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Rituximab therapy for deep toe ulcer with microscopic polyangiitis refractory to corticosteroids and cyclophosphamide

Dear Editor,

Selective B-cell depletion using rituximab, a chimeric anti-CD20 monoclonal antibody, has shown beneficial effects in treating antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis including microscopic polyangiitis (MPA).[1] Rituximab has been shown to result in stable remission in patients with

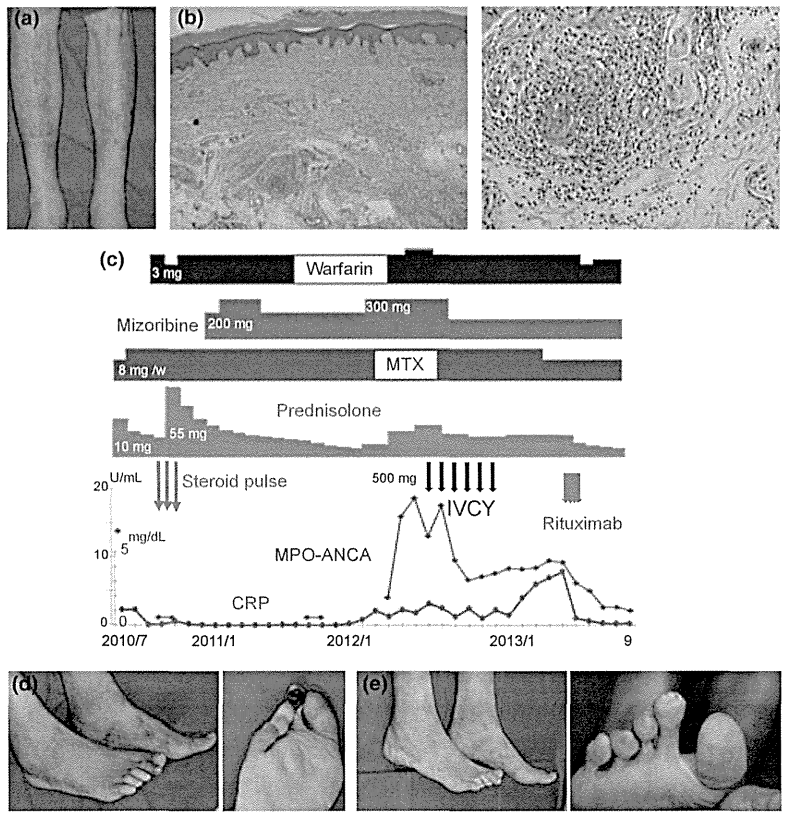

Figure 1. (a) Physical examination revealed tender erythematous nodules, livedo racemosa with purpura, and inflammatory plaques on his leg edema. (b,c) A skin biopsy of the nodule showed necrotizing vasculitis in the lower dermis and subcutaneous fat (hematoxylin–eosin, original magnifications: [b] ×40; [c] ×200). (d) Clinical course. (e,f) Deep ulcer with right second toe (e) at start of rituximab and (f) 4 months later. ANCA, antineutrophil cytoplasmic antibody; CRP, C-reactive protein; IVCY, i.v. cyclophosphamide; MPO, myeloperoxidase; MTX, methotrexate.

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神経症候群（第2版）

—その他の神経疾患を含めて—

III

VII　先天代謝異常

DNA修復障害

コケイン症候群

久保田雅也

VII 先天代謝異常

DNA修復障害

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Cockayne syndrome

久保田雅也

Key words：紫外線過敏，低身長，基底核石灰化，難聴，DNA修復欠損

1．概念・定義

Cockayneが1936年にDwarfism with retinal atrophy and deafnessとして7歳と6歳の姉弟をまとめたものがコケイン症候群(Cockayne syndrome: CS)の最初の報告である[1]．共通する特徴として難聴と精神発達遅滞，小頭，低身長，くぼんだ眼，冷たい手足，親しみやすい性格，視神経萎縮と網膜色素変性症を挙げた．1946年には同名の論文でこの2人の10年後の所見を記載し，難聴や白内障，視力低下，関節拘縮が進行することを報告した[2]．その後Sugarmanら[3]がCSの徴候を表1のようにまとめた．CSは発症年齢，重症度，症状の進行の速さにより3つの臨床型に分類される．CS I型(古典型)は最も多くみられ，胎生期および出生直後の成長は正常であるが，2歳までに成長障害が出現し退行する．いったん自力歩行可能な時期もしくは介助歩行可能な時期があることが多い．平均寿命は10歳代後半である．CS II型(先天性)は，出生時からの成長障害を特徴とし，移動はほとんどは不能で7歳以下で亡くなることが多い．CS III型(遅発型)は，ほぼ正常の成長・精神運動発達の後，10歳代での発症を特徴とする．実際にはCS I型の中にはCS II型との中間に位置づけられる重症例もあるが，症状の進行の推定には便利な分類である．Natale[4]は第4群として成人発症の紫外線感受性のみの群を提唱し，上記3群の境界の不明瞭さを回避するため重症型，中等症型，軽症型に分類している．またCOFS(cerebro-oculo-facio-skeletal症候群)はCSや色素性乾皮症(XP)と同様の遺伝子変異が見いだされており，CS II型と重なる場合も多く，CSスペクトラムの中の最重症型とも考えられる．このXPとの合併(CS/XPB，CS/XPD，CS/XPG)もある．

表1　CSの特徴(文献[3]より引用)

大症状	小症状
低身長(小人症)	日光過敏
精神発達遅滞	脊椎後彎(亀背)
小頭症	関節拘縮
小脳失調	視神経萎縮
網膜色素変性症	う歯
感音性難聴	大きく冷たい手足
早発老化徴候(特徴的な顔貌)	性腺機能低下
脳内石灰化	

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2. 疫　　学

日本における全国調査ではCS発生頻度は100万出生あたり2.77人(95％信頼区間2.19-3.11)という値が報告された[5]．本調査で詳細な病歴のあった47例の内訳はCS I型41例，CS II型2例，CS III型3例，CS/XPD 1例であった．本調査は小児科，小児神経科関連の調査であり，実際にはこれより多い可能性はある．西ヨーロッパの調査(フランス，イタリア，オランダ，イギリスの合同調査)では遺伝子診断されたCSの発生頻度は100万出生あたり2.7人であった[6]．CS発生頻度に人種差や地域での差は少ないと思われる．

3. 病　　因

CSの患者から得られた細胞は，相補性試験により2つの相補性群CSA，CSBに分類され，関連する遺伝子としてはそれぞれERCC8(excision repair cross-complementing group)，およびERCC6が見いだされたが，CSの臨床的多様性や上記臨床型とは必ずしも関連しない．患者細胞の紫外線高感受性が明らかになり，紫外線障害によるRNA合成の回復が起こらず，転写された遺伝子の損傷修復(転写と共役した修復(transcription-coupled repair: TCR))の不全が病態と関連すると推測されるに至った[7]．ただしこれのみではCSの多様性は説明がつかず，CSBに限ってもTCR以外にp53転写反応，低酸素への反応，insulin-like growth factor-1(IGF-1)への反応，housekeeping genesの転写，オートファジーとの関連，ミトコンドリアの恒常性維持など多様な機能が推定され病因に関与している．

4. 病　　態

本症候群の病態を早発老化としてとらえる視点は古くからあるが，生理的な老化との違いや，多様な表現型がDNA修復機構(TCR)の破綻とどう関係するかについては不明な部分が多い．DNA修復機構の破綻と酸化ストレスの関与，微小血管障害説，最近ではオートファジーの関与などが神経変性の機序として考えられている．癌抑制遺伝子p53はCSBと共同で異常な細胞増殖を停止させて(cell senescence)発癌を防ぐ機能をもつが，それと裏腹に機能が過剰な場合生体の老化を促進する．同じDNA修復障害でもこの2面性のうち発癌(細胞の不死化)に傾くのがXPであり，発癌は免れるが老化に傾くのがCSという考え方もある[8]．

CSA，CSBは核だけでなくミトコンドリア(mt)内にも存在し，酸化ストレスなどで損傷したmtDNAの塩基除去修復(BER)にも関わっている[9]．またCSB欠損細胞はmtが増加し，オートファジーの低下を招き(down-regulation)，free radical生成や損傷mtの集積が起こる．CSBはmtDNAのdamage sensorとして機能しmtオートファジーを誘導する．オートファジーはmTOR(mammalian target of rapamycin)により抑制されることから，autophagic stimulatorとしてのリチウムやラパマイシン(mTOR inhibitorでもある)による治療が考えられているが，まだ実験段階である[9]．

剖検脳の解析では大脳白質内に毛細血管のねじれ(string vessels)[10]が見いだされ(図1)，軟膜下小動脈分枝，大脳皮質の毛細血管密度がともに高齢対照に匹敵するほど増加し，血管形成の異常と老化と類似の機序が想定された[11]．頭部MRIでは白質優位に容積減少が起こっている(図2)．

末期腎不全となり腹膜透析を導入した8歳CSの腎病理を示す(図3)．糸球体の全節性硬化，基底膜の肥厚と蛇行，内腔の狭小化した尿細管，わずかな基底膜の二重化，広汎な足突起の消失を認めたが，メサンギウム細胞の増殖と基質の増加は認めなかった．膜性腎症に似るが本態は不明である．

5. 診断と鑑別診断

典型例は表1の徴候を参考に臨床診断が可能である．精神遅滞，低身長，典型的顔貌，CT上の基底核石灰化は特に早期診断に重要であるが，CS I型では後者2つは3-4歳以降に出現することが多く，診断される平均年齢は5-6歳である．

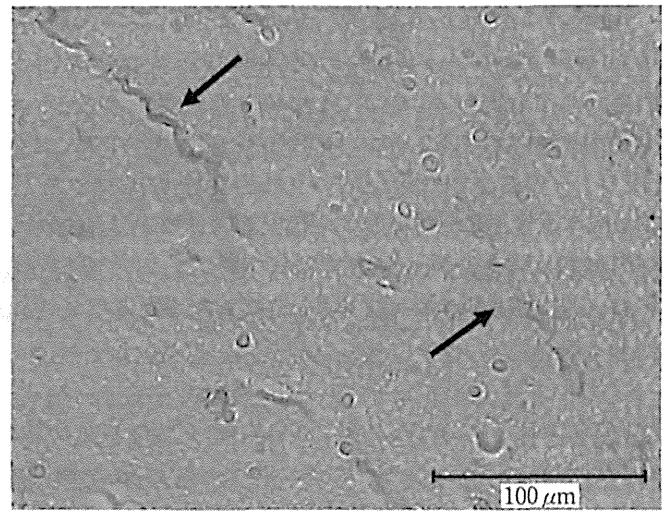

図1　7歳CS I型女児の大脳白質病理(collagen type IV染色)
string vessels(矢印)を認める.

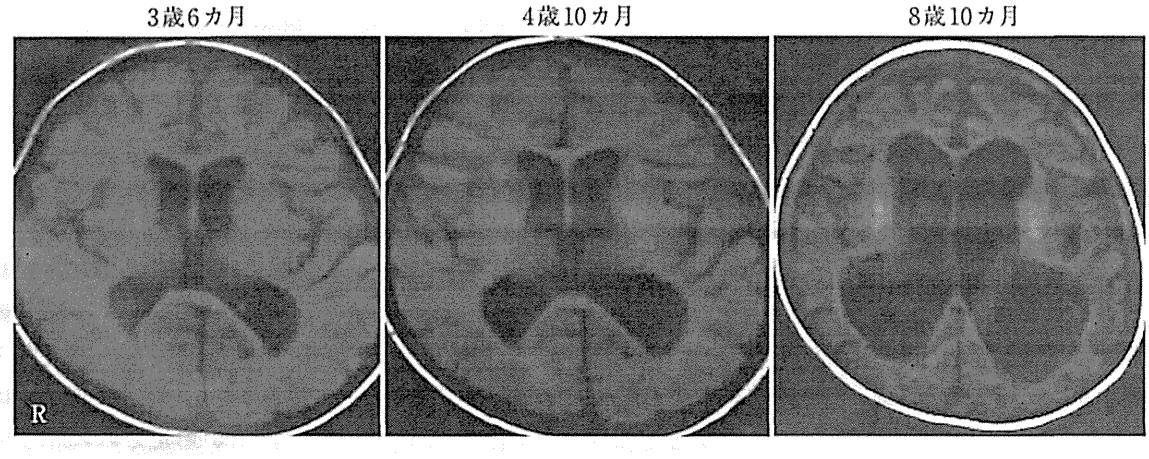

図2　8歳CS I型女児の頭部MRI(T1強調画像)の変化
白質優位に萎縮が進んでいる.

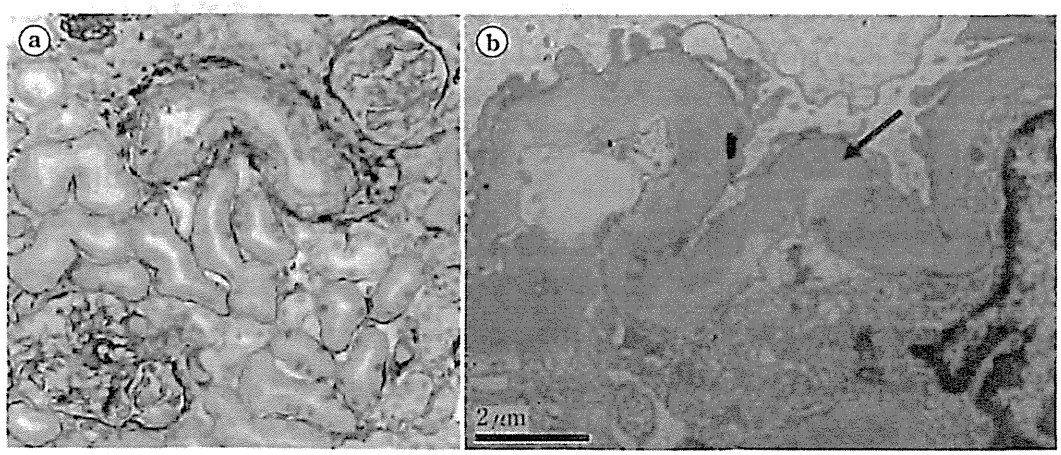

図3　8歳CS I型女児の腎病理
a. PAM染色：硬化・虚脱した糸球体周囲には内腔の狭小化した尿細管が認められる.
b. 電顕所見：基底膜の肥厚と蛇行(矢印)を認める.

表2 CS I型の臨床徴候と検査データ

	生存例21例 (うち男14例)	死亡例20例 (うち男10例)	p	合計41例
平均年齢(歳)	16.1(21例)	18.9(18例)	NS	
体 重(kg)	15.3(21例)	12.6(14例)	0.04	
身 長(cm)	103.5(20例)	96.2(10例)	0.02	
成長障害	20例(20例)	16例(16例)	NS	36/36(100%)
精神遅滞	21例(21例)	20例(20例)	NS	41/41(100%)
歩行可能	11例(20例)	10例(18例)	NS	21/38(55.3%)
有意語あり	18例(20例)	12例(19例)	0.046	30/39(76.9%)
経口摂取可能	19例(20例)	6例(17例)	0.0001	25/37(67.6%)
日光過敏	17例(19例)	17例(18例)	NS	34/37(91.9%)
窪んだ眼	19例(20例)	19例(19例)	NS	38/39(97.4%)
難 聴	16例(19例)	12例(12例)	NS	28/31(90.3%)
白内障	11例(17例)	9例(14例)	NS	20/31(64.5%)
網膜色素変性	14例(17例)	11例(11例)	NS	25/28(89.3%)
視神系萎縮	6例(14例)	6例(10例)	NS	12/24(50%)
側 彎	9例(19例)	3例(12例)	NS	12/31(38.7%)
足関節拘縮	18例(19例)	12例(13例)	NS	30/32(93.8%)
齲 歯	10例(16例)	8例(9例)	NS	18/25(72%)
高血圧	3例(10例)	6例(10例)	NS	9/20(45%)
腎不全	1例(21例)	9例(13例)	<0.001	10/34(29.4%)
貧 血	2例(21例)	8例(15例)	0.004	10/36(27.8%)
涙液分泌低下	2例(12例)	6例(9例)	0.02	8/21(38.1%)
発汗低下	10例(15例)	8例(10例)	NS	18/25(72%)
手指振戦	8例(18例)	9例(12例)	NS	17/30(56.7%)
下肢深部反射亢進	12例(19例)	6例(9例)	NS	18/28(64.3%)
痙攣発作	4例(20例)	2例(13例)	NS	6/33(18.2%)
睡眠障害	2例(17例)	5例(11例)	0.04	7/28(25%)
体温調節障害	8例(18例)	4例(7例)	NS	12/25(48%)
下痢傾向	6例(19例)	5例(9例)	NS	11/28(39.3%)
基底核石灰化	17例(17例)	11例(12例)	NS	28/29(96.6%)
末梢神経伝導速度の異常	6例(13例)	3例(6例)	NS	9/19(47.4%)
ABR異常	14例(17例)	4例(4例)		18/21(85.7%)
ALT(IU/L)	63.9(20例)	62.7(19例)	NS	
AST(IU/L)	114.8(20例)	119.8(19例)	NS	
BUN(mg/dL)	18.2(20例)	40.5(17例)	0.002	
Cr(mg/dL)	0.49(20例)	1.67(16例)	0.03	
尿タンパク陽性	2例(16例)	9例(11例)	0.0003	11/27(40.7%)

全国調査によるCS I型の臨床徴候と検査データを**表2**に示す[5]. CS I型41例で90%以上に認めた徴候としては成長障害, 紫外線過敏, 難聴, 窪んだ眼に代表される顔貌の特徴, 足関節拘縮, 精神遅滞, CT上の基底核石灰化であった[5]. これに網膜色素変性, 白内障, 齲歯が続く. 表には小頭に関しては触れていないがCS I型15例の平均頭囲は44.9±1.8cmであり著明な小頭といえる. このほか, ハスキーで高音の声や縮瞳傾向は共通してみられることが多い. またいわゆる自閉性がなく, 病期が進んでも人なつこさは変わらない.

CSの客観的診断には患者皮膚由来の培養線維芽細胞を用いて, ①紫外線照射後の不定期DNA合成能(unscheduled DNA synthesis: UDS)測定, ②紫外線感受性試験, ③相補性群試験な

どのDNA修復テスト，④遺伝子解析，⑤タンパク解析，⑥RNA合成回復試験(RRS)などがある．

一般の血液・生化学・尿検査に特異的異常はない．肝機能低下(ALT，AST上昇)は早期から認めるが平均100IU/Lを推移し臨床的に問題になることは少ない．腎機能低下は5-6歳頃から始まり10歳前後で明らかになるがその進行は症例による(表2)．クレアチニンは筋量低下のため過少評価されることがありシスタチンC併用でのフォローが望ましい．

小頭症，低身長，白質ジストロフィーを伴う疾患は鑑別の対象になるが表1，2の徴候と経過などを参考にすると困難ではない．思いつくことが重要である．

6. 治療と予後

現在のところ根本的な治療はなく対症療法がすべてである．紫外線対策として，外出時にはサンスクリーン剤を外用し，皮膚露出を避け，UVカット眼鏡を着用する．XPに比較すると紫外線過敏は軽症であることが多いが夏場は要注意である．紫外線過敏による紅斑などには比較的弱めの3-4群のステロイド外用剤を塗布する．

成長障害は栄養のみの問題ではないが，摂食機能低下が神経症状の進行(主に仮性球麻痺による)により出現し，いわゆる悪液質を悪化させるので適切な栄養指導は必要である．体重減少が続く場合，経鼻胃チューブ留置や胃瘻からの経腸栄養剤の注入に切り替える栄養管理は重要となる．Nanceら[12]の37人のCS患者の平均死亡年齢は12歳であったが，表2のように我が国のCSI型のそれは18.9歳であり，栄養管理を含めたケアの改善が関連していると推測している．

CSの腎不全は表2に示すようにCSI型の中でも死亡例に高率に認められる．生存例と比較しBUN・Crの高値，尿タンパク陽性，腎性貧血は有意差があり，尿酸，血圧フォローなども定期的に5-6歳以降には行うべきであろう[13]．全国調査における死亡例20例のうち9人が末期に腎不全となっている．腎不全の進行に対し腹膜透析が既に試みられている．降圧剤としては安全性の面からCa拮抗剤が第一選択である[13]．視機能低下に対する眼科フォロー，関節拘縮予防のためのリハビリ，装具，唾液分泌の低下による齲歯の治療，体温調節障害に対する適切な環境温度設定，睡眠障害(入眠・覚醒障害，夜間睡眠中の中途覚醒が頻回)に対してはベンゾジアゼピン系薬剤やラメルテオン(メラトニン受容体刺激薬)，進行性感音難聴に対しては補聴器装用などが必要となる．包括的治療を要するCSのケア指針がコケイン症候群研究会HPにあるので参照されたい[http://www.cockaynere searchcare.jp/]．

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神経症候群（第2版）

—その他の神経疾患を含めて—

IV

VIII　先天異常/先天奇形

染色体異常・先天奇形症候群

Seckel症候群

久保田雅也

VIII 先天異常/先天奇形

染色体異常・先天奇形症候群

Seckel症候群

Seckel syndrome

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Key words：低身長，小頭症，ATR遺伝子，DNA損傷修復

1. 概念・定義

Seckel症候群は，Seckelが1960年に自験2例を含めて初めて報告した胎児期からの成長障害，均衡型低身長，小頭症，知的障害，特異な顔貌で特徴づけられるまれな常染色体劣性遺伝を呈する疾患である．顔貌の特徴として大きな眼，大きく突出した鼻，狭い顔，下顎後退などを挙げた[1]．Majewskiら[2]は，①子宮内発育遅延，②出生後の発育遅延(身長−5SD以下)，③小頭症(頭囲−4SD以下)，④重度知的障害，⑤顔貌の特徴を臨床診断基準として挙げた．

骨年齢遅延，高口蓋，大泉門早期閉鎖，頭蓋縫合早期癒合症，両側性視神経萎縮と網膜変性，軽度の感音難聴が報告されている[3]．骨病変は一般にまれで軽度である．精神発達遅滞に関しては約半数はIQ 50以下とされるが軽度にとどまる例もある．10％に痙攣発作が起こるがコントロールは容易である．血液学的異常として3系統の血球減少，急性骨髄性白血病や染色体不安定性も一部の症例にみられる[3]．

原発性常染色体劣性小頭症(MCPH)とSeckel症候群(SCKL)スペクトラムは以前は身長により区別されていたが，身長はもはや区別する特徴ではなく，これらの表現型が独立疾患よりスペクトラムを構成する[3]．共通の遺伝子変異で両者の報告がある．MCPHは神経発生(neurogenesis)そのものの減少，SCKLはゲノム不安定性による胎児期からのアポトーシスが原因との仮説もある．

以下の病因や鑑別で述べるようにSCKLの表現型を有する多数の遺伝子が見いだされ，MCPHや小頭性骨異形成性原発性小人症II型(type II microcephalic osteodysplastic primordial dwarfism: MOPD2)との重複があり，遺伝子型・表現型相関はさらに検討が必要である．

2. 疫　　学

これまで60例以上が報告されているが正確な発生頻度は不明である．1:30,000−1:250,000との推定がある．変異遺伝子の確認は200家系未満とされる[3]．

3. 病　　因

SCKLの原因遺伝子は多岐にわたるが，障害されたDNAの修復(DNA損傷修復)に関わる遺伝子変異が関連する．SCKLの遺伝子変異の研究はO'Driscollら[4]による染色体3q22.1−q24にあるataxia−telangiectasia and RAD3−related protein(ATR)遺伝子変異を有するパキスタンの血族婚2家系5例の報告を嚆矢とする(SCKL1)．ホモ接合の一塩基置換(2101A>G)が同定され，選択的スプライシングの効率が変化し，ATRタンパク発現が低下した．このATRは細胞DNA障害反応および修復メカニズムの中心的役割を担い以下のような機能がある[3]．①serine/threonine protein kinaseで，電離放射線，紫外線またはDNA複製障害などの遺伝子毒性スト

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レスでチェックポイントシグナルを活性化する. ②基質コンセンサス配列[ST]-Qを認識する. ③BRCA1, p53/TP53などをリン酸化し, 集合的にDNA複製や細胞分裂を抑制し, DNA修復, 組換えおよびアポトーシスを促進する. ④DNA障害部位で, histone variant H2AX/H2AFXの'Ser-139'をリン酸化し, DNA障害反応メカニズムを調節する. ⑤FANCD2ユビキチン化に必要である. ⑥脆弱部位の安定性と効率性の維持に必須である. ⑦ATRとATM(ataxia telangiectasia mutated)は, 緊密に関係するキナーゼで, DNA障害により活性化される. ⑧DNA damage binding proteins/complexes(ATRのATRIP; ATMのMRN)による反応で, ATM/ATRは鍵となるタンパクのリン酸化によりDNA障害チェックポイントを開始する.

その他Seckel-likeの原因としてはretinoblastoma-binding protein 8(RBBP8)遺伝子のホモ接合体変異(SCKL2)[5], MNAT1遺伝子(SCKL3)[6], centromere protein J(CENPJ)遺伝子変異(SCKL4)[7], centrosomal protein 152-kD(CEP152)遺伝子変異(SCKL5)[8], centrosomal protein 63 kDa(CEP63)遺伝子変異(SCKL6)[9]など多数報告されている.

SCKL4のCENPJ遺伝子はMCPHの原因遺伝子でもあり大脳や脊髄に多く発現し, 発生初期には特に前頭葉の神経上皮に多く局在する. 機能的には中心小体発生に関与する中心体タンパク発現に関わる. SCKL5のCEP152遺伝子も中心体機能に関与し, CEP152の機能が失われると, ATMシグナル伝達経路の活性化とH2AXリン酸化とがともに増強され, 複製ストレスによって生じるゲノム複製時の異常が集積される[3].

さらに最近ATRタンパク質と相互作用してDNA修復チェックポイントの活性化調節に必須であるATR interacting protein(ATRIP)をコードするATRIP遺伝子変異が新たに疾患責任変異として同定されている[10].

4. 病　　態

細胞にはDNA損傷などが起こった場合, その異常を検知する機構があり, 細胞周期制御系のチェックポイントが活性化される. なかでもATR kinaseやATM kinaseが活性化され, 細胞はDNA修復・複製終了までG1期やG2期で停止する. ATMはDNA二本鎖切断応答に関与しており, ATRはDNA複製ストレスやDNA損傷により露出した一本鎖DNAに結合しDNA損傷応答(DNA damage response: DDR)と称される細胞応答を調節する. DDRは, 細胞周期制御系のチェックポイント活性化によりDNA損傷を感知し, DNA修復を活性化させ, 細胞死, 細胞周期停止といった転写プログラムを活性化させる細胞内シグナル伝達を行う.

Murgaら[11]はマウスにヒトSCKLの変異として知られるATR遺伝子変異A/G transitionを導入すると, ヒト遺伝子の場合と同様にスプライシング異常がみられ, ヒトSCKL特有の症状(子宮内発育遅延, 小頭, 小顎および額後退を含む顔貌異常, 小さな脳, および脳梁欠損), 老化徴候, 汎血球減少などをマウスが示すことを報告した. 彼らは胎児期からのDNA損傷曝露が幼若マウスを老化の加速に導くプログラムの始まりではないかと推測している[11]. ATR遺伝子の機能不全のため胎児期からDDRが機能せず, ゲノムは安定性を失い, ゲノム複製時の異常の集積が多様な症状を生じると考えられる(ATR-Seckel症候群). Ogiら[10]のATR-ATRIP-Seckel症候群は小眼球, 小顎, 歯科的異常, 骨格異常を伴いSCKLの遺伝子型-表現型の多様性をさらに示した.

またMcIntyreら[12]はCenpjの低形質対立遺伝子を有するマウスを作成し, 中心体機能の異常がヒトSCKL特有の症状を示すことを報告した. このマウスは胎児期からDNA損傷増加やアポトーシスなどのゲノム不安定性を示すが, 注目すべきはMurgaら[11]におけるようなATR/ATM依存性のDDR, 細胞内シグナル伝達は関与していなかったことである. 胎生期の有糸分裂失敗に起因する細胞死の増加がCENPJ-Seckel症

候群の均衡型成長障害の原因であろうと推測された．いずれも発生早期からのゲノム不安定性増加が病態の中心にあると考えられている．

5. 診断と鑑別診断

SCKLの診断は1．で挙げた臨床診断基準に基づく[2]．SCKLの特徴的顔貌は，ほかの小頭を伴う症候群からの重要な鑑別のポイントとなる．Dubowitz症候群，de Lange症候群，Bloom症候群，Nijmegen断裂症候群，およびFanconi症候群などが鑑別すべき疾患として挙げられる．コケイン症候群は成長障害，低身長など共通するものが多いが一般に出生時の低身長，小頭症はなく，皮膚の紫外線感受性を認め，顔貌は特異的でCT上基底核に石灰化を認めることから鑑別はそう困難ではない．

またSCKLはMOPD2と表現型が重なる．両者は子宮内発育遅延，著明な均衡型低身長，小頭症が共通するが，MOPD2はSCKLと比較し，成長障害はより重篤であり(成人身長<100 cm)，骨の異常を伴い，知的障害は軽度であることが鑑別となり，責任遺伝子は染色体21q22.3上のpericentrin(PCNT)である[13]．

Ozawaら[14]はPCNT遺伝子の変異が確認されたMOPD2を報告している．それによると本症女児は非血縁の両親に在胎35週，出生時体重850 g(−5.9 SD)，身長31.0 cm(−10.2 SD)，頭囲24.5 cm(−6.2 SD)で生まれた．2歳7カ月時には体重6,325 g(−4.3 SD)，身長58.5 cm(−8.4 SD)，頭囲36 cm(−7.5 SD)と著明な成長障害を認め，発達指数はデンバー発達スクリーニングテストで60と遅滞を認めた．またまばらな毛髪，後退した額，短い下向き傾斜眼瞼裂，くちばし様の鼻，高口蓋，小顎，小さな口，薄い唇など一部はSCKLと共通であった．長管骨の過剰管状形成，遠位大腿骨の骨幹端カッピングと象牙骨端と短指症も認めた．本患者の頭部MRIを図1に示す．厚脳回，白質容量減少，シルビウス裂の不十分な発達などの形成不全を認める．脳構造の重篤さからすると発達は良好といえる．

図2に特異な顔貌と小頭症からSCKLと臨床診断されている5歳女児の頭部MRIを示す．本患者は在胎37週3日，出生時体重2,205 g(−2.2 SD)，頭囲28.7 cm(−3.2 SD)，身長43 cm(−2.9 SD)で仮死なく出生した．発音は不明瞭だが会話は可能で言語療法を行い，軽度発達遅滞の状態である．現在頭囲40.5 cm(−5.5 SD)と著明な小頭を認める．MRI上シルビウス裂の厚脳回，前頭葉低形成を認める．一般にSCKLの中枢神経系の異常としては全前脳胞症，Chiari 1型奇形，裂脳症，脳梁欠損，厚脳回，髄梢化障害などの報告がある．両症候群ともに大脳半球の発生学的な異常はあるが，特異性に欠け，これのみでは診断は困難である．実際に臨床的にSCKLと診断された例にもPCNT遺伝子変異が見いだされている[15]．それによるとPCNT遺伝子変異をもつSCKLはもたないSCKLより成長障害が顕著(−6−−8 SD対−4−−5 SD)であったがMOPD2よりも軽く(−7−−13 SD)，また骨病変も有し，知的にも正常もしくは軽度遅滞であった．PCNT遺伝子変異ではATR依存性G2/Mチェックポイント停止に欠陥があってもATRの下流のリン酸化に異常はないことがATR-Seckel症候群との相違である．表現型としてはSeckel-MOPD2 spectrumともいえるが，MOPD2がモヤモヤ病など脳血管障害を呈することがあるので鑑別は重要となる[16]．表現型のみでこれらの症候群を確定するのは現在困難であり遺伝子診断と併せて検討すべきである．

6. 治療と予後

根本的治療法はなく対症療法のみである．低身長に対する有効な治療法は今のところない．まれに貧血，汎血球減少や急性骨髄性白血病の報告があるが化学療法への忍容性(tolerance)が低い可能性がある[17]．生命予後は概して良好とされる．

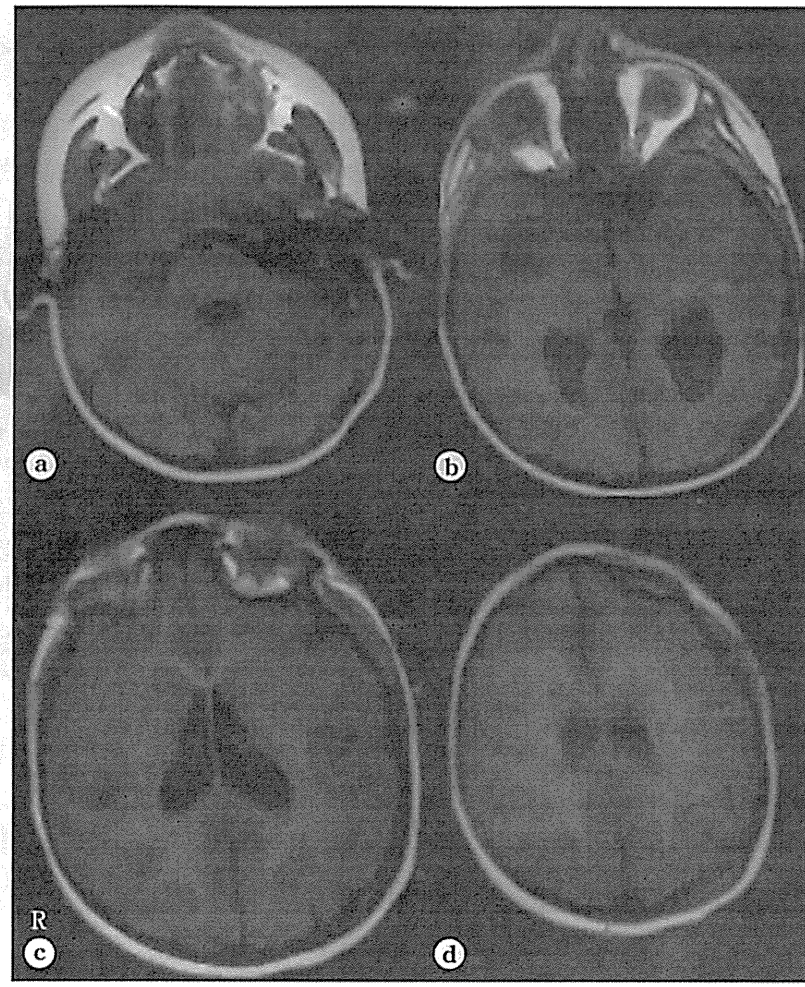

図1 小頭性骨異形成性原発性小人症II型(type II microcephalic osteodysplastic primordial dwarfism: MOPD2)2歳7カ月 女児の頭部MRI
厚脳回, 白質容量減少, シルビウス裂の不十分な発達などの形成不全を認める.

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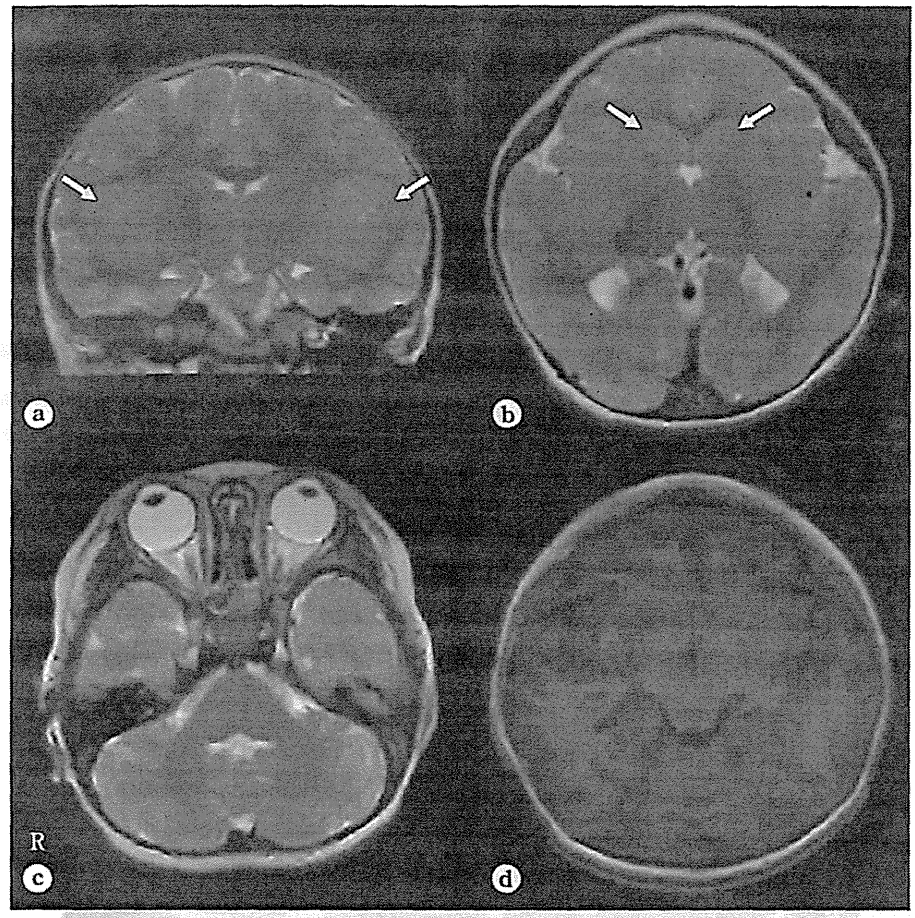

図2　Seckel症候群5歳女児の頭部MRI

前頭葉低形成，シルビウス裂の皮質形成異常(a，矢印)，やや大きな尾状核(b，矢印)を認める．

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Review Article

Canavan disease: Clinical features and recent advances in research

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Abstract Canavan disease (CD) is a genetic neurodegenerative leukodystrophy that results in the spongy degeneration of white matter in the brain. CD is characterized by mutations in the gene encoding aspartoacylase (ASPA), the substrate enzyme that hydrolyzes *N*-acetylaspartic acid (NAA) to acetate and aspartate. Elevated NAA and subsequent deficiency in acetate associated with this disease cause progressive neurological symptoms, such as macrocephaly, visuocognitive dysfunction, and psychomotor delay. The prevalence of CD is higher among Ashkenazi Jewish people, and several types of mutations have been reported in the gene coding ASPA. Highly elevated NAA is more specific to CD than other leukodystrophies, and an examination of urinary NAA concentration is useful for diagnosing CD. Many researchers are now examining the mechanisms responsible for white matter degeneration or dysmyelination in CD using mouse models, and several persuasive hypotheses have been suggested for the pathophysiology of CD. One is that NAA serves as a water pump; consequently, a disorder in NAA catabolism leads to astrocytic edema. Another hypothesis is that the hydrolyzation of NAA in oligodendrocytes is essential for myelin synthesis through the supply of acetate. Although there is currently no curative therapy for CD, dietary supplements are candidates that may retard the progression of the symptoms associated with CD. Furthermore, gene therapies using viral vectors have been investigated using rat models. These therapies have been found to be tolerable with no severe long-term adverse effects, reduce the elevated NAA in the brain, and may be applied to humans in the future.

Key words aspartoacylase, Canavan disease, leukodystrophy, *N*-acetylaspartic acid, spongy degeneration.

Canavan disease (CD) is an autosomal-recessive progressive neurodegenerative disease that belongs to a group of genetic disorders recognized as leukodystrophy. CD is neuropathologically characterized by the swelling and spongy degeneration of white matter in the brain. CD was first reported by Canavan in 1931[1] and was identified as a distinct disease by Bertrand and Van Bogaert in 1949.[2] Although CD has been reported in communities throughout the world, it was shown to be more prevalent in Ashkenazi (Eastern European) Jewish people.[3] The disease has been attributed to a deficiency in aspartoacylase (ASPA) activity. ASPA is a zinc carboxypeptidase enzyme that is responsible for the breakdown of aspartic acid or *N*-acetylaspartic acid (NAA), the absence of which results in the accumulation of NAA in the brain. ASPA is normally found in oligodendrocyte progenitor cells and oligodendrocytes in the brain, with smaller amounts being reported in microglia and brainstem neurons. NAA, one of the most prevalent small molecules in the brain, is hydrolyzed to acetate and aspartate in oligodendrocytes.[4]

Many researchers initially believed that the high NAA associated with CD led to the impeded production of myelin and subsequent spongy degeneration in the brain,[5,6] but this is now being disputed. Cloning of the human ASPA gene has enabled molecular genetic studies of CD.[3]

Clinical course of CD

Three clinically distinct groups of CD have been identified: (i) the congenital form with severe symptoms in the first few weeks of life; (ii) the infantile form, the most common form in which the disease is apparent by 6 months of age; and (iii) the juvenile form, in which the disease is apparent by the age of 4 or 5.[5] Infants with CD typically appear to be normal in the first few months of life. Early signs of CD include irritability and hypotonia with poor head control. The common symptoms of CD include head lag, macrocephaly, hypotonia, ataxia, inadequate visual tracking, poor sucking ability, and intellectual disabilities.[7,8] In many cases, developmental delays and macrocephaly become noticeable after 6 months of age. In spite of profound delays, CD patients can sometimes interact with others, smile, and reach for objects. CD patients later develop optic atrophy, and hypotonia of the arms and legs converts to limb stiffness and spasticity, and axonal hypotonia persists. These patients become increasingly debilitated with age, often having seizures and being unable to move or swallow voluntarily. The long-term prognosis of a typical CD case is still poor; death typically occurs before adolescence, while some patients with milder forms survive beyond their second decade of life.

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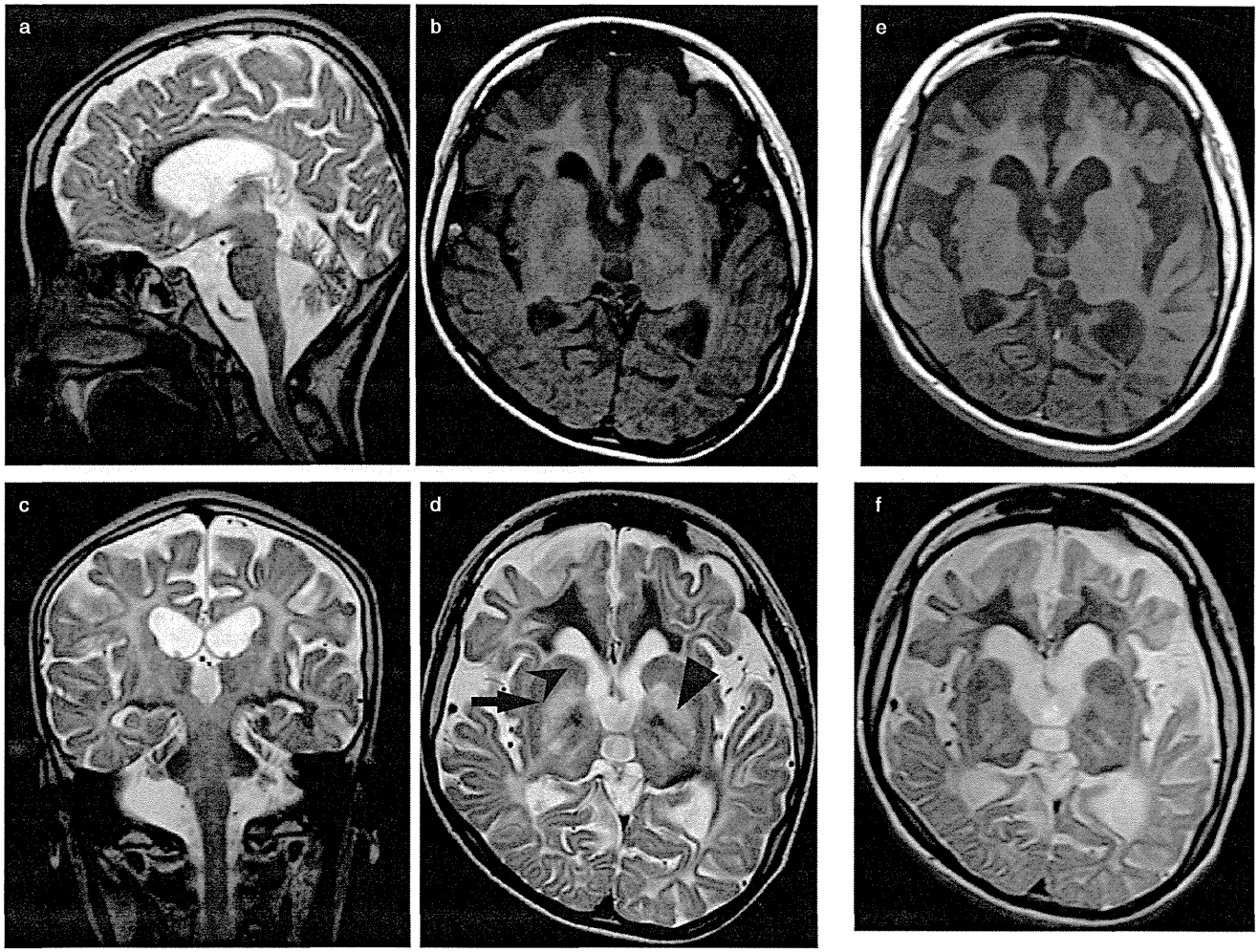

Fig. 1 Chronological features of magnetic resonance imaging (MRI) in a female Japanese Canavan disease patient at (a–d) 15 years and (e,f) 25 years of age. (b,e) T1 and (a,c,d,f) T2-weighted MRI show the involvement of the diffuse white matter, including the corpus callosum and internal capsule, as well as the (▶) globus pallidus. The (➡) putamen and (➤) caudate nucleus were spared. There are signs of diffuse cerebral and cerebellum atrophy.

Clinical examination for diagnosis

The specific method currently used to diagnose CD is urine testing.[9] CD is caused by a deficiency in ASPA, which hydrolyzes NAA to aspartate and acetate in the brain. Therefore, urinary NAA is markedly higher in CD patients, often more than 100-fold, than in normal individuals. Slightly elevated NAA (approximately 4–6-fold) have been reported in other cases of leukodystrophy.[10,11] Therefore, this diagnostic procedure is accurate for the screening and chemical diagnosis of CD, with a good cost–benefit ratio. Genetic testing for the ASPA gene mutation can also lead to a definite diagnosis of CD. Cultured skin fibroblasts were previously shown to manifest this enzyme deficiency, even in the absence of an ASPA gene mutation.[3,12] Microscopy shows spongy degeneration throughout the white matter, demonstrating vacuole formation in the myelin sheaths, astrocyte swelling, and deformed mitochondria.

In neurophysiological examinations, electroencephalograms can be diffusely slow with paroxysmal features. Evoked potentials are often delayed or absent, whereas the nerve conduction velocity is typically normal.

Neuroimaging of CD

Computed tomography of the head has shown diffuse hypodensity in the white matter of the brain, while magnetic resonance imaging (MRI) showed diffuse cerebral white matter degeneration. The most severe abnormalities are present in the subcortical white matter with a mildly swollen aspect, and central white matter structures, such as the periventricular rim of the white matter and the internal capsule, are generally preserved. The central white matter also becomes involved as the disease progresses, and white matter atrophy has been reported. The globus pallidus and thalamus are often involved, whereas the

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putamen and caudate nucleus are spared, which is characteristic of CD (Fig. 1).[13] Nuclear magnetic resonance spectroscopy (MRS) has shown that NAA is higher in the brains of CD patients than in those of normal individuals (Fig. 2).[14]

Differential diagnosis

Macrocephaly has been reported in Alexander disease, Tay–Sachs disease, and other neurodegenerative diseases. Hydroxymethylglutaric aciduria also leads to macrocephaly and involvement of the white matter. Spongy degeneration of the brain can occur with viral encephalitis, mitochondrial disease, and other metabolic diseases.

Molecular basis of CD

The human ASPA gene, which is localized on the short arm of chromosome 17 (17p13-ter), was cloned by Kaul *et al.* in 1991.[15] The human ASPA gene spans 30 kb and contains five introns and six exons. Over 96% of CD patients among Ashkenazi Jewish populations have either of two mutations. One is a missense mutation in codon 285, which causes glutamic acid to be substituted with alanine (Glu285Ala). The other is a nonsense mutation on codon 231, which converts tyrosine to a stop codon (Tyr231X). The carrier frequency of these two mutations among Ashkenazi Jewish populations has ranged from 1:37 to 1:40, with a prevalence rate of 1 per 6400–13500 live births.[4,16]

Mutations are different and more diverse in non-Jewish patients. The most common mutation in non-Jewish patients, a missense mutation that substitutes alanine for glutamic acid (Ala305Glu), has been detected in codon 305.[17]

More than 50 mutations have been identified in the human ASPA gene, most of which are single base pair changes in the coding region that typically result in the loss of ASPA enzymatic activity. While all patients in whom mutations have been detected have exhibited psychomotor limitations, their onset and severity varied depending on the specific mutation.[18,19]

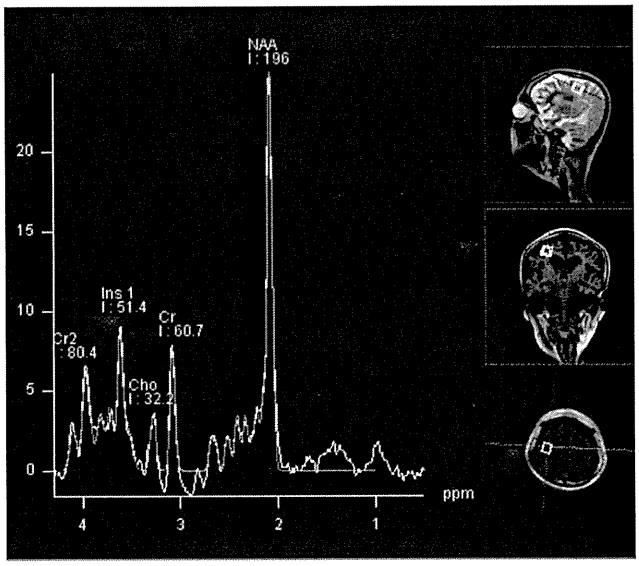

Fig. 2 Features of ^{1}H magnetic resonance spectroscopy in a female Japanese Canavan disease patient (same as in Fig. 1). The highly elevated *N*-acetylaspartic acid (NAA)/choline ratio (6.1; normal range, 1.0–2.4) was characteristic.

Japanese case of CD

Our questionnaire survey identified only one CD patient in Japan, and this is also the only case that has been reported with the missense mutation I143T.[20–22] The patient, a woman, is now 26 years old. She had macrocephaly, gross motor development retardation, and hypotonia since early infancy. She was diagnosed with CD at the age of 4. She could not sit alone due to slowly progressive spastic tetraplegia, but was relatively frequently able to attend school. She had difficulty swallowing at the age of 17 because of progressive bulbar paralysis, and was subsequently fed via a nasogastric tube. She underwent laparoscopic anti-reflux surgery for gastroesophageal reflux disease at the age of 20. Given that the bulbar paralysis is not currently considered to be severe, she does not require any respiratory devices. Although the frequency of tonic seizures increased after the age of 25, levetiracetam has effectively reduced the number of seizures experienced. Figure 1 shows MRI done at the ages of 15 and 25. Subcortical-dominant diffuse white matter was found to be involved. The anterior part of the corpus callosum was highly degenerated. The bilateral globus pallidus and thalamus were also involved, whereas the putamen and caudate nucleus appeared to be spared. Although there are signs of diffuse brain atrophy including the cerebellum, the size of the brainstem has been preserved.

Figure 2 shows MRS of a white matter region at the age of 15. Consistent with previous studies, high NAA concentration and elevated NAA/choline ratio were found to be characteristic in the Japanese patient. Figure 3 shows the ^{99m}Tc-ethyl cysteinate dimer single-photon emission computed tomography done at the age of 15. A frontal predominant decrease in cerebral blood flow was observed.

Possible pathological mechanism responsible for CD

N-Acetylaspartic acid appears to be synthesized exclusively in neurons and has been isolated from mitochondrial and microsomal fractions.[23] NAA and its related dipeptide *N*-acetylaspartyl-glutamate (NAAG) are transported from cytoplasm to the extracellular space by transporters, and NAA is taken up by oligodendrocytes through a dicarboxylic acid transporter prior to being hydrolyzed by ASPA (Fig. 4).

N-Acetylaspartic acid serves as a clinical marker of the neuronal metabolic integrity of the brain. In contrast with the decrease reported in NAA in many other neurodegenerative diseases, CD is unique because it is associated with elevated NAA in the brain. A marked rise of NAAG concentration has also been reported in patients with a Pelizaeus–Merzbacher-like syndrome, in which there is an absence of myelin.[24] Establishing why increases in NAA or NAAG lead to white matter degeneration or

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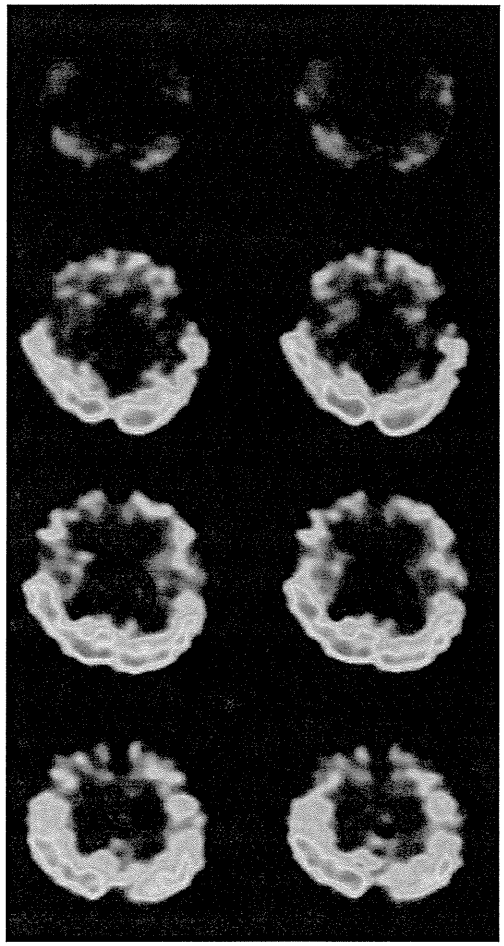

Fig. 3 ^{99m}Tc-ethyl cysteinate dimer single-photon emission computed tomography of a female Japanese Canavan disease patient. The frontal decrease in cerebral blood flow is characteristic. This was obtained from the same case as in Figures 1,2.

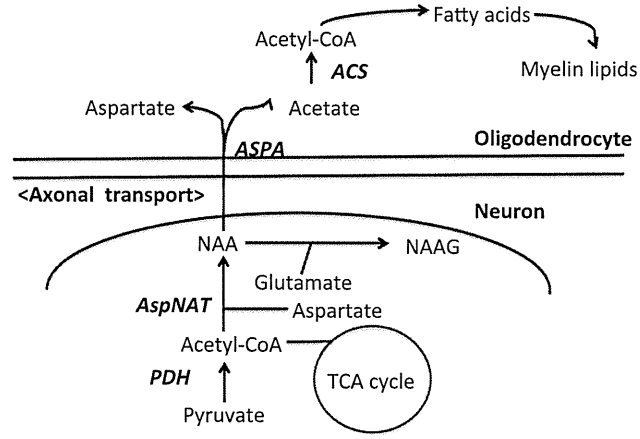

Fig. 4 Schematic representation of *N*-acetylaspartic acid (NAA) synthesis in neurons and degradation in oligodendrocytes. ACS, acetyl CoA synthetase; ASPA, aspartoacylase; AspNAT, aspartate *N*-acetyltransferase; NAAG, *N*-acetyl-aspartyl-glutamate; PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid.

dysmyelination is very important, but the precise function of NAA in the development of the central nervous system (CNS) remains unknown.

Several hypotheses have been proposed to explain the pathophysiology of CD in the CNS.

First, demyelination may reflect the direct action of NAA on oligodendrocyte NMDA receptors. No current, however, was evoked by NAA in oligodendrocytes in a rat study. Therefore, the action of NAA or NAAG on oligodendrocyte NMDA receptors is unlikely to be a major contributor to white matter damage.[25]

Second, NAA may serve as a molecular water pump to remove metabolic water from mitochondria and neurons through its hydrolysis into acetate and aspartate by ASPA. This hypothesis corresponds to astrocytic edema and the formation of vacuoles in CD as a result of the accumulation of NAA.[26] A previous study, however, showed that NAA was non-toxic even at high concentration,[27] and no functional improvement was reported in CD mice even after NAA decreased due to the expression of an introduced normal ASPA gene.[28] An immunohistochemical study of the Nur7 mouse model of CD showed that aquaporin 4 (AQP4) was located throughout the cytoplasm in CD mice, but it was located exclusively in the astrocytic end-feet in control mice. This indicates that the astroglial regulation of water homeostasis may be involved in the partial prevention of spongy degeneration, and AQP4 may be a potential therapeutic target for CD.[29]

Third, NAA may be essential for lipid synthesis and myelination in the CNS during the period of postnatal myelination.[12] CD is characterized not only by an increase in NAA but also by a decrease in acetate and aspartate,[12,30,31] and a reduction in free acetate for lipid synthesis subsequent to the loss of ASPA function may contribute to the disease etiology. Spongiform degeneration in CD brains has been attributed to the failure of NAA to act as an acetate carrier from mitochondria to the cytosol, leading to impaired lipogenesis.[32,33] Therefore, one of the main causes of CD may be a decline in acetyl groups in the absence of ASPA activity. Non-polar and polar lipid levels, critical for myelin synthesis, were found to 21–38% lower in ASPA knockout mice than in wild type, whereas other lipids were not altered significantly.[32] Moreover, a reduction of cerebroside and sulfatide, component glycolipids of myelin in the white matter, was also reported both in the rat CD model and in human CD patients. The reduction observed in lipid level, however, may not have directly correlated with the clinical severity of the disease. These results suggest that the pathogenesis of CD is not restricted to a deficiency of acetate.

Fourth, NAA may play an important role in maintaining the metabolic integrity of oligodendrocytes. Elevation in oxidative stress markers was shown to precede the loss of oligodendrocytes and demyelination in the early days following birth.[34]

Last, besides the role of acetate in myelin formation and maintenance, acetylation also modulates the function of nucleosomal histones, which are components of chromatin. Therefore, a decrease in acetate may alter the expression of genes considered to be important for the maturation of

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oligodendrocytes.[35] Although NAA is produced and localized primarily in neurons,[36] high NAA concentration has also been reported also in immature oligodendrocytes. NAA, however, was not detected in mature oligodendrocytes or astrocytes, which suggested the important function of ASPA in immature oligodendrocytes.[37] In rat cortical cultures, the presence of ASPA activity as well as the expression of ASPA mRNA and protein have been reported in non-myelinated oligodendrocytes.[31,38,39] Although the direct uptake of NAA by oligodendrocytes has not yet been reported, axonal transport of NAA has been demonstrated.[40] These findings suggest that the maintenance of myelin is impaired in the absence of NAA-derived acetate. ASPA plays a critical role in the maturation of oligodendrocytes and has also been shown to contribute to the pathophysiology of CD.[41] Furthermore, in an adult ASPA knockout mouse study, disruptions have been observed in cell cycle regulation, the acetylated state of nuclear histones, and continuous neurogenesis in neural cell progenitors, as well as severe reduction in certain myelin proteins.[42] ASPA may be involved in the epigenetic regulation of myelin maturation and maintenance through the supply of acetate.

Therapeutic approaches to CD

A therapy that affects the progression of CD has not yet been established. Seizures need to be controlled by anticonvulsants. Patients with CD may need nasogastric feeding or feeding by gastronomy. Acetazolamide was found to be beneficial in reducing intracranial pressure, but did not reduce white matter swelling or NAA level.

Dietary supplementation is one of the non-invasive therapies that have been positively correlated with improvement in NAA level in CD patients. Lithium citrate decreased whole-brain NAA in both rat models and human subjects.[43] More recent studies noted improved scores in gross motor functioning and visual tracking in CD patients treated with lithium citrate from an early age compared to untreated control groups of CD patients.[44] Acetate supplementation represents another potential therapy for CD that is easy and inexpensive.[45] Oral treatment with glyceryl triacetate (GTA) in CD mice led to a 17-fold increase in acetate in the brain and improved motor function, while NAA level in the brain was not significantly increased.[46] This therapy is now being used in CD patients. Although high-dose GTA (up to 4.5g/kg per dose) treatment in CD infants resulted in no improvement in their clinical status, no significant side-effects or toxicity were observed. The importance of earlier intervention has been suggested.[47] Another possible supplement is triheptanoin, an odd-carbon triglyceride, which is a dietary anaplerotic substrate that provides ketone bodies capable of traversing the blood–brain barrier and increasing the mass of tricarboxylic acid (TCA) cycle intermediates. Triheptanoin was shown to be effective in the treatment of mitochondrial oxidation and pyruvate metabolism.[48,49] A previous study reported that interventions with triheptanoin therapy reduced oxidative stress, promoted long-term survival of oligodendrocytes, and increased myelin in the brain in the nur7 mouse model.[50] The novelty of that study lies in the potentially anaplerotic substrate, with the aim of supporting TCA cycle oxidative integrity in addition to fatty acid synthesis during developmental myelination. The early provision of triheptanoin as an alternative energetic substrate to the nur7 mouse model promoted myelination by reducing the metabolic demands placed on the oxidation of glucose by fatty acid synthesis.[50] NAA was found to be higher in the brains of neonatal triheptanoin mice than in control mice, and triheptanoin had no effect on NAA. NAA is known to have a negative impact on anti-oxidant defenses; therefore, antioxidants may have therapeutic application in CD patients.[51]

Several studies recently attempted to use gene therapies for the treatment of CD. A therapy using adeno-associated virus (AAV) was used in the tremor rat, a genetic model of CD, and ASPA activity was subsequently detected in the CNS neurons of this rat. Although NAA was also reduced in the brain, motor functions remained unimproved.[28]

The application of gene therapy for CD currently faces several challenges. The varied rates of disease progression and small number of patients have confounded any interpretation of the effects of this therapy. Moreover, it is difficult to attempt a cohort study of age-matched or similar-phenotype patients due to variations in the mutations that cause CD.

Leone *et al.* reported the findings of a long-term follow up of gene therapy with an AAV vector carrying the ASPA gene (AAV2-ASPA) in 13 CD patients.[52] Each patient received 9×10^{11} vector genomes via intraparenchymal delivery at six brain infusion sites. The gene therapy was tolerable, no severe long-term adverse effects were noted, elevated NAA in the brain was reduced, the progression of brain atrophy was slowed, and improvements were observed in the frequency of seizures.[52] Moreover, neurological examination showed significant improvement in motor functions in younger cohorts of treated CD patients, indicating the possible advantage of early therapeutic intervention.[53]

Conclusion

In addition to the accumulated medical research on CD, parent and family community support has been increasing. Internet forum or family websites are also meaningful for CD patients.[19] The prognosis of childhood CD has gradually improved due to advances in comprehensive care. Future research will hopefully facilitate development of a safe and therapeutic approach for CD patients and improve their quality of life.

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