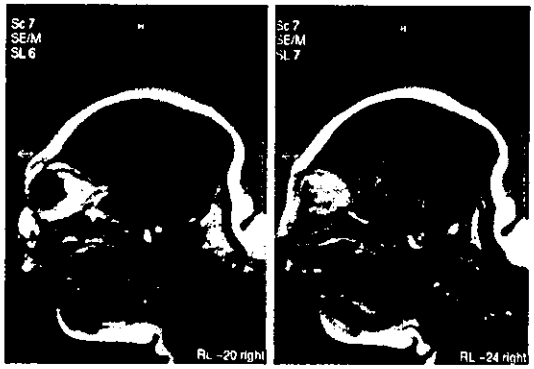

Fig. 1　Cranial MRI at the age of 2 months showed hypoplasia of cerebrum. However, cerebellum, brain stem and thalamus had almost normal formation and structures.

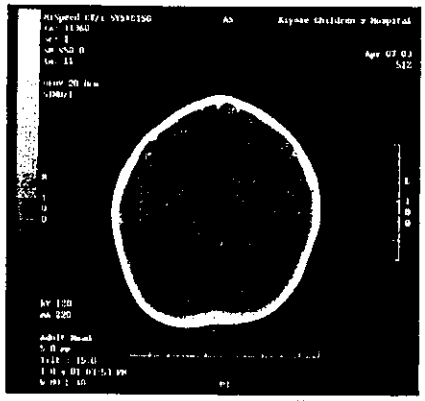

Fig. 2　Cranial CT scan at the age of 14 months showed hypoplasia of anterior portion of cerebrum. However, there were no anatomical abnormalities.

臨床経過：出生後、0～1日にかけて無呼吸発作をみとめたが、自然に軽快した。その後は呼吸状態を含めて全身状態は安定していた。生後1カ月時に、頭蓋の特徴、頭部MRI画像(Fig. 1)所見、染色体異常を認めないことなどから原発性小頭症と診断した。生後10カ月時に、全身の強直発作が出現してきた。11カ月になり発作は連日みとめられるようになった。脳波では、左前頭部から前側頭部に棘波をみとめた。症候性局在関連性てんかん、二次性全般化発作と診断しバルプロ酸(VPA、20 mg/kg/day)を開始した。VPA開始後発作は消失している。患児は現在、定頸をみとめず有意語もみられない発達遅滞を示している。

症例2：3歳10カ月の女児
主訴：小頭、けいれん
家族歴：特記すべきことなし
妊娠・分娩歴：妊娠中は特記すべきことなし。在胎40週、出生体重3,036 g、経膣分娩にて出生し仮死はなかった。身長47 cm、頭囲29 cm（－3.0 SD）であった。
臨床経過：出生後、小頭をみとめ精査が行われた。染色体異常なく、頭蓋の特徴、頭部CT (Fig. 2)所見、先天感染の否定などから原発性小頭症と診断した。その後、1歳時と1歳2カ月時に、発熱に伴い全身の強直間代けいれんを約5分間みとめ熱性けいれんと診断されている。経過をみていたところ、1歳9カ月の時、無熱時に全身の強直けいれんが約2分間出現した。脳波に異常なく経過観察となったが、2歳2カ月時に再度同様の無熱性けいれんが20分以上にわたり出現した。脳波では、右前頭部に棘波をみとめ症候性局在関連性てんかん、二次性全般化発作と診断した。VPA (20 mg/kg/day) を投与し発作は抑制されている。現在3歳10カ月にて、独歩、小走り可能で有意語は4～5個みられている。DQは56と判定されている。

症例3：4歳10カ月の男児
主訴：小頭、けいれん
家族歴：特記すべきことなし
妊娠・分娩歴：在胎28週より頭が小さいことを指摘されていた。在胎39週5日、生下時体重2,344 g、身長45.6 cm、頭囲29 cm（－3.5 SD）にて出生した。
臨床経過：定頸3カ月、寝返り9カ月、座位11カ月としだいに発達の遅れが目立ってきていた。6カ月時に、他院にて頭蓋の特徴、頭部MRI所見、染色体正常および先天感染の否定などから原発性小頭症と診断された。生後9カ月時に、右側へ眼球偏位し脱力する発作をくりかえし他院にてカルバマゼピン（CBZ）投与が開始となった。1歳2

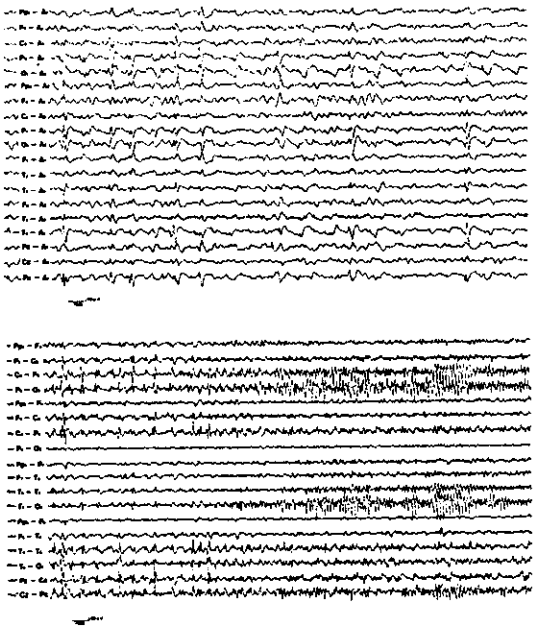

Fig. 3 EEG at the age of 12 months, asleep. Top : Interictal EEG, monopolar montage, showed sporadic spikes mainly in the posterior regions. Bottom : Ictal EEG, bipolar montage, showed posterior discharges characterized by bursts of sharp activities.

カ月時、右眼球偏位からチアノーゼとなり、その後右上下肢の間代性けいれんより全般性の間代性けいれんとなる発作が重積し他院へ入院となった。脳波では、非発作時には左後頭部および側頭部あるいは両側の後頭部に棘波をみとめ、眼球右方偏位する発作時には、頭頂から後頭部中心に鋭波をバースト状に認めた(Fig. 3)。以上より症候性局在関連性てんかん(後頭葉てんかん)、発作型は複雑部分発作および二次性全般性強直間代発作と診断されVPAついでゾニサマイド(ZNS)が追加投与となった。しかし発作は難治であり、時に重積となることもあった。その後、CBZ、ZNSは中止しフェニトイン(PHT)、ニトラゼパム(NZP)、臭化ナトリウムが追加投与となり発作は減少していた。DQは46と判定されている。4歳10カ月時に当院転院となった。現在VPA 20 mg/kg/day (血中濃度52.4 μg/ml)、PHT 13 mg/kg/day (同23.4 μg/ml)、NZP 0.3 mg/kg/day (同24.8 ng/ml)、臭化ナトリウム40 mg/kg/day投与にて、1回約5分間の同様の発作が1カ月に1回程度みられている。頭部MRI画像を(Fig. 4)に示す。

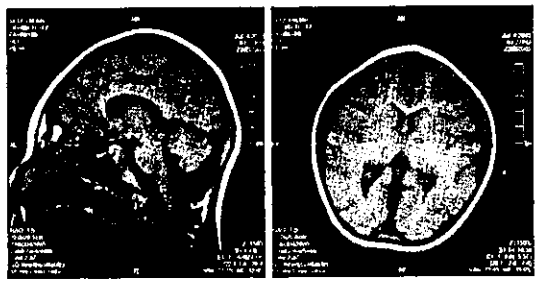

Fig. 4 Cranial MRI at the age of 4 years. Microcephaly was noted. Bilateral frontal lobe was relatively small compared to the other parts. Slight macrogyria could be seen in bilateral temporoparietal region. Myelination was age-matched.

考　察

小頭症は、正常頭囲より−3.0 SD以下のものを総称する疾患名であり有病率は0.2%と報告されている[1]。その原因はさまざまであり、小頭のみのもの、いいかえれば脳の発達障害に基づく精神、神経症状のみのものと、他の身体所見に異常を合併するものに分かれる。さらに内因性のもの(原発性、Paine症候群、Alpers症候群、Seckel症候群など)、染色体異常によるもの(Down症候群、13 trisomy、18 trisomy、4 p−症候群など)、外因性のもの(多発性のう胞性脳軟化症、X線被爆、巨大細胞封入体症、先天性トキソプラズマ症、胎児性アルコール症候群など)に分かれる[2]。しかし、小頭症まではいかない−2.0 SDから−3.0 SD未満の頭囲の児でも精神もしくは運動発達に異常をみとめることも多く、単に頭囲のみから症状を予測することは困難であり、小頭症であるからすべて症状が重篤とは限らない。頭囲の測定に関しては、実際の臨床の場では計測部位が一定していないことがあり、計測値を比較する時に混乱を招くことがある。一般に頭囲の測定方法には次の二通りがある。すなわち、1)外後頭結節と前頭隆起を通る周径(OFC)、2)外後頭結節と眉間を通る周径(OGC)である。現在は厚生労働省による身体

発育調査ではOGCに統一されているため今回もOGCを用いた[3]。原発性小頭症は、常染色体劣性遺伝とされている。別名、真性小頭症とかPenrose microcephalyとかtrue microcephalyとも呼ばれている。頭部の形態的特徴としては、神経頭蓋が顔面頭蓋に比して著しく小さく、とくに前額部の発達が悪く後方に傾斜しslopingと表現される。後頭部は平坦であり、後頭蓋窩の発達は正常であるため全体として頭頂部に向けて尖頭状をなす。今回の3症例は、特徴的な頭蓋の形、頭部MRI所見、染色体検査正常、先天感染の否定などから原発性小頭症と診断した。多発奇形や染色体異常に伴う小頭症のてんかん合併例の報告は散見される[4]が、原発性小頭症の児に合併したてんかんのまとまった報告は我々が探したところ見当たらなかった。今回の症例を検討した結果、症例1は、症候性局在関連性てんかん（前頭葉てんかん）で発作型は二次性全般性間代発作と考えられた。発作はVPA投与により速やかに抑制でき再発もみられないためてんかんとしては軽症例とおもわれた。しかし重度の発達遅滞を伴っているため今後の注意深い経過観察が必要である。症例2も、症候性局在関連性てんかん（前頭葉てんかん）で発作型は二次性全般性強直間代性発作と診断した。発作はVPA（15 mg/kg/day）投与にて抑制されている。症例3は、今回の3症例の中では最も難治な発作を合併した例であり、脳波上では多焦点性に棘波を認めていたが、後頭葉てんかんと診断されている。以上のように、原発性小頭症に合併したてんかんの予後は様々であり、これがどの様な機序で表現型が分かれるかは不明である。

原発性（真性）小頭症は常染色体劣性遺伝を示し、1885年にはすでに真性小頭症（microcephaly vera）という用語がGiacominiにより提唱されている[5]。この疾患では、出生時すでに頭囲の低下をきたしており、一般的には重度の小頭と中等度の精神遅滞をみることが多いが、運動発達は正常に近い。脳の画像診断上は、脳回の減少が軽度認められる例がある以外は著明な構造異常を認めず、てんかんの合併はまれとされている[6]。Bondらの原発性小頭症を持つ23家系51例の解析でもてんかんの合併は1例もなかったと報告されている[7]。最近、連鎖解析による遺伝子マッピングが進み、この疾患の遺伝子座は単一ではなく、少なくとも5つの遺伝子座が臨床的に区別できない原発性小頭症を発症しうることが明らかになった。このうち2つの遺伝子座、MCPH1およびMCPH5については原因遺伝子が特定されている。MCPH1は、8番染色体短腕上の原発性小頭症の遺伝子座として1998年に報告された[8]。この原因遺伝子であるmicrocephalinは、2002年に原発性小頭症の遺伝子としてはじめて同定され、このタンパク質が神経幹細胞、前駆細胞においてDNA修復に関わっている可能性も示唆されている[9]。MCPH5は、1番染色体長腕上の遺伝子座で、2000年に報告されている[10]。この原因遺伝子も発見されており、ASPMと命名されている[11]。そして、この遺伝子も神経幹細胞、前駆細胞の分裂、増殖に関与することが示唆されている。遺伝子異常が関与する小頭症の発生メカニズムについては、神経幹細胞や前駆細胞の分裂・増殖の障害、個々の神経幹細胞や前駆細胞による神経細胞産生の減少、神経細胞のアポトーシスの増加、神経細胞の成熟および成長の障害、グリア細胞産生の障害などがさまざまに組み合わさって起こると考えられている[5]。しかし、いまだ同定されていない遺伝子座および遺伝子も多数あると推測されており、てんかん合併のメカニズムについても、今後は細胞生物学的手法を用いた解析により解明されることが期待される。

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日本小児科学会雑誌　108巻7号　993～996（2004年）

小児難治てんかんに対する新プロトコールリポステロイド療法

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要　旨

West症候群において，初発の1例とACTH療法後に再発した2例の難治性全般てんかんの計3例に対し，従来のプロトコールを改訂したリポステロイド(LS)療法を施行した．投与量及び回数は0.25mg/kg/doseのLSを，従来の計7回投与から計12回静脈内投与に増量した．効果は初発の1例では発作の消失及び脳波所見の著明な改善を認めた．再発の1例では発作の50%以上の減少及び脳波所見の改善がみられたが，再発のもう1例では発作及び発作波とも不変であった．投与中及び投与後に明らかな副作用はみられなかった．又，従来法に比べて効果判定が早く出来ると思われた．他に有効な方法がない例や，既存の療法で副作用が疑われる症例にLS療法は有用であり，投与回数を増加した新プロトコールにおいても安全に施行出来ると考えられた．

キーワード：難治てんかん，West症候群，リポステロイド療法，副作用，新プロトコール

緒　言

West症候群は小児の難治性てんかんの代表的疾患である．現在我が国においてはその治療として，ビタミンB6及び各種抗てんかん薬内服，合成ACTH療法などが主に行われている．その中でACTH療法は有効性は明らかなものの，大脳萎縮，重症感染症，低カリウム血症，下垂体前葉機能低下などの重大な副作用の報告がある[1]．そのため，副作用を軽減する目的で投与量を減量したり，投与期間を短縮するなど投与方法を工夫する試みがなされると共に，新しい治療法を開発する試みがなされている．West症候群に対するリポステロイド(LS)療法は1996年山本らによって報告された[2]．近年その有効性並びに副作用の少なさが注目されており，West症候群を始めとする小児難治性てんかんに対し複数の施設で使用され始めている[3]．

しかし，その適応や使用量，施行方法に関しては統一された見解はなく，一般的には山本らの投与方法がプロトコールとして用いられている．しかし最近，従来の方法では効果判定に時間がかかる事が問題視され，投与スケジュールの見直しを求める意見が出されている[4]．又，以前の報告ではACTH療法とLS療法の比較において再発率に差を認めなかったと報告したが[2]，以降の未発表例を含めた8例のLS療法有効例のうち5例（62.5%）でLS投与終了後6カ月以内に発作の再発を認めており，従来のACTH療法の再発率の報告（33～56%）[5]に比べると再発率が高かった（未発表自験例）．今回我々は3例の小児難治性てんかんの患児に対し，LS療法の投与スケジュールを変更して施行したので，効果と副作用について報告する．

（平成15年7月29日受付）（平成16年5月13日受理）
別刷請求先：（〒216-8511）川崎市宮前区菅生2—16—1
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対　象

対象は5カ月の初発のWest症候群1例と12カ月と2歳1カ月のWest症候群ACTH療法後に発作の再発を認めた難治性てんかん2例の計3例とした．再発例の2例はACTH療法で，一時的に発作の減少を認めたものの，3カ月以内に発作の再発を認め，各種抗てんかん薬に抵抗性であった．また，2例とも最重度の精神運動発達遅滞を呈していた．対象3例の概要を表1に示す（表1）．

方　法

LS療法に関しては保護者よりインフォームドコンセントを得た．LSはデキサメサゾンとして0.25mg/kg/doseを最初の2週間は隔日で7回静脈内投与，次の2週間は週に2回の計4回投与，最後の1週間が週に1回の計1回投与，合計12回静脈内投与した（総投与量3.0mg/kg）．今回の3症例に対するLS療法は入院にて施行し，発作回数を観察すると共に，脳波検査及び頭部MRI検査を投与前後で施行し比較検討した．尚，有効性の判定はLS投与終了時点において，発作頻度が75%以上減少を著効，50%～75%減少を有効，25%～50%減少を軽度有効，25%以下の減少を無効，発作の増加を増悪として評価した．

表1 症例の概要

症例	性	月齢	発症月齢	発症時てんかん分類	主な発作	現在までの治療	発作頻度	脳波所見
1	F	5	5	潜因性 West	Epileptic spasms シリーズ形成	Vit B6 各種抗てんかん薬	5回程度／日	ヒプスアリスミア
2	F	25	5	潜因性 West	Epileptic spasms 単発	Vit B6 各種抗てんかん薬 ACTH（2クール） ケトン食 γ-glb	20回程度／日	全般性棘徐波複合頻発
3	F	12	3	潜因性 West	Epileptic spasms 単発	Vit B6 各種抗てんかん薬 ACTH	10回程度／日	全般性棘徐波複合頻発

表2 LS療法の効果

症例	LS療法の効果発現時期	発作	脳波所見の変化	頭部MRIの変化	他の副作用	有効性
1	2回目（3日目）より減少 4回目（1週間）より消失	消失	Focal sharpへ	なし	認めず	著効
2	4回目より減少	50%以上減少	発作波の50%以上減少	なし	認めず	有効
3	効果なし	不変	不変	なし	認めず	無効

結　果

(1) 有効性の検討（発作頻度と脳波変化）

3症例の効果，効果発現の時期などについてのまとめを表2に示す（表2）．症例1では2回目の投与後より，発作回数が減少し，4回目の投与後（投与開始より1週間）より発作の消失を認めた．脳波ではヒプスアリスミアの所見は消失したが，focal sharpが残存した．症例2では4回目の投与（投与開始1週間）より，発作回数が減少し，最終的には50%以上発作回数が減少した．投与前脳波所見では，全般性の棘除波複合が頻発していたが，投与後発作波の頻度も著明に減少した．症例3では発作回数，脳波所見とも不変であった．LS療法が著効したと考えられる症例1の脳波所見の推移を図1，図2に示す（図1）（図2）．症例1，症例2において現在6カ月以上の経過観察中であるが，症例1においては現在までけいれん発作の再発は認めていない．症例2においては発作頻度はLS療法前に比べ約50%減少を維持しているが，脳波所見は全般性の棘徐波複合であり，発作波の出現頻度はLS療法以前と同等に戻っており今後引き続き経過観察が必要と思われる．

(2) 頭部MRI検査

症例1では投与前のMRIは異常所見を認めず，投与後のフォローにおいても，同様に異常所見は認めなかった．症例2，3においては，投与前より軽度大脳半球の萎縮を認めたが，投与終了後のMRIにおいて小児放射線科医の読影上，視察上投与後萎縮の進行は認めなかった．

(3) その他の身体所見，検査所見

LS投与中の体重増加，体温変動は正常範囲であった．一般診察において浮腫や満月様顔貌は認めなかった．高血圧も出現せず，適宜施行した一般採血において治療を要する感染症，電解質異常は認めなかった．

考　案

LSは大豆油を単層の卵黄レシチンで取り囲んだ構造の直径約0.2μmの脂肪微粒子に，脂溶性の高いパルチミン酸デキサメサゾン（D-PAL）を保持させた静注用薬剤である．ラットを用いた動物実験によれば，炎症部にD-PALが集積し，水溶性デキサメサゾン（D-PHOS）の5～6倍の抗炎症作用を持つとされている[6]．適応が認められているのは慢性関節リウマチのみであるが，難治てんかん以外にも肺ヘモジデローシス[7]やopsoclonus-polymyoclonia症候群[8]での有効例も報告されている．

山本らの報告以後，West症候群をはじめとする乳幼児期の難治てんかんに対する使用例の報告が散見する．それらは山本らの方法（デキサメサゾンとして0.25 mg/kg/doseを1週間に1回を4回静脈内投与，2週間に1回を2回投与，最後月に1回を1回投与，合計7回静脈内投与）（総投与量1.75mg/kg）で施行されており，その効果に関しては，著効したとするもの[3]，一部の症例で限局した効果のみであったとするもの[9]と評価が分かれている．しかしその副作用については，

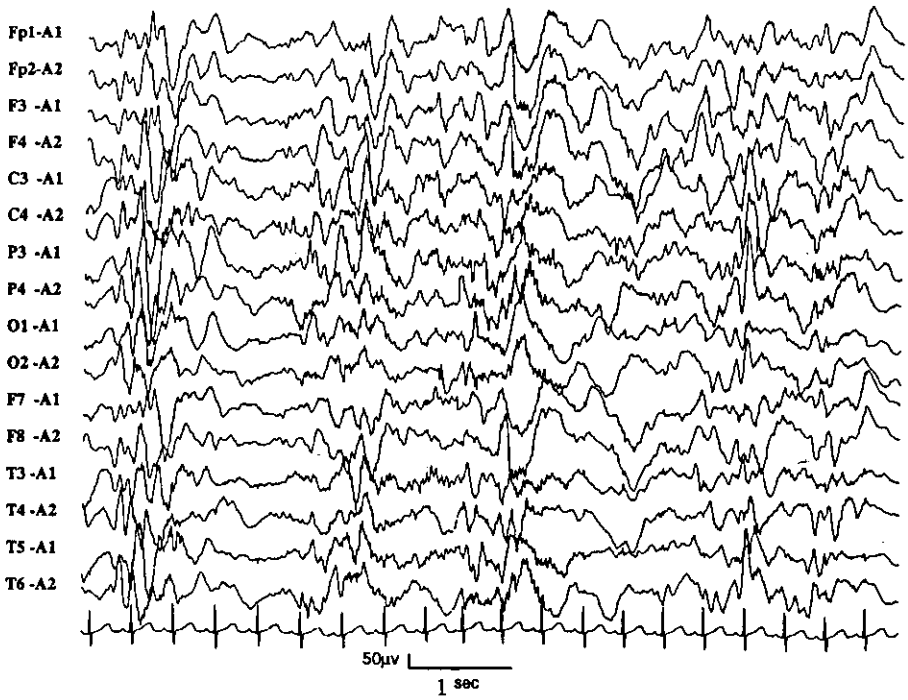

図1 症例1脳波. LS療法前
広汎性棘徐波が繰り返し出現. 一部は同期性がなくヒプスアリスミアの所見と考えられた.

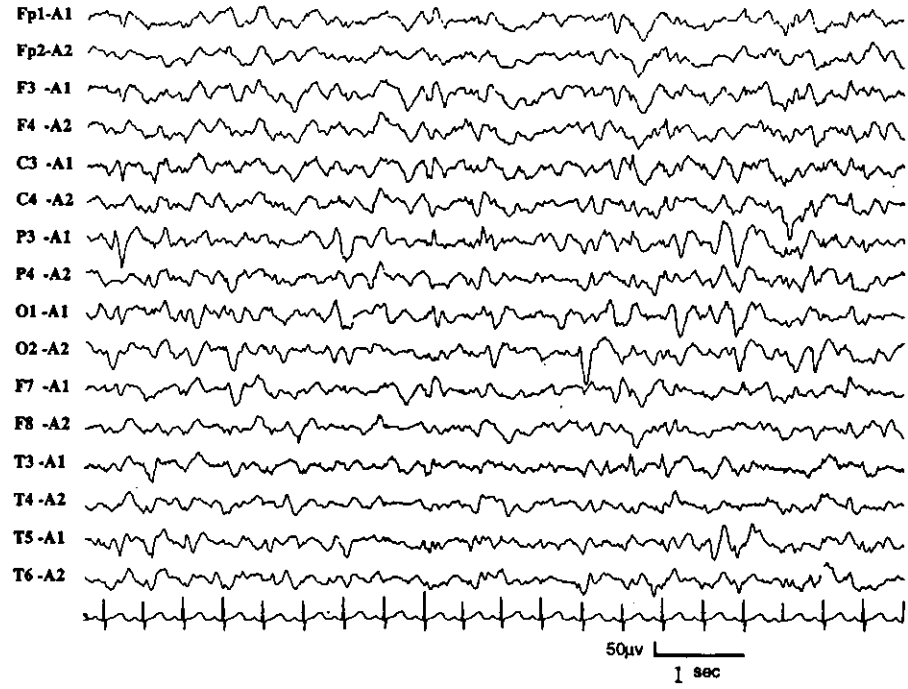

図2 症例1脳波. LS療法後
左頭頂部及び右後頭部に局在性鋭波が残存する. ヒプスアリスミアの所見は軽快している.

認めないかACTH療法に比べ軽度であると一致した結果が得られている. 柳垣らは症候性West症候群9例, 症候性全般てんかん2例, 症候性局在関連てんかん1例の計12例の難治てんかんに対するLS療法の結果を報告している[4]. 彼等はその考察の中で, 脳波及び発作の改善を認めた症例においても, 効果発現に4週間以上かかった事を指摘し, 投与量や投与回数の見直しの必要性に言及している. また, 岩井らは[10]ラット

を用いた動物実験においてD-PALとD-PHOSと脳内濃度の測定を行っており，1回の投与のみでは両者に差を認めなかったが，5日間連続投与ではD-PALが有意に高濃度を維持したと報告している．この動物実験の結果からみると，1週間に1回の投与では効果の持続が弱い可能性も考えられる．又，再発率が高い理由として，総投与量の少なさが影響していると考えられた．

これらの事情を考慮し，今回は投与計画を改めLS療法を施行した．症例が少なく，有効性および再発率についての検討は今後症例の蓄積を必要とすると思われたが，ACTH療法後の再発例では効果の低い印象であった．しかし，投与量増量による顕著な副作用の出現はなく，今回の投与方法でも安全に行えると思われた．また，有効例においては4回投与時には発作回数の減少を認めており，効果判定に時間がかかるという欠点は補えていると考えられた．再発率に関しては今後の経過観察が必要である．一方で，今回の投与計画では外来治療が困難になる点が新たな問題と思われた．

てんかんに対するLS療法は，作用機序に関しても不明な事が多く，ステロイドそのものの効果であるのか，あるいは責任病巣に留まる事が効果の増強につながっているのかなど検討すべき課題が多く，従来のステロイド療法との比較も必要であろう．又，適応症例や至適投与方法についての検討もまだ不十分である．しかし，治療抵抗性の難治てんかんや，ACTH療法による重大な副作用が予測されるような症例に対しては，試みる価値があると考えられた．今後も効果及び副作用の両面より，適応症例及び至適投与方法について症例数を増やして検討していく必要があると思われた．

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ELSEVIER

A Successful Treatment With Pyridoxal Phosphate for West Syndrome in Hypophosphatasia

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We report a 2-month-old male with West syndrome associated with infantile hypophosphatasia. The male infant was born at term to a healthy mother after an uneventful pregnancy. He was born by cesarean section because of breech presentation. He was observed to have short extremities, and radiographs were consistent with achondroplasia. The serum alkaline phosphatase level was 2 IU/dL. Intractable tonic seizures developed 2 days after birth, and an electroencephalogram revealed a burst-suppression pattern for the first 2 months of life. The seizures were uncontrollable with conventional antiepileptic drugs. At the age of 2 months, he had a series of infantile spasms, and the electroencephalogram indicated hypsarrhythmia. Treatment with high-dose pyridoxal phosphate eliminated his seizures.

Yamamoto H, Sasamoto Y, Miyamoto Y, Murakami H, Kamiyama N. A successful treatment with pyridoxal phosphate for West syndrome in hypophosphatasia. Pediatr Neurol 2004;30:216-218.

Introduction

Hypophosphatasia is a rare disease marked by subnormal alkaline phosphatase activity in serum and many organs, rachitic bone manifestations, and an increase in urinary phosphoethanolamine. Subnormal serum activity is the hallmark of this disease and reflects a generalized deficiency in the activity of tissue-nonspecific alkaline phosphatase isoenzyme (TNSALP) [1]. It is classified as fetal type, infant type, child type, and adult type, with a more serious and poorer prognosis in the younger patients [2]. We report a 2-month-old male with West syndrome associated with infantile hypophosphatasia. The patient had intractable seizures and a burst-suppression pattern which evolved into hypsarrhythmia in the electroencephalogram. This report is the first case where high-dose pyridoxal phosphate therapy was effective for refractory seizures in West syndrome associated with hypophosphatasia.

Case Report

The patient was born at 38 weeks via cesarean section secondary to breech presentation. During early pregnancy, a twin gestation was evident, but a repeat ultrasound at 11 weeks revealed only one fetus. The remaining pregnancy was uneventful. His birth weight was 2795 gm. After delivery, he had an initial Apgar of 6 and required resuscitation. He had gradually experienced respiratory distress requiring intubation. On examination, he had short bowed extremities and a soft skull. Radiographs were consistent with achondroplasia. His skull was only ossified around the face and forehead, and long bones were short and had metaphyseal cupping (Fig 1). On admission, his serum calcium was 9.5 mEq/L and serum alkaline phosphatase was 2 IU/dL which was extremely low. Increased levels of urinary phosphoethanolamine were identified after hospitalization. His condition was diagnosed as fetal type hypophosphatasia based on the physical examination, radiologic findings, and laboratory findings. Intractable tonic seizures developed 2 days after birth, and the electroencephalogram revealed a burst-suppression pattern for the first 2 months. The cranial magnetic resonance imaging findings were normal.

The seizures were refractory to conventional antiepileptic drugs, such as phenobarbital, phenytoin, clonazepam, and sodium valproate. At the age of 2 months, he had a series of infantile spasms, and the electroencephalogram revealed hypsarrhythmia (Fig 2). In addition, the levels of cerebrospinal fluid γ-aminobutyric acid measured by high-performance liquid chromatography were less than 0.005 nmol/mL. He was diagnosed with West syndrome associated with hypophosphatasia and was begun on high-dose vitamin B_6 (pyridoxal phosphate, 30 mg/kg/day). The seizures decreased remarkably on the day after administration and disappeared by the third day. Electroencephalographic findings at 3 months of age indicated remarkable improvement, and epileptic discharge was not observed (Fig 3). Cerebrospinal fluid examination was performed again

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Received May 15, 2003; accepted August 6, 2003.

doi:10.1016/j.pediatrneurol.2003.08.003 • 0887-8994/04/$—see front matter

Figure 1. The whole-body x-ray reveals profound skeletal hypomineralization.

at the same period, but the levels of cerebrospinal fluid γ-aminobutyric acid were still less than 0.005 nmol/mL which was extremely low. Seizures never recurred, but the patient died of pneumonia at 18 months of age.

Discussion

Hypophosphatasia is a rare metabolic bone disease which highlights the importance of alkaline phosphatase in skeletal mineralization. It is characterized clinically by defective skeletal mineralization that manifests as rickets in infants and children and osteomalacia in adults. Perinatal hypophosphatasia is the most severe form. It is expressed in utero and may result in stillbirth. The pregnancy may also be complicated by polyhydramnios.

Caput membraneceum and limbs that are shortened and deformed from profound skeletal hypomineralization are evident at birth. Radiographic survey of the skeleton enables perinatal hypophosphatasia to be readily distinguished from even the most severe types of osteogenesis imperfecta and congenital dwarfism. Indeed, the radiographic changes may be considered diagnostic. However, the findings are diverse and there is marked patient-to-patient variability [3].

Our patient was diagnosed with perinatal hypophosphatasia. Deficiency of the TNSALP gene is associated with defective skeletal mineralization [4]. Mice that lack TNSALP by homologous recombination with embryonic stem cells have normal skeletal development. However, at approximately 2 weeks of life, homozygous mutant mice develop seizures which are subsequently fatal. Defective metabolism of pyridoxal 5′-phosphate (PLP), characterized by elevated serum PLP levels, results in reduced levels of the inhibitory neurotransmitter γ-aminobutyric acid in the brain. The mutant seizure phenotype can be rescued by the administration of pyridoxal phosphate and a semisolid diet [5]. However, it is suggested that the physiologic role of TNSALP in humans is different from that in knockout laboratory mice [6]. The cause of intractable seizures in hypophosphatasia is still unknown.

In our patient, the levels of cerebrospinal fluid γ-aminobutyric acid were extremely low at the time of initial seizure onset and at the time of the disappearance of seizures; therefore the antiepileptic mechanism of pyridoxal phosphate was unknown. Pyridoxine-dependent seizures associated with hypophosphatasia in an infant were reported by Nunes et al. [7]. The main difference between the present report and the above report is in the development of West syndrome over time and differences between pyridoxine and pyridoxal phosphate. Earlier treatment of the infant in the present report with pyridoxine phosphate would have resulted in clinical reasons identical to those specified in the Nunes et al. report. Litmanovitz et al. reported two missense mutations of the TNSALP gene in

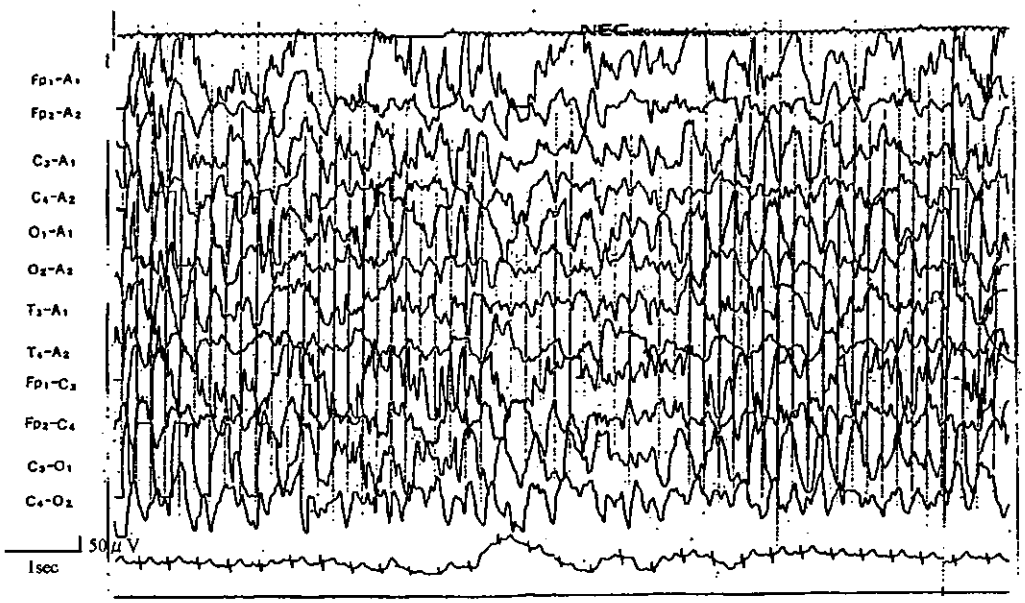

Figure 2. Hypsarrhythmia in the electroencephalogram is observed at 2 months of age.

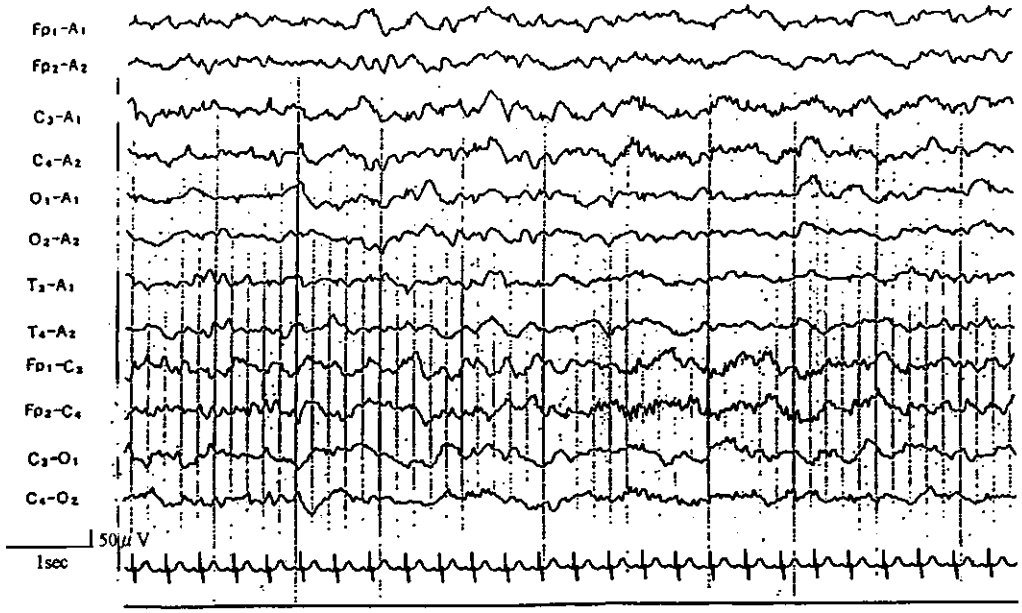

Figure 3. Electroencephalogram at 3 months of age after the administration of pyridoxal phosphate.

neonatal hypophosphatasia associated with seizures [8]. They observed that the seizures responded to vitamin B_6 and stated that the phenotype-genotype correlation indicated that G309R was a deleterious mutation that could lead to seizures and a lethal outcome. The present study is the first case to report the electroencephalographic changes in West syndrome associated with hypophosphatasia by administration of pyridoxal phosphate, and the changes in the levels of cerebrospinal fluid γ-aminobutyric acid during the therapeutic period.

The authors greatly appreciate the expert advice of Professor Takeshi Horiuchi, and also thank Miho Fukuda for her helpful suggestions.

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Pediatrics International (2004) **46**, 394–397

Original Article

Studies on cerebrospinal fluid ionized calcium and magnesium concentrations in convulsive children

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Abstract

Background: The concentrations of ionized calcium (iCa) and ionized magnesium (iMg) were measured in the cerebrospinal fluid (CSF) of convulsive and non-convulsive children, to investigate the relationship between seizure manifestation and CSF iCa and iMg concentrations. Standard concentrations of CSF iCa and iMg were also established.

Methods: CSF samples from 23 patients, ages 0–15 years, with various forms of seizures and 26 age-matched non-convulsive children were collected by lumbar puncture. CSF was obtained anaerobically and the concentrations of CSF iCa and iMg were measured with an electolyte analyzer (Stat Profile Ultra M1, NOVA, USA) immediately after the lumbar puncture.

Results: The concentrations of CSF iCa were significantly higher in non-convulsive children younger than 11 months old compared with children older than 12 months. The concentrations of CSF iMg in non-convulsive children did not differ significantly with aging. The concentrations of CSF iCa in convulsive children did not differ significantly from the concentrations of non-convulsive children. The concentrations of CSF iMg in convulsive children were significantly lower than in non-convulsive children.

Conclusion: These results suggest that seizure manifestation is related to age-dependent changes in iCa and decreased iMg in the developing brain.

Key words acid-base balance, cerebrospinal fluid, convulsion, ionized calcium, ionized magnesium.

Magnesium (Mg) is the second most abundant intracellular cation and the fourth most abundant cation in the body. Mg is a cofactor for more than 325 cellular enzymes involved in cellular energy production, membrane functions, gating of ionized calcium (iCa) channels, transmembrane flux of ions, regulation of adenylate cyclase, and iCa release, inside many types of cells. In addition, ionized magnesium (iMg) has numerous structural functions, stabilizes cell membranes, and acts as a iCa antagonist. Mg plays a role in control of neuronal activity, cardiac excitability, neuromuscular transmission, vasomotor tone, and blood pressure, among other functions.[1] Ionized Mg acts as a Ca channel blocker and hypomagnesemia presents as tetany or seizures. An increase in pH decreases iMg and iCa activities. Although iMg is affected by a change in plasma acidity (pH), the change is not as large as that for iCa.[2] The H ion competes with iMg and iCa for protein and other ligand binding sites, thereby increasing iMg and iCa activities. A rise in pH results in the reverse, with a drop in plasma iMg. Clinically, certain epileptic seizures can be induced by hyperventilation which raises the pH, and others can be inhibited by a ketogenic diet which lowers the pH. In this study, the concentrations of iMg and iCa were measured in the cerebrospinal fluid (CSF) of convulsive and non-convulsive children to investigate the relationship between seizure manifestation and CSF iMg and iCa concentrations. Standard concentrations of CSF iMg and iCa were also established. This is the first report to study the relationship between CSF iMg and iCa and seizure manifestation.

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Received 22 July 2003; revised 27 November 2003; accepted 27 November 2003.

Materials and methods

Cerebrospinal fluid was obtained from 23 patients, ages 0–15 years (mean 28 months), with various forms of seizures which were the first seizure in their life time, respectively: febrile seizure, seizures following acute gastroenteritis, and situation-related seizures. In total, 26 age-matched (mean

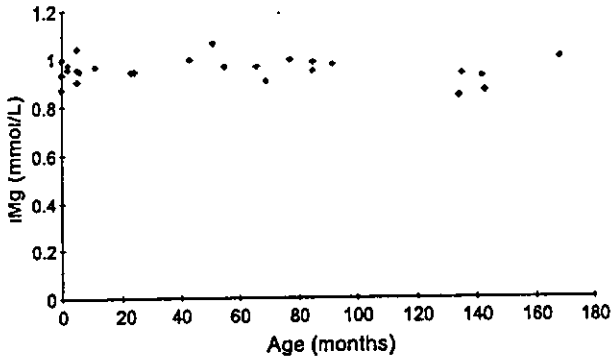

Fig. 1 Concentrations of cerebrospinal fluid ionized magnesium in non-convulsive children.

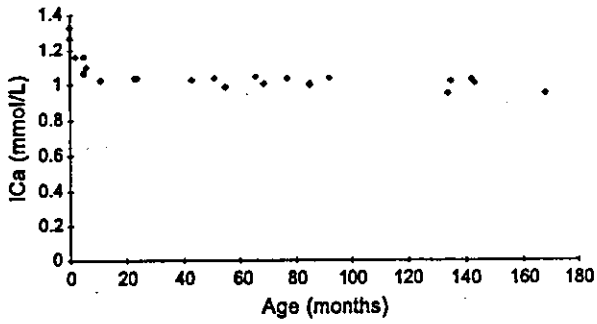

Fig. 2 Concentrations of cerebrospinal fluid ionized calcium in non-convulsive children.

55 months) non-convulsive children's CSF samples were obtained from patients who were examined using lumbar puncture for diagnosis of possible meningitis and then were demonstrated to be normal. None of the controls had any neurological abnormalities. CSF was collected by lumbar puncture anaerobically within an hour after the cessation of seizure activity, from April 2002 to February 2003. The types of seizures were generalized tonic or tonic-clonic, and the duration of each seizure was between 1 and 5 min (mean 3 min). The concentrations of CSF iMg and iCa were measured with an automatic ion selective electrode analyzer (Stat Profile Ultra M1, NOVA, USA) immediately. The concept and inherent advantages of this electrolyte analyzer system have been described previously.[3] The concentrations of CSF iMg and iCa were normalized to pH 7.4 for purpose of direct comparison. This research received prior approval by the University Institutional Review Board, and informed consent was obtained from each patient or parents of each patient in the convulsive and non-convulsive group. The convulsive and non-convulsive children were placed into six groups for analysis. Each of the results was analyzed for the six groups using the Mann–Whitney *U*-test.

Results

The six groups were as follows: Group A, six convulsive children younger than 11 months old; Group B, 10 non-convulsive children younger than 11 months old; Group C, 17 convulsive children older than 12 months; Group D, 16 non-convulsive children older than 12 months; Group E, all 23 convulsive children; Group F, all 26 non-convulsive children. The concentrations of CSF iMg in non-convulsive children did not differ by age and were held within a narrow range (Fig. 1). The concentrations of CSF iCa were significantly higher in non-convulsive children younger than 11 months old compared with children older than 12 months, and after 12 months CSF iCa was also maintained in a narrow range (Fig. 2). The concentrations of CSF iMg in convulsive children older than 12 months were significantly lower than in non-convulsive age-matched children. The concentrations of CSF iCa in convulsive children did not differ significantly from the concentrations of non-convulsive children. These results are listed in Table 1 and Table 2.

Discussion

Extrapolating from Ca studies where iCa, not total Ca was found to be physiologically active, it is anticipated that iMg and not total Mg is also physiologically active. Whole blood maintains a very narrow normal range for iMg.[4] This study revealed that CSF iMg and iCa were also maintained in a very narrow range. Intracellular total Mg greatly exceeds extracellular or serum total Mg concentrations. In contrast, intracellular iMg appears to be quite comparable to extracellular iMg. In addition, iMg passes through the cell membrane relatively quickly suggesting that the two iMg reservoirs are in dynamic equilibrium.[5] These observations suggest that the extracellular measurement of iMg reflects the dynamic intracellular–extracellular Mg homeostasis. Concentrations of neurotransmitters in CSF are determined by the rates of synthesis, release, and degradation of the parent compounds as well as the rate and efficiency of elimination from brain and CSF. Maturational changes in storage pool, rates of turnover, transport systems, intra- and extraneuronal metabolism, rates of CSF production, and brain and spinal column morphology, all may alter CSF neurotransmitter concentrations.[6] In previous studies, several investigators reported that the CSF concentrations of several neurotransmitters in younger children were considerably higher than those of older children and adults.[7] In the present study, no significant correlation was observed between age and the CSF concentrations of iMg. The concentrations of CSF iMg were extremely stable despite age, time, and the volume of CSF taken. In contrast, the present study documented an

Table 1 Concentrations of cerebrospinal fluid (CSF) and ionized magnesium in convlusive and non-convulsive children

	Age ≤ 11 months	Age ≥ 12 months	Total
Convulsive group (n = 23)	Group A (n = 6) 0.96 ± 0.02 a,b	Group C (n = 17) 0.89 ± 0.02 a,d	Group E (n = 23) 0.90 ± 0.01 e
Non-convulsive group (n = 26)	Group B (n = 10) 0.95 ± 0.01 b,c	Group D (n = 16) 0.95 ± 0.01 c,d	Group F (n = 26) 0.95 ± 0.01 e

All data expressed as mmol/L CSF (mean ± SE). Letters indicate significance between values with the same letter: a-c, not significant; d-e, $P < 0.05$.

Table 2 Concentrations of cerebrospinal fluid (CSF) and ionized calcium in convlusive and non-convulsive children

	Age ≤ 11 months	Age ≥ 12 months	Total
Convulsive group (n = 23)	Group A (n = 6) 1.11 ± 0.05 a,c	Group C (n = 17) 1.00 ± 0.01 a,d	Group E (n = 23) 1.03 ± 0.02 e
Non-convulsive group (n = 26)	Group B (n = 10) 1.16 ± 0.01 b,c	Group D (n = 16) 1.01 ± 0.01 b,d	Group F (n = 26) 1.07 ± 0.02 e

All data expressed as mmol/L CSF (mean ± SE). Letters indicate significance between values with the same letter: a, $P < 0.05$; b, $P < 0.01$; c–e no significant difference between groups.

inverse correlation between age and CSF concentrations of iCa. The lower concentrations of CSF iCa after 12 months old may be related to the general increasing seizure susceptibility in children. The importance of age-matched non-convulsive children in studies of CSF neurochemicals in the developing brain is emphasized. However, there is no normal control data for CSF iMg and iCa, and the relationship between seizure manifestation and CSF concentrations of iMg and iCa has not been previously reported in children. Approximately 50% of convulsive and control children had fever at the moment of lumbar puncture and the influence of fever to the measurement results was not clear, but fever has been demonstrated not to affect some CSF neurochemicals.[8]

There is a serial study, by Lux and Heinemann, about the movement of extracellular iCa during the aberrant depolarization of a neuronal cell.[9-12] According to the report, decreased concentrations of extracellular iCa in cortical IV and V layers and in the cone cell blanket of hippocampal CA1 and CA3, were observed using microelectrodes. When the concentrations of intracellular iCa increase after iCa flows into a cell, non-specific depolarizing membrane current is activated and bursting activity occurs. Sugaya *et al.* also reported the relationship between the bursting activities and the inflow of iCa into a neuronal cell.[13,14] There was another report which described the relationship between the urinary concentrations of Ca and febrile convulsions.[15] These results suggest that the dynamics of iCa in neuronal cells play an important role in the seizure manifestation.

Magnesium exists as three forms *in vivo*: protein binding Mg, anion-bound Mg, and iMg. Tissues respond to the ionized fraction of Mg, not the total concentration, where cations may be bound to protein or small ligands.[16] The measurement of iMg in whole blood, plasma or serum has been difficult historically, but became easier in 1992 with the use of ion-selective electrodes.[3] However, there is no report of reference concentrations of iMg in CSF or changes in the concentrations of CSF iMg in convulsive children. Acid-base balance influences the measurement results of CSF iMg and iCa. With increased acidity, H ion enters cells and the charge is balanced by iMg and iCa leaving cells. Alkalinizing results in the reverse, with a drop in iMg. In this study, we collected CSF anaerobically and analyzed it immediately after the lumbar puncture. We normalized iCa and iMg values to pH 7.4 using a correction formula in the instrument to exclude the effects of crying and sample preservation.[17] The concentrations of CSF iCa were significantly higher in control children younger than 11 months old compared with in children older than 12 months. This result suggests that the decreasing concentrations of iCa in the brain may relate to the increasing age-dependent seizure threshold in childhood after 12 months of age. In contrast, the concentrations of CSF iMg did not differ with aging, but the concentrations of CSF iMg decreased after convulsions. These results suggest that the concentrations of CSF iMg are held within a narrow range in normal children. Studies on convulsive subjects indicate that CSF iMg concentrations are significantly lower than normal. In the N-methyl-D-aspartate receptor, which is one of the brain's excitatory neurotransmitter glutamic acid receptors, a glycine binding site, a sodium and Ca ion channel, an Mg binding site, is also implicated. And, it is said that the subunits constituting the glutamic acid receptor, change with age.[18] These results suggest that there is a relationship

between the changes in concentrations of extracellular iMg in the brain and seizures in childhood. Although the differences are statistically significant, the fact that variables (e.g. circadian changes, sex, pharmaceutical influences, and dietary influences) were not controlled, make these findings preliminary. More patients in each range need to be studied.

Acknowledgments

The authors greatly appreciate the expert advice of Terry L Shirey PhD, the director of scientific affairs, NOVA biomedical, and also Professor Yasushi Koitabashi for his helpful suggestions.

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Brain & Development 26 (2004) 377–379

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

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Original article

Spontaneous improvement of intractable epileptic seizures following acute viral infections

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Received 9 June 2003; received in revised form 4 September 2003; accepted 25 September 2003

Abstract

In general, epileptic seizures become more serious following infections. However, transient and permanent improvement of epileptic seizures has been observed following acute viral infections, without a recent change in anti-epileptic therapy. Questionnaires were sent to 73 institutions, throughout Japan, where pediatric neurologists care for children with epilepsy to characterize this phenomenon through clinician survey. Completed surveys were received from 11 institutions, and 21 cases were selected for the study. The age of the patients were 6 months to 17 years. The West syndrome or epilepsy subsequent to West syndrome cases were 16 out of 21. Two cases of symptomatic generalized epilepsy and one case each of symptomatic partial epilepsy, continuous spike-waves of slow sleep and severe myoclonic epilepsy in infancy were also reported. These seizures disappeared within 2 weeks subsequent to viral infections such as, exanthema subitum, rotavirus colitis, measles and mumps. The disappearance of intractable epileptic seizures following acute viral infections might be related to the inflammatory processes or the increased levels of antibodies after viral infections.

Keywords: Spontaneous improvement; Acute viral infection; Intractable epilepsy

1. Introduction

Epileptic seizures generally become more serious following infections. However, it is well known that in rare instances, epileptic seizures, mostly seizures in West syndrome disappear or decrease in severity after acute viral infections without changes to anti-epileptic medications. This evidence has prompted us to analyze clinical data of this phenomenon through a multi-center survey throughout Japan. The goal of our study was to better characterize this phenomenon through clinician survey.

2. Subjects and methods

Questionnaires were sent to Pediatric neurologists in 73 university hospitals, children's hospitals, and epilepsy centers in Japan. The questionnaires reported: the type of epilepsy or epileptic syndrome according to the international classification of the ILEA, 1989; the infectious disease that the patient experienced; the start of seizure remission in relation to the start of the illness; the duration of remission; any changes in the EEG during the disappearance of seizures; any changes in the serum concentrations of anti-epileptic drugs during the disappearance of seizures; any additional medications given for the illness; recurrence of seizures; and the suspected reasons for the disappearance of seizures.

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0387-7604/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.braindev.2003.09.012

3. Results

Completed surveys were received from 11 institutions, and 21 cases were selected for this study based on the criteria. The criteria fulfilled the conditions in which patient's frequent seizures had disappeared for at least 1 month after viral infections without changes to anti-epileptic therapy. The age of patients ranged from 6 months to 17 years. The West syndrome or epilepsy subsequent to West syndrome was diagnosed for 16 out of 21 cases. Two cases were symptomatic generalized epilepsy. Symptomatic partial epilepsy, continuous spike-waves of slow sleep (CSWS), and severe myoclonic epilepsy in infancy (SMEI) were reported concurrently in another case. Thirteen patients with either West syndrome or epilepsy subsequent to West syndrome were symptomatic, and three patients were cryptogenic in etiology. The patient's international classification of epilepsy or epileptic syndromes are presented in Table 1. The preceding infections were four cases of exanthema subitum, four cases of rotavirus gastroenteritis, three cases of measles, three cases of upper respiratory infections, one case of mumps and cytomegalovirus infection, and five cases of probable common cold. The type of infectious disease encountered was listed in Table 2. Seizures disappeared an average of 4.5 days, (with a range of 1–14 days) after the onset of infection. In four patients with West syndrome and in one patient with CSWS, the seizures did not recur. The mean duration of follow-up was 34 months with a range from 3 months to 4 years. In 13 patients, the seizures recurred. In these patients, the duration of remission had a median of 7 months and a range from 1 to 30 months. During the remission, the EEG was improved in two-thirds of patients including those with CSWS syndrome. No significant changes were seen in the serum concentrations of anti-epileptic drugs during the remission. Possible reasons for the resolution of seizures in these patients are: (1) an immunologic or inflammatory processes; (2) increased serum concentration levels of anti-convulsant due to dehydration with the illness; (3) increased levels of antibodies after viral infections (similar to immunoglobulin therapy in intractable epilepsies; (4) suppression of immunopathological processes by anti-inflammatory cytokines, such as interleukin-10 and transforming growth factor-β.

Table 1
The classification of epilepsy or epileptic syndromes encountered (*n*)

West syndrome and subsequent epilepsy post West syndrome (16)
Cryptogenic type (3), symptomatic type (13)
Lennox-Gastaut syndrome (2)
Symptomatic localization-related epilepsy (1)
Severe myoclonic epilepsy in infancy (1)
Continuous spike-waves of slow sleep (1)

Table 2
The types of infectious diseases encountered (*n*)

Probable common cold (5)
Rotavirus gastroenteritis (4)
Exanthema subitum (4)
Upper respiratory infection (3)
Measels (3)
Mumps (1)
Cytomegalovirus infection (1)

4. Discussion

Patients with intractable epilepsy in infancy, particularly West syndrome, rarely show spontaneous remission of seizures. This aspect of the natural history of these epilepsies has been insufficiently recognized. Hrachovy reported that spontaneous remission of West syndrome may occur as early as 1 month after spasm onset and the remission rate increased to 25% 12 months after onset without effective therapy, such as adrenocorticotropic hormone (ACTH) or valproate, but author did not describe any events triggering spontaneous remission [1]. The disappearance of seizures most often occurs following a viral infection. West first described in his syndrome a patient with such a remission after a brief febrile illness [2]. Some patients with intractable epilepsy respond to the therapy with immunoregulatory or anti-inflammatory agents such as high-dose immunoglobulin, ACTH or corticosteroids [3, 4]. The participants of the present survey proposed the following mechanisms for the disappearance of intractable epileptic seizures following acute viral infections: increased serum concentrations of anti-epileptic drugs with secondary to dehydration, increased levels of antibodies after viral infections (similar to immunoglobulin therapy), and the suppression of immunopathological processes by anti-inflammatory cytokines, such as interleukin-10 or transforming growth factor-β. Increased vascular permeability of blood–brain barrier under the condition in the intractable epilepsies, such as West syndrome or Lennox-Gastaut syndrome was proposed by Ariizumi et al. [5]. The increased vascular permeability allows immunoglobulins to easily cross the blood–brain barrier following acute viral infections (also similar to immunoglobulin therapy). However, these speculations are not based on the experimental or laboratory data. In this study, we could not find a reasonable explanation as to the relationship between the spontaneous improvement of intractable epilepsies and acute viral infections. In 2002, Hattori identified the spontaneous remission of spasms following acute viral infections in 25 patients with West syndrome on the base of data analysis of Japanese medical literature between 1970 and 2000 [6]. In this study, exanthema subitum was most predominant infectious disease that

leads to resolution of the seizures. He also stated that these spontaneous remissions following acute viral infections have not been duly appreciated in the English medical literature. Better understanding of such mechanisms may lead to a new therapeutic approach to intractable epilepsies in infancy.

The participants in the survey:

- Kimio Minagawa (Otaru)
- Eiji Nakagawa (Tochigi)
- Masatoshi Ito (Shiga)
- Tomiyuki Akiyama (Okayama)
- Harumi Yoshinaga (Okayama)
- Shigeru Yanagaki (Tokyo)
- Mana Kurihara (Atsugi)
- Toshio Hanai (Fukuoka)
- Tomoyuki Nakazawa (Tokyo)
- Toshiyuki Iwasaki (Sagamihara)
- Hitoshi Ueda (Osaka)
- Hiroshi Murakami (Kawasaki)

Acknowledgements

We would like to thank those who participated in the survey.

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Brain & Development 26 (2004) 43–46

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

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Original article

Hypouricemia in severely disabled children II: influence of elemental enteral nutrition on the serum uric acid levels

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Received 24 October 2002; received in revised form 3 April 2003; accepted 4 April 2003

Abstract

The previous study showed that both valproic acid (VPA) and a bedridden state decreased the serum uric acid level, and VPA-induced renal tubular dysfunction was suspected to be one cause of hypouricemia in severely disabled children. However, it was uncertain what factor of bedridden state influences the uric acid level in severely disabled children. Among many factors of a bedridden state that might influence the uric acid level, we examined the influence of elemental nutrition on the serum uric acid level in severely disabled children because many severely disabled children with marked hypouricemia receive elemental nutrition. Thirty-one severely disabled children were included in this study, who were divided into two groups—group A: 11 patients with elemental nutrition; group B: 20 patients with non-elemental nutrition. The laboratory data in both groups were analyzed statistically, using the *t*-test. The uric acid level was significantly decreased in group A compared with group B ($p < 0.01$) without elevation of urinary excretion of uric acid. Other laboratory data, except phosphate and potassium, did not differ between the two groups significantly. An elemental diet may be one factor that decreases the uric acid level in severely disabled children.

Keywords: Hypouricemia; Severely disabled children; Elemental diet; Enteral nutrition

1. Introduction

Severely disabled children receiving enteral nutrition for a long time suffer from various complications because of the severity of the underlying disorder needing the enteral nutrition and the enteral nutrition itself [1,2]. In a previous paper [3], we reported that the uric acid level was significantly decreased in non-ambulatory, severely disabled children treated with valproic acid (VPA). Both VPA and the non-ambulatory state decreased the uric acid level, statistically. VPA may cause renal tubular dysfunction, however, it remains unknown what factor in severely disabled children caused the hypouricemia in the previous study.

Regarding the etiology of hypouricemia in severely disabled children, apart from the effect of VPA, many factors of a bedridden state, such as nutrition (components of an enteral diet, calories, and elemental diet), hypoactivity, malabsorption, and other complications are suspected to influence the uric acid level. In this study, we examined the influence of elemental nutrition on the serum uric acid level in severely disabled children because many severely disabled children with marked hypouricemia receive elemental nutrition [4].

2. Patients and methods

2.1. Patients

Thirty-one severely disabled children were included in this study, and were followed in the outpatient clinic for pediatric neurology of Niigata City General Hospital from January 2001 to May 2002. To eliminate the possibility of a confounding effect of VPA, all the patients included in this study were given VPA for at least 6 months.

Twenty-four of these 31 patients were in group A (non-ambulatory patients taking VPA) in the previous study [3] and another seven patients being added in this study. Eighteen were boys and 13 were girls. They were 1–19 years of age. Twenty-two of these children had

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0387-7604/03/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/S0387-7604(03)00094-9

cerebral palsy and mental retardation as sequelae of perinatal brain insults, two sequelae of acute encephalitis, two sequelae of anoxic encephalopathy, one Sotos syndrome, one Cornelia de Lange syndrome, one 22q.11.2 deletion syndrome, one linear nevus sebaceus syndrome, and one Rett syndrome. There were no signs of inborn errors of metabolism, syndrome of inappropriate secretion of anti-diuretic hormone, or malnutrition in our patients.

The patients were divided into two groups according to whether they received elemental enteral nutrition. Group A: 11 patients receiving elemental enteral nutrition; group B: 20 patients receiving non-elemental nutrition. In group A, nine patients had Elental® containing 4.7 g protein/100 kcal, and two had Elental P® containing 3.1 g protein/100 kcal for at least 1 year. In group B, 10 patients ate usual diet and nine had Ensure liquid® containing 3.52 g protein/100 kcal, and one Racol® containing 4.38 g protein/100 kcal. All patients had various types of epilepsy and were treated with VPA. VPA was administered either alone (seven patients) or in combination with other anti-epileptic drugs (24 patients): 12 clonazepam, two diazepam, two nitrazepam, three clobazam, three zonisamide, two clorazepate, three phenytoin, and three carbamazepine. The average dosages of VPA in groups A and B were 27.8 ± 6.4 mg/kg/day and 23.9 ± 13.0 mg/kg/day, respectively, which were not significantly different.

2.2. Method

Laboratory data including serum sodium, potassium, phosphate, uric acid, creatinine, total protein, hemoglobin, and urine pH, sodium, phosphate, uric acid, creatinine, and β2-microglobulin obtained routinely in outpatient clinic were used. To assess the renal tubular function in all groups, we measured the fractional excretion of uric acid (FEUA), fractional excretion of sodium (FENa), percent tubular reabsorption of phosphate (%TRP), and urinary excretion of β2-microbulin. FENa and FEUA were calculated using the formula: $FE_x = (U_x \times P_{cr}/P_x \times U_{cr}) \times 100$. The tubular reabsorption rate for phosphate was calculated with the formula: TRP = 1 − FE phosphate.

2.3. Data analysis

For comparison of the laboratory data between the patients in groups A and B, statistical analysis was performed using Student's *t*-test. The $p < 0.05$ was considered significant. Calculations were performed using the statistical software package StatView 5.0 (SAS Institute Inc., Cary, NC). All results are presented as means ± standard deviation.

3. Results

(Table 1) Patients in the two groups were similar in average age and sex. The uric acid level was significantly decreased in group A compared with group B ($p < 0.01$) (Fig. 1). The inorganic phosphate and potassium levels were significantly decreased in group A compared with group B ($p < 0.05$). A significant difference in FEUA was not recognized between groups A and B. No statistically significant differences were found between the two groups with respect to other parameters, such as serum sodium and creatinine, urinary pH, urinary β2-microglobulin, %TRP, and FENa. Nutritional factors, such as total protein, hemoglobin, and calories, were not significantly different between the two groups. Other adverse effects of VPA, such as liver dysfunction, hematologic abnormalities, and weight gain were not recognized in any patients.

4. Discussion

The results suggested that hypouricemia was more common in severely disabled patients receiving elemental nutrition compared with ones receiving a non-elemental diet. However, it is still unknown whether a component of the elemental diet itself or a secondary change of the gastrointestinal tract influences the uric acid level, or whether the pathological condition needing the elemental nutrition has something to do with hypouricemia. Although the phosphate and potassium levels were also decreased in group A, the reason is unclear. This might be a reflection of subclinical renal tubular dysfunction caused by VPA [3].

An elemental diet contains no purine. A long-term effect of purine-free nutrition on protein and uric acid homeostasis is not well recognized. It is known that hypouricemia is commonly recognized in patients receiving total parenteral nutrition in purine-free regimens [5–7]. However, purine deprivation evidently leads to an increase in de novo synthesis and the uric acid level is maintained within the normal range [8]. Several authors [5–7] have reported that a decreased plasma uric acid level is due to enhanced FEUA

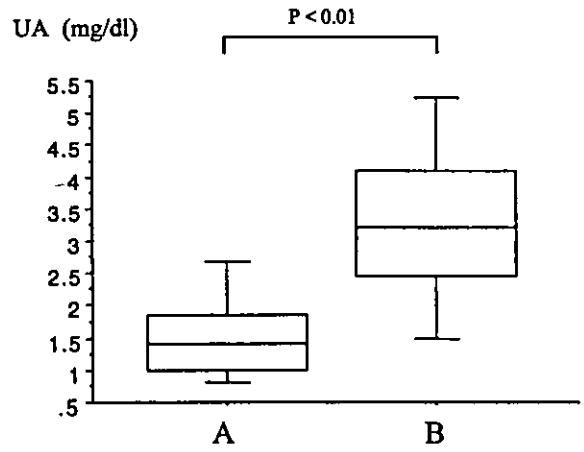

Fig. 1. Box and whisper plots of the serum uric acid levels in groups A and B. Upper line indicates 90 percentile and lower line indicates 10 percentile. UA, uric acid.