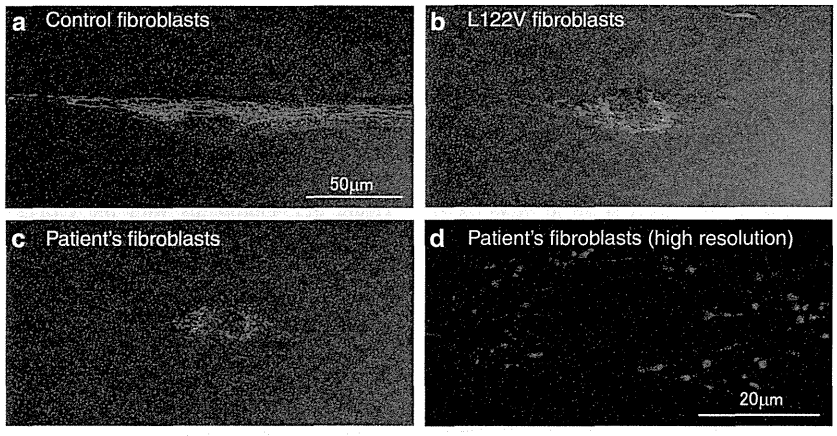

Figure 2 Mitochondrial morphology. (**a–c**) Merged images from differential interference contrast (DIC) and MitoTracker Red. (**a**) Control fibroblast. (**b**) Fibroblast with the p.L122V mutation. (**c**) Fibroblast with the p.A154T mutation. (**d**) Fluorescent image of MitoTracker Red from the p.A154T mutated cell. Bars: **a–c**, 50 μm; **d**, 20 μm. A full color version of this figure is available at the *Journal of Human Genetics* journal online.

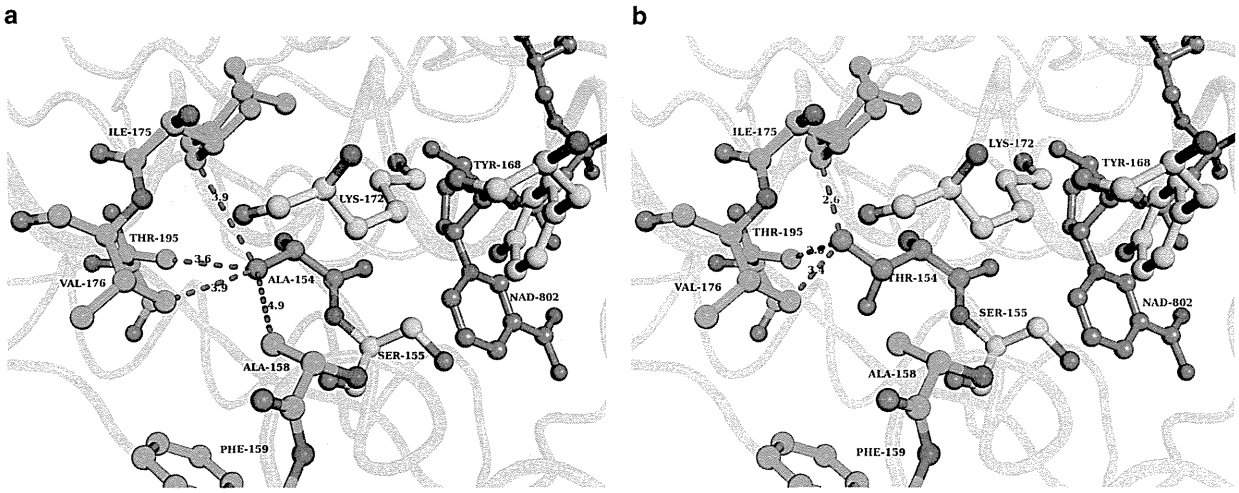

Figure 3 Structural analysis. (**a**) Environment of residue Ala154 as seen in PDB ID 2023. Oxygen atoms are shown in red, nitrogen in blue and carbon is color coded as follows: Ala154 in magenta, the catalytic triad comprising residues Ser155, Tyr168 and Lys172 in yellow, and NAD in blue. Ala158, Phe159, Ile175, Val176 and Thr195 (Cγ) are some of the residues pointing toward the side chain of Ala154, creating a hydrophobic pocket. These are highlighted in green. Ile175 has a double conformation. The relevant distances are shown with red dashes. (**b**) Possible steric clashes in HSD10 disease due to mutation of Ala154 into Thr154. Thr154 is shown in magenta. Ala154 was mutated to Thr154 using PDB-entry 2023 by the program COOT. The expected steric clashes of the Thr154 side chain with Ile175, Val176 and Thr195 are highlighted by red dashes.

and fatty acyl-CoA substrates such as 2-methyl-3-hydoxybutyryl-CoA are predicted to be equally affected.

DISCUSSION

This is believed to be the first report of HSD10 disease in Asia. Since the discovery of the first patient in 2000,[1] fewer than 30 patients have been described.[1,2,5,9–21] Typically, this disorder is suspected when patients with neurological degeneration or psychomotor retardation show similar urinary organic acid or blood acylcarnitine profiles with T2 deficiency. However, our patient experienced a severe ketoacidotic episode with blood pH 7.01 and blood total ketone level of 14 mM after a 5-day history of gastroenteritis. This clinical picture is similar to T2 deficiency, although the onset of the first severe ketoacidotic episode at the age of 6 years is late compared with that in typical T2-deficient patients who develop such crises around the age of 6 months to 2 years.[7,8] The first patient described by Zschocke *et al.*[1] had metabolic decompensation with ketonuria on day 2 of life. Disturbance in isoleucine catabolism may be attributed to such reversible metabolic decompensation in HSD10 disease, and appears to be independent from pathophysiology of neurodegeneration in HSD10 disease.

In the patients with HSD10 disease described thus far, broad clinical heterogeneity has been found.[5,30] The classical presentation that is observed in most patients, which was called the infantile form by

Zschocke,[5] is characterized by a period of more or less normal development in the first 6–18 months of life. This is followed by a progressive neurodegenerative disease course in conjunction with progressive cardiomyopathy, leading to death at the age of 2–4 years or older. Patients with a common mutation c.388C>T (p.R130C) present with the infantile form. Some patients with other mutations have more severe neonatal forms. Atypical presentation was reported in three families. (1) Only one patient with c.745G>C (p.E249Q) mutation developed normally in the first 5 years of life and then showed neurological deterioration.[14] This was classified as the juvenile form by Zschocke.[5] (2) The proband of a family with c.495A>C (p.Q165H) mutation showed growth retardation, feeding difficulty and microcephaly but his neurological status remained normal at up to age 5 years. Moreover, his male cousin with the same mutation achieved normal neurodevelopment until his current age of 8 years, with a height and weight in the 25th percentile.[17] (3) Four boys in a large family showed X-linked intellectual disability, choreoathetosis and abnormal behavior with a normal urinary organic acid profile, and they had an apparent synonymous mutation that affected splicing efficiency in the HSD17B10 gene.[13] Our patient with a novel c.460G>A (p.A154T) mutation showed no neurological degeneration, at least until age 6.5 years, and normal growth. Hence, our patient had a milder phenotype than in patients with juvenile HSD10 disease.

There is evidence that the neurological degeneration observed in HSD10 disease is not caused by a deficiency in the isoleucine metabolism-related 2M3HBD activities of HSD17B10.[17,21] Instead, defects in neuroactive steroid metabolism[21] and/or the non-enzymatic function of the protein required for mitochondrial integrity and cell survival[17] may be responsible for the neurological manifestations. The HSD17B10 protein is one of three component proteins of mitochondrial RNase P, which is essential for mitochondrial translation.[6] Reduced function as a component of RNase P may contribute to clinical severity. The p.R130C mutation common for infantile form reduced not only its mutant HSD10 level but also that of another RNase P component, MRPP-1, suggesting that HSD10 is important for the maintenance of the MRPP1–HSD10 subcomplex of RNase P.[31] Analysis of the consequences of the A154T mutation on the tertiary structure suggests that A154T mutation affects enzyme activity of both 2-methyl-3-hydroxybutyryl-CoA and neurosteroids. The enzymological characterization of the expressed HSD17B10 A154T variant is required to confirm this observation. Mitochondrial morphological changes using MitoTracker staining have been reported,[17] and we also observed punctate and fragmented mitochondrial organization in our patient. Mitochondrial respiratory chain complex IV activity was decreased in both fibroblasts with A154T and those with L122V, although the decreased level did not fulfill the minor diagnostic criteria of Bernier *et al.*[27] Mitochondrial respiratory chain enzyme assay was reported to be normal in fibroblasts with V65A mutation. Further investigation in other fibroblasts with HSD10 disease is necessary to confirm that reduced complex IV activity is one of the characteristics in HSD10 disease.

We have described a patient with mild phenotype HSD10 disease with a novel A154T mutation, who is believed to be the first patient with HSD10 disease in Asia. Accumulation of more data on phenotype–genotype correlation of HSD10 disease is important to understand the molecular basis of the disease.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Ketone body metabolism and its defects

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Abstract Acetoacetate (AcAc) and 3-hydroxybutyrate (3HB), the two main ketone bodies of humans, are important vectors of energy transport from the liver to extrahepatic tissues, especially during fasting, when glucose supply is low. Blood total ketone body (TKB) levels should be evaluated in the context of clinical history, such as fasting time and ketogenic stresses. Blood TKB should also be evaluated in parallel with blood glucose and free fatty acids (FFA). The FFA/TKB ratio is especially useful for evaluation of ketone body metabolism. Defects in ketogenesis include mitochondrial HMG-CoA synthase (mHS) deficiency and HMG-CoA lyase (HL) deficiency. mHS deficiency should be considered in non-ketotic hypoglycemia if a fatty acid beta-oxidation defect is suspected, but cannot be confirmed. Patients with HL deficiency can develop hypoglycemic crises and neurological symptoms even in adolescents and adults. Succinyl-CoA-3-oxoacid CoA transferase (SCOT) deficiency and beta-ketothiolase (T2) deficiency are two defects in ketolysis. Permanent ketosis is pathognomonic for SCOT deficiency. However, patients with "mild" SCOT mutations may have nonketotic periods. T2-deficient patients with "mild" mutations may have normal blood acylcarnitine profiles even in ketoacidotic crises. T2 deficient patients cannot be detected in a reliable manner by newborn screening using acylcarnitines. We review recent data on clinical presentation, metabolite profiles and the course of these diseases in adults, including in pregnancy.

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Ketone body metabolism

Acetoacetate (AcAc) and 3-hydroxybutyrate (3HB) are the two main ketone bodies. They are 4-carbon carboxylic acids, hence, accumulation results in ketoacidosis. Under normal physiological conditions, ketone bodies are the only energy vectors from the liver to brain when glucose supply is low (Mitchell and Fukao 2001; Sass 2012). It should be noted that brain can use ketone bodies as fuels. In special conditions, other substrates are used. An example is the abnormal hyperlactacidemia that accompanies hypoglycemia in patients with glycogen storage disease type 1. In this case, lactate may be an important source of energy for the brain. Ketogenic diets, which have low carbohydrate and high fat content, have been used to treat GLUT1 deficiency (Klepper et al 2002; Klepper and Voit 2002; Morris 2005) and pyruvate dehydrogenase deficiency (Falk et al 1976; Morris 2005). Intractable epilepsy is the best-known indication of the ketogenic diet (Morris 2005; Neal et al 2008). Oral 3HB supplementation has also been used experimentally to treat conditions such as hyperinsulinemic hypoglycemia and multiple acyl-CoA dehydrogenase deficiency (Plecko et al 2002; Van Hove et al 2003).

Figure 1 provides an overview of ketone body metabolism. Free fatty acids (FFA) are supplied from adipose tissues. In the

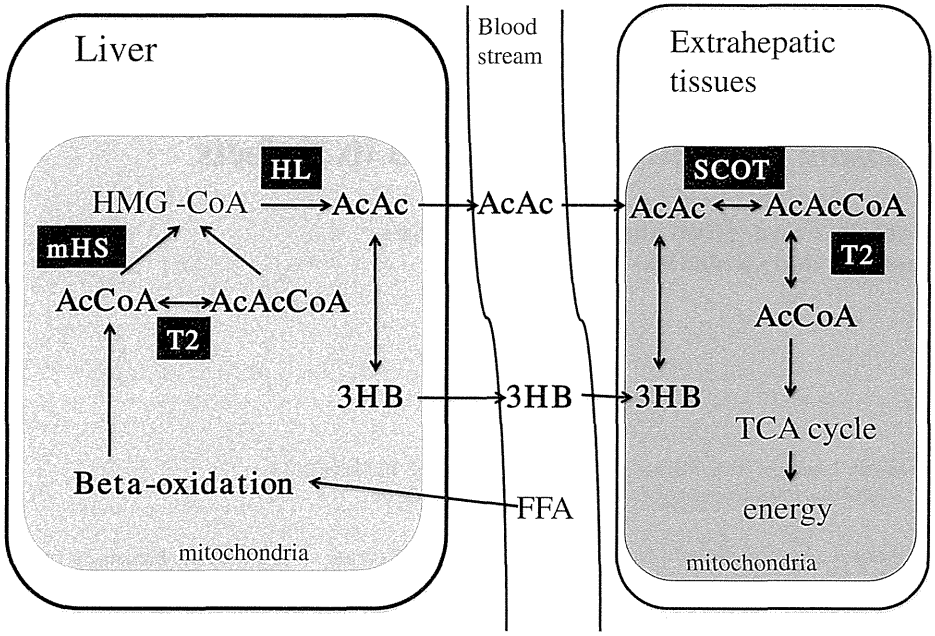

Fig. 1 Summary of ketone body metabolism. *left* Ketogenesis in liver. The HMG-CoA pathway of ketone body formation is much more active in liver than elsewhere. *center* The ketone bodies, 3HB and AcAc, diffuse from liver mitochondria to the circulation and then to extrahepatic tissues including brain. *right* In extrahepatic tissues, SCOT and T2 mediate the production of acetyl-CoA for use in energy production or synthesis. Abbreviations are the same as those in the text except for Ac-CoA (acetyl-CoA), AcAc-CoA (acetoacetyl-CoA), TCA (tricarboxylic acid cycle)

hepatocytes, fatty acid beta-oxidation produces plenty of acetyl-CoA and acetoacetyl-CoA. They are condensed to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA)by mitochondrial HMG-CoA synthase (mHS). AcAc is produced from HMG-CoA by HMG-CoA lyase (HL). AcAc is in part reduced to form 3HB. Both AcAc and 3HB diffuse to the bloodstream. In extrahepatic tissues, 3HB is changed back into AcAc, which then is activated to acetoacetyl-CoA by succinyl-CoA:3-oxoacid CoA transferase (SCOT). Next, mitochondrial acetoacetyl-CoA thiolase (T2) transfers an acetyl group to free CoA, producing two molecules of acetyl-CoA. These steps are essential for energy production from ketones in extrahepatic tissues. Brain has no other fatty acid-derived source of energy and ketone bodies are an essential aspect of brain metabolism during fasting (Mitchell and Fukao 2001).

In this article we review ketone body metabolism and the four reported inborn errors of ketone body synthesis and utilization, concentrating on new findings of clinical importance.

Control of ketone body synthesis

Ketogenesis is controlled by hormones. Glucagon and catecholamines induce FFA mobilization from adipose tissue and fatty acid oxidation and ketogenesis. Insulin suppresses these steps (Fukao et al 2004a). Ketogenic stresses including fasting, febrile illnesses, vomiting and diarrhea, induce both FFA oxidation and ketone body synthesis. Gastroenteritis is one of the most common causes of ketosis in children.

Evaluation of ketone body metabolism

Circulating ketone body levels are an important parameter of energy metabolism. They must be interpreted in relation to the clinical state and to the levels of other energy metabolites at the time when the ketone body level was obtained. Clinical history must include the duration of fasting, previous nutritional status and the presence of any acute stress. The most important other energy metabolites are blood glucose and FFA level. Use of the following considerations will allow most patients to be rapidly assigned to a general diagnostic category, from which further investigation can lead to a definitive diagnosis.

In this review, we discuss plasma total ketone body (TKB) levels. In some centers, 3HB and AcAc are measured separately. Their sum provides the TKB level. Some centers measure only 3HB, which is more chemically stable than AcAc and which is not volatile. AcAc accounts for a variable fraction of TKB, depending upon the redox state of the mitochondrial matrix (Mitchell and Fukao 2001). Therefore, TKB level cannot be accurately estimated from the 3HB level alone.

Figure 2 shows blood TKB levels as a function of fasting time for control children (Bonnefont et al 1990). Young children (defined as less than 7 years of age in the study shown) develop ketosis faster than older children. A TKB level of 2 to 5 mM is seen in control young children after a 24 h fast. At least two reasons may explain the effect of aging to progressively delay the increase of ketone body levels during fasting. First, energy demands as a function of body weight decrease more than two-fold between infancy and adulthood (Eckert 1988; http://www.health.gov/dietaryguidelines/2010.asp) and

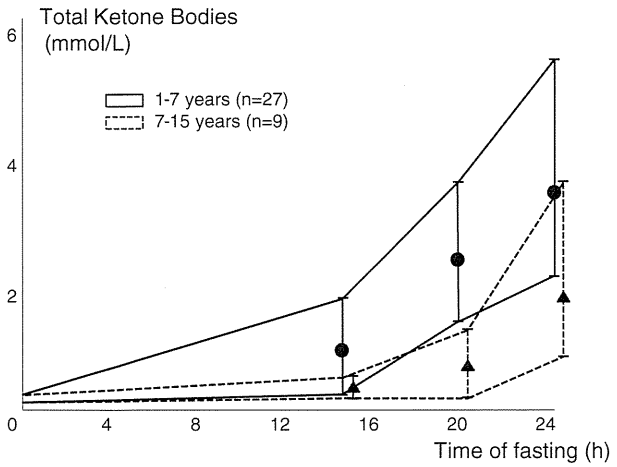

Fig. 2 Plasma total ketone body (TKB) levels as a function of fasting time and age, in groups of children aged 1–7 years and 7–15 years. Results are expressed as 10–90 percentiles with mean values. Redrawn from the data of Bonnefont et al 1990

second, the increase of muscle mass during childhood and adolescence provides a reservoir of protein that can serve for gluconeogenesis.

Blood TKB should be interpreted in relation to blood glucose, insulin and plasma FFA levels. Unfortunately, FFA analysis is not widely performed, despite its diagnostic value, and FFA data are not available in all case reports of defects in fatty acid oxidation and ketone body metabolism. The ratio of FFA/TKB is especially useful for the evaluation of ketone body metabolism. Defects in ketogenesis and fatty acid oxidation are suggested by a ratio above 2.5 and defects in ketolysis, by a ratio of less than 0.3 (Bonnefont et al 1990). Examples of clinical evaluation of ketone body metabolism in acutely ill children in Fig. 3.

Inborn errors of ketogenesis

Two inherited disorders directly affect ketogenesis, deficiency of mitochondrial HMG-CoA synthase (mHS, *HMGCS2* gene) and deficiency of HMG-CoA lyase (HL, *HMGCL* gene) (Table 1).

mHS deficiency

mHS deficiency was first described in 1997 (Thompson et al 1997). We are aware of 12 case reports that contain sufficient detail to be summarized data in Table 2 (Thompson et al 1997; Morris et al 1998; Aledo et al 2001, 2006; Bouchard et al 2001; Zschocke et al 2002; Wolf et al 2003; Pitt et al 2009; Carpenter et al 2010; Hogg et al 2012; Loughrey et al 2013; Ramos et al 2013; Sass et al 2013). This disorder has been characterized clinically by hypoglycemic crises. Most patients presented with symptomatic hypoglycemia, often during a gastroenteritis, and showed an absence of clinical symptoms between acute episodes. Hepatomegaly was noted at hypoglycemic crises in most patients. Severe metabolic acidosis was noted in several patients (Wolf et al 2003; Carpenter et al 2010; Sass et al 2013). The predominant laboratory finding is non(hypo)ketotic hypoglycemia with high FFA levels. Table 3 shows high FFA and low ketone body levels at hypoglycemic crises or monitored fasting tests. This is similar to long-chain fatty acid beta-oxidation defects, but in contrast to these conditions, blood CK level is not usually elevated in mHS deficiency. Fasting tests are usually unnecessary for diagnosis but may be useful for assessing fasting intolerance. So far, there are no established specific markers in urinary organic acids and blood acylcarnitine profiles, although the presence of urinary 4-hydroxy-6-methylpyrone (Pitt et al 2009; Carpenter et al 2010; Hogg et al 2012) and of elevated acetylcarnitine (Aledo et al 2006) has been suggested as a possible marker in decompensated patients. Ketonuria does not preclude the diagnosis of mHS deficiency (Hogg et al 2012; Sass et al 2013). If a patient has non-ketotic hypoglycemia and acidosis, but no other metabolic abnormality suggestive of a fatty acid oxidation defect, mHS deficiency should be considered. Usually, patients have experienced only one hypoglycemic crisis (Table 2), suggesting that early diagnosis may permit effective prevention of crises. Notably, two of these 12 patients died, each before 2 years of age, and permanent brain damage can result from the hypoglycemic crises of mHS deficiency (Sass et al 2013; Loughrey et al 2013) .

HL deficiency

More than 100 patients have been reported since the first description in 1976 (Faull et al 1976a, b); nine of these were from Japan (Muroi et al 2000a, b). Two pathways, ketogenesis from fatty acid oxidation and leucine catabolism, are affected. In most patients the first hypoglycemic crisis occurs before 1 year of age. One third may have neonatal onset. In acute episodes, laboratory tests show non(hypo)-ketotic hypoglycemia with high FFA and severe metabolic acidosis with liver dysfunction and hyperammonemia. Urinary organic acid analysis is often diagnostic because leucine metabolites, 3-hydroxy-3-methylglutarate, 3-methylglutaconate, 3-methylglutarate, 3-hydroxyisovalerate, and 3-methylcrotonylglycine are present.

In the Japanese series (Muroi et al 2000a, b), five of nine patients had neonatal onset. Two patients experienced hypoglycemia even after 10 years of age. Developmental delay was noted in three patients and epilepsy was recorded in three patients.

Patients with HL deficiency may develop hypoglycemia and other complications even in their teens and adulthood and HL deficiency may be diagnosed only as adults. We are aware of three such reports. The first describes a 36-year-old woman

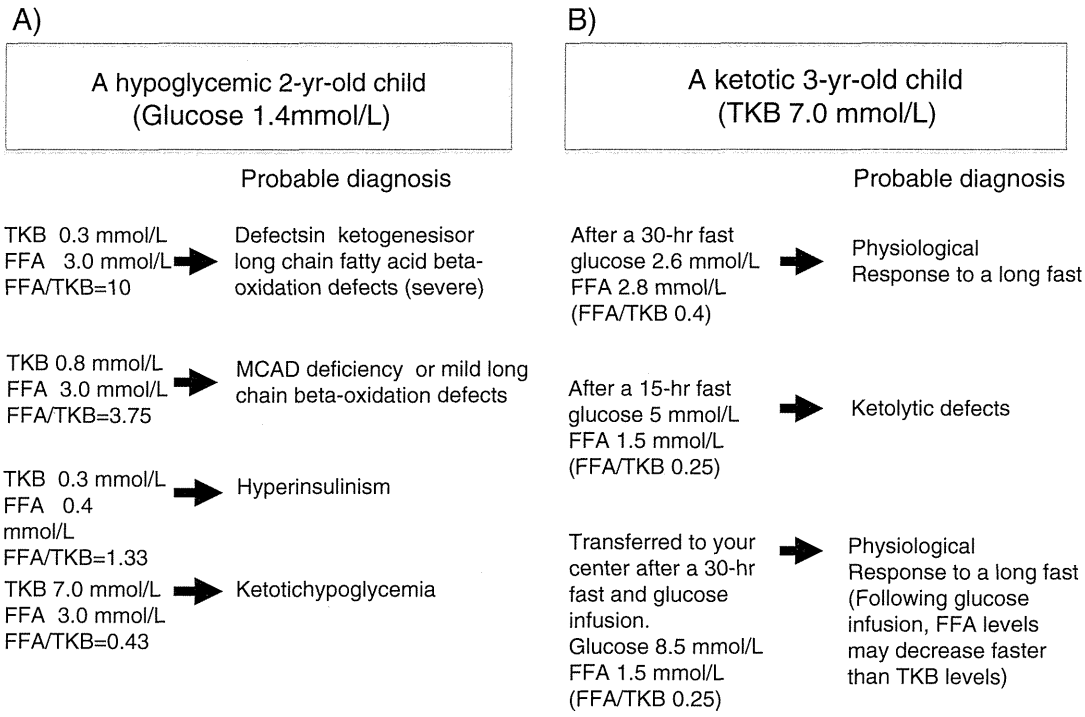

Fig. 3 Examples of the clinical evaluation of ketone body metabolism in acutely ill children. **a** A 2-year-old child has hypoglycemia (glucose 1.4 mmol/L). Possible diagnoses are shown if he has TKB and FFA levels as indicated. **b** A 3-year-old child has hyperketonemia (TKB 7.0 mmol/L). Possible diagnoses are shown if he has TKB and FFA levels as indicated. These examples illustrate the importance of combining clinical history and defining metabolite patterns, as described in the text

with seizures, recurrent metabolic disturbances, and severe leukoencephalopathy (Bischof et al 2004). The other reports describe a 23-year-old man with dilated cardiomyopathy (Leung et al 2009), and a previously asymptomatic 29 year-old man who presented with hypoglycemic coma (Reimao et al 2009).

Inborn errors of ketolysis

Two inherited disorders of ketolysis are known, succinyl-CoA:3-oxoacid CoA transfease (SCOT, *OXCT1* gene) deficiency and mitochondrial acetoacetyl-CoA thiolase (T2, *ACAT1* gene) deficiency (Table 1). T2 deficiency is known as beta-ketothiolase deficiency and also as an inborn error of isoleucine catabolism (Daum et al 1971, 1973). The step catalyzed by T2 in ketolysis can also be catalyzed to some extent by another mitochondrial enzyme, medium-chain 3-ketoacyl-CoA thiolase (Middleton 1973). If SCOT is completely lacking, ketolysis is completely blocked, but if functional T2 is completely absent, some ketolysis is still possible. This may explain in part why permanent ketosis is often observed in SCOT deficiency but not in T2 deficiency.

SCOT deficiency

SCOT deficiency was first described in 1972 (Tildon and Cornblath 1972) and follows an autosomal recessive mode of inheritance. More than 30 patients have been reported or are known to the authors (Cornblath et al 1971; Tildon and Cornblath 1972; Perez-Cerda et al 1992; Sakazaki et al 1995; Kassovska-Bratinova et al 1996; Pretorius et al 1996; Niezen-Koning et al 1997; Rolland et al 1998; Snyderman et al 1998; Song et al 1998; Fukao et al 2000, 2004b, 2006, 2007a, 2010b, 2011; Baric et al 2001; Berry et al 2001; Longo et al 2004; Yamada et al 2007; Merron and Akhtar 2009; Shafqat et al 2013). This disorder is clinically characterized by intermittent ketoacidotic episodes and asymptomatic intervals between episodes. There are no characteristic urinary organic acids except for large amounts of 3HB and AcAc. If present, permanent ketosis, i.e., the existence of ketosis at all times, even during asymptomatic periods when the patient is well-nourished and not fasting, is pathognomonic for SCOT deficiency but is not present in all SCOT-deficient patients. SCOT enzyme activity should be assayed in all suspected patients. About one half of patients develop their first ketoacidotic crisis in the neonatal period.

Table 4 summarizes five Japanese patients. GS02 and his younger sister (GS02s) are typical SCOT-deficient patients