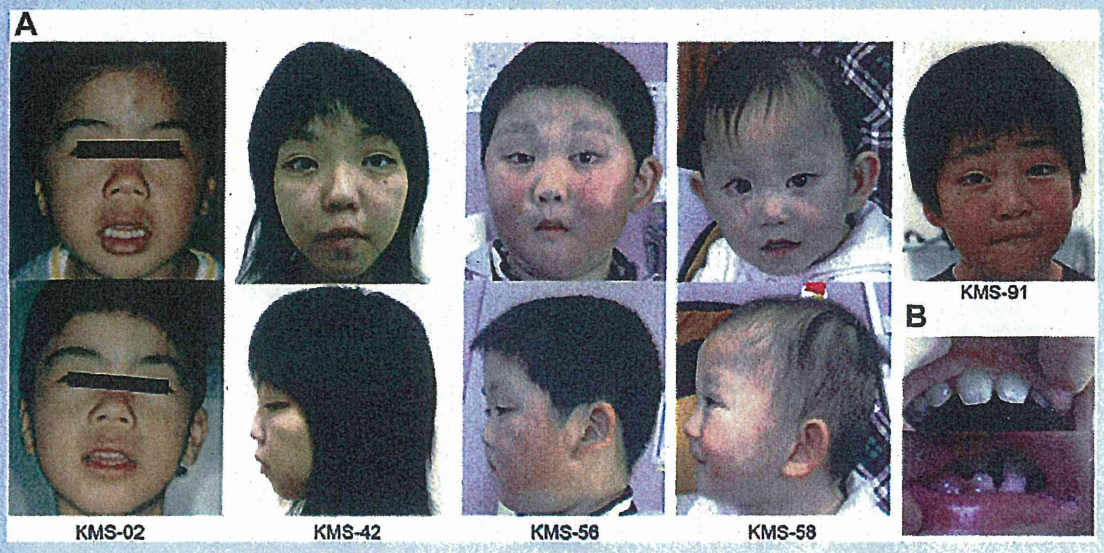

FIG. 4. Clinical features of patients with Kabuki syndrome with a *MLL2* non-truncating-type mutation. A: Facial features of patients with KS and a *MLL2* non-truncating-type mutation. B: Patient KMS-56 showed abnormal dentition (hypodontia with wide interdentium).

Kokitsu-Nakata et al., 2012; Tanaka et al., 2012; Bogershausen and Wollnik, 2013; Makrythanasis et al., 2013] (Human Gene Mutation Database Professional 2012.3; https://portal.biobase-international.com/hgmd/pro/gene.php). Our mutation-positivity rate for either gene was 67.9% (55/81), and that for *MLL2* only was 61.7% (50/81); these figures are compatible with those reported in a review (55–80%) [Banka et al., 2012b]. Mutation-negative patients suggest the existence of unknown genes to cause KS or misdiagnosis.

As for the phenotype–genotype relationship, Banka et al. [2012b] suggested that feeding problems, kidney anomalies, premature thelarche, joint dislocation, and palatal malformation were more frequently observed in patients with *MLL2*-mutations than in patients with normal *MLL2* sequence. Hannibal et al. [2011] reported that renal anomalies were more common in patients who had *MLL2* mutations compared to those who did not. Li et al. [2011] reported that short stature and renal anomalies were more frequent in patients with *MLL2*-mutations than in those with normal *MLL2* sequence. In our study, premature thelarche was observed only in patients with *MLL2* mutations, but this was not significant ($P = 0.1137$). The frequencies of kidney anomalies, hip joint dislocation, and short stature were not different when comparing those with and without *MLL2* mutations ($P = 0.3030$, $P = 1.0000$, and $P = 0.0717$, respectively; Supplemental Table V). High arched eyebrows, palatal malformation (cleft palate/lip), low posterior hairline, and short fifth finger were more frequently observed in individuals with *MLL2* mutations than in patients with normal *MLL2* ($P = 0.0118$, $P = 0.0284$, $P = 0.0493$, and $P = 0.0137$, respectively; Supplemental Table V).

X-inactivation skewing in patients with KS has been discussed since the discovery of the *KDM6A* deletion in a female with KS

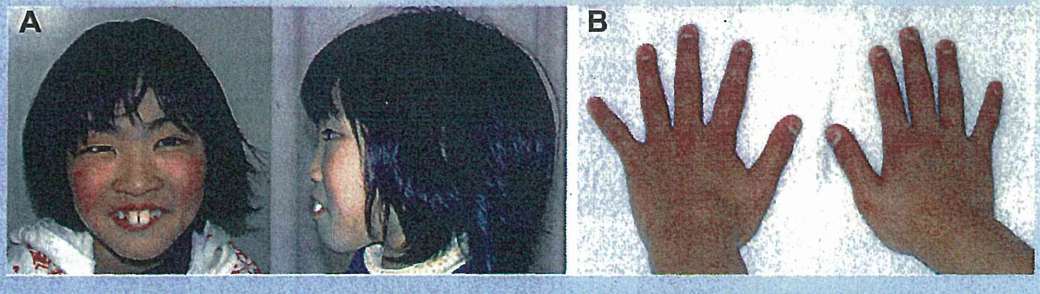

FIG. 5. Clinical features of patients with Kabuki syndrome with a *KDM6A* truncating-type mutation. A: Facial features of patient KMS-81 harboring a *KDM6A* mutation (c.1909_1912del, p.Ser637Thrfs*53). She showed large front teeth with wide interdentium. B: Hand image of KMS-81. Short fifth finger was not remarkable.

[Lederer et al., 2012; Miyake et al., 2013]. In two female patients reported here, patient KMS-65, who had an in-frame deletion, showed a random X-inactivation pattern, but patient KMS-81, who had a truncating-type mutation, showed marked skewing. X-inactivation skewing was also reported in two affected females with *KDM6A* deletion reported by Lederer et al. [2012]. cDNA sequence analysis of patient KMS-81 indicated that the mutant allele of *KDM6A* was expressed at a similar level to the wild-type allele under NMD inhibition. This result suggests that *KDM6A* mostly escapes X-inactivation in female lymphoblastoid cells. Interestingly, *KDM6A*/*Kdm6a* escapes X-inactivation in humans and mice, and in mice its expression level from the inactive X chromosome (Xi) was reported as 15–35% of that from the active X chromosome (Xa) [Greenfield et al., 1998; Xu et al., 2008]. We calculated the hypothetical expression assuming a 30% *KDM6A* expression level from Xi and 100% expression from Xa (Supplemental Fig. 2). In patient KMS-81, who showed marked skewing (98:2), either the mutant X chromosome or the wild-type X was inactivated in 98% of cells. If the mutant were inactivated, the expression level would be below 1 ($1.0 \times 0.98 + 0.3 \times 0.02 = 0.986$). If the wild-type were inactivated, the expression level would also be below 1 ($1.0 \times 0.02 + 0.3 \times 0.98 = 0.314$). The KS phenotype is usually unassociated with Turner syndrome (45,X), with the *KDM6A* expression level at 1.0 [Miyake et al., 2013]. It is possible that having a *KDM6A* expression level of 1.0 is essential for a normal human phenotype. Similarly, males with only one copy of *KDM6A* do not manifest KS. We previously mentioned the possibility of *UTY* compensation for *KMD6A* (Supplemental Fig. 2) [Miyake et al., 2013], although human UTY lacks demethylase activity [Hong et al., 2007; Lan et al., 2007]. The recent evidence that $X^{Utx-}X^{Utx-}$ homozygous mice demonstrated a more severe phenotype than $X^{Utx-}Y^{Uty+}$ mice indicates that UTY can compensate for the loss of UTX in embryonic development [Shpargel et al., 2012]. Because mouse and human UTY show 75% identity, and 95% identity in the Jumonji C domain [Shpargel et al., 2012], it is likely that normal human males who have only one copy of *KDM6A* are supplemented by *UTY* in a demethylase-independent manner.

Interestingly, $X^{Utx-}Y^{Uty+}$ mice showed small body size [Shpargel et al., 2012]. Similarly, the human *KDM6A*-mutated group exhibited short stature and postnatal growth retardation.

Regarding our mutation detection methods, HRM analysis and Sanger sequencing are both imperfect. Next-generation sequencing is more sensitive (especially for single nucleotide variants and small insertions/deletions), faster, and cheaper due to multiple gene screening and the potential to multiplex. However, a microdeletion involving *MLL2* or *KDM6A* or low-level mosaicism of a single nucleotide variant might be missed by this method. Therefore, in patients who test mutation-negative, more comprehensive approaches might be necessary. In conclusion, we investigated *MLL2* and *KDM6A* mutations and their clinical consequences in patients with KS. The majority of the clinical features were observed at a similar frequency among patients with either *MLL2* or *KDM6A*-mutations. The genetic basis of the patients who tested mutation-negative (20–45%) remains elusive. Further studies are necessary to understand the whole picture of the genetic aspects of KS and its genotype–phenotype relationships.

ACKNOWLEDGMENTS

We thank the patients and their parents for participating in this work. We also thank Ms. Y. Yamashita, Ms. E. Koike, Ms. S. Sugimoto, Ms. N. Watanabe, Ms. K. Takabe, and Mr. T. Miyama for their technical assistance. This work was supported by research grants from the Ministry of Health, Labour and Welfare of Japan (H. Saitsu, N. Matsumoto, N. Miyake), the Japan Science and Technology Agency (N. Matsumoto), the Strategic Research Program for Brain Sciences (N. Matsumoto), a Grant-in-Aid for Scientific Research on Innovative Areas-(Transcription cycle)-from the Ministry of Education, Culture, Sports, Science and Technology of Japan (N. Matsumoto), a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (N. Matsumoto), a Grant-in-Aid for Young Scientists from the Japan Society for the Promotion of Science (H.S., N. Miyake), the Takeda Science Foundation (N. Matsumoto, N. Miyake), the Yokohama Foundation for the Advancement of Medical Science (N. Miyake), and the Hayashi Memorial Foundation for Female Natural Scientists (N. Miyake).

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症例報告

脳幹部腫瘍との鑑別に組織生検が有用であった多発性硬化症の11歳男児例

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Diagnostic value of brain biopsy in a pediatric multiple sclerosis mimicking brain stem glioma

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(Accepted March 4, 2013)

summary

Diagnosis of multiple sclerosis (MS) is difficult when the lesion mimics glioma or cerebral enchephalitis. We report a case of pediatric MS initially suspected as brain stem glioma. An 11-year-old boy developed left foot joint pain followed by progressive symptoms such as left arm and leg weakness, dysarthria, paraplegia, and decreased level of consciousness. He subsequently developed respiratory distress requiring endotracheal intubation and mechanical ventilation. Magnetic resonance imaging showed a mass measuring 2 cm in the medulla oblongata. Although this mass was initially suspected as a glioma, the patient's acutely progressive disease course was not consistent with this diagnosis. Open biopsy revealed inflammation and demyelination, but no malignant cells were detected. He was treated with steroid pulse therapy, which showed dramatic effects. Nine months later, he developed another episode characterized by several neurological symptoms, and the diagnosis of MS was clinically confirmed. Open brain stem biopsy is technically demanding, but this case demonstrates that appropriate neurosurgical evaluation can play an important role in diagnosis by ruling out glioma and confirming MS.

Key words——brain stem glioma; multiple sclerosis; clinically isolated syndrome; tumefactive multiple sclerosis; Bickerstaff's encephalitis

抄　録

多発性硬化症の診断は，病巣が単発性の場合，しばしば脳腫瘍や脳炎・脳症との鑑別が困難になる．今回われわれは延髄に2 cm大の腫瘤性病変を認め，当初脳幹部グリオーマが疑われたが，最終的に多発性硬化症の診断に至った11歳男児例を経験した．患児は下肢痛の出現後，約2週間の経過で四肢麻痺，意識障害，呼吸不全が進行した．急性の臨床経過がグリオーマの臨床経過と合致せず，診断が困難であったため，手術自体の危険性を説明の上，組織生検を施行した．組織像では明らかな腫瘍細胞を確認しなかったこと，及び症状が急性に進行していることから非腫瘍性疾患の可能性を考え，ステロイドパルス療法を施行したところ速やかに回復し，ほぼ障害を残さずに退院した．その後初発から9か月後に他の部位に再発し，臨床的に多発性硬化症の診断に至った．脳幹部の組織生検は容易ではないが，適切な治療法選択の上で極めて重要な役割を果たした．

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はじめに

多発性硬化症（multiple sclerosis, MS）は中枢神経系の慢性炎症性脱髄性疾患であり，時間的・空間的多発を特徴とする[1]．しかし，MS 初回発症の脱髄性病変と考えられている clinically isolated syndrome（CIS）において，病巣が単発性の場合，他疾患との鑑別が困難となる場合もある．臨床像や検査所見が腫瘍に類似した MS は，tumefactive multiple sclerosis と呼ばれ，2 cm 以上の病巣，mass effect，浮腫，辺縁の途切れた不完全な造影効果を示す open ring enhancement などを特徴とする[2]．これらはしばしば画像所見のみでは鑑別は困難で，組織生検が有効となる．しかし病変が脳幹部の場合，生検自体が侵襲的になり得ること，十分な組織を採取することが困難なことから生検を行うかの判断はしばしば難しい[3,4]．今回われわれは延髄に限局した腫瘤性病変を認め，臨床的に診断が困難であったことから組織生検を行い，治療に結びついた一例を経験したので報告する．

症　例

症　例：11 歳男児

家族歴：母：2 年前にくも膜下出血，後遺症で記憶障害あり，父：痛風

既往歴：特記事項なし

主　訴：歩行障害，傾眠傾向

現病歴：発症 1 か月前に，軽い上気道炎症状があった．入院 2 週間前から左足関節痛，3 日前より左上下肢に力が入りにくい感覚を覚えていた．2 日前からは嘔吐，構音障害が出現，両下肢の脱力感を感じるようになった．受診当日には自力で起き上がることも不可能となり，傾眠傾向を認めたため，前医に入院した．頭部 MRI 検査で延髄右側に腫瘤性病変を認め，脳腫瘍の疑いで当院に紹介され，ICU に入院した．

入院時現症：体温 37.1℃，心拍数 66 回/分，呼吸数 16 回/分，血圧 96/60 mmHg，Japan Coma Scale I-1, Glasgow Coma Scale E4V5M6．瞳孔は両側 6.0 mm で，対光反射は正常，眼振はなかった．徒手筋力テストでは，左腸腰筋は 4/5，右上下肢は 5/5．それ以外は 2/5，深部腱反射は左上肢で軽度低下，左膝蓋腱反射は亢進，右上下肢では正常であった．左 Babinski 反射は陽性であった．

検査所見：入院時血液一般，生化学検査，髄液検査に異常はなかった（表 1）．血清中のウイルス関連検査は全て陰性，オリゴクローナルバンド陰性，IgG index の上昇は認めなかった．抗 GQ1b 抗体を含め抗ガングリオシド抗体は陰性，抗アクアポリン 4 抗体も陰性であった．

表 1　入院時検査所見

末梢血一般検査			
WBC	6900/μl	BUN	8.4 mg/dl
Neu.	74.8%	Cr	0.34 mg/dl
Lym.	18.1%	CRP	<0.2 mg/dl
Eos.	0.1%	TP	6.7 g/dl
Baso.	0.2%	Alb	4.1 g/dl
Mono	5.1%	CPK	71 U/l
Hb	14.3 g/dl	Na	137 mEq/l
Plt	32.9*10⁴/μl	K	4.2 mEq/l
		Cl	101 mEq/l
生化学検査		Ca	9 mg/dl
AST	20 IU/l	IP	3.8 mg/dl
ALT	22 IU/l	BS	110 mg/dl
LDH	167 IU/l	NH3	55 μg/dl
血液ガス分析（静脈）		各種ウイルス抗体価	
pH	7.417 mmHg	HHV6 IgG	40 倍
pCO2	42.2 mmHg	HHV6 IgM	陰性
HCO3	26.3 mmmol/l	EBV-IgM	陰性
B.E.	2.3 Mmol/l	CMV-IgM	陰性
髄液検査（第 22 病日）		血清ウイルス検査(PCR 法)	
細胞数	1/μl	HHV-6, 7	陰性
タンパク	22.8 mg/dl	EBV	陰性
糖	57 mg/dl	CMV	陰性
オリゴクローナルバンド	陰性	parvovirusB19	陰性

入院時 MRI 所見：延髄右側に FLAIR 画像と T2 強調画像で高信号，T1 強調画像で低信号を呈する比較的境界明瞭な 2 cm 大の腫瘤性病変を認めた．ガドリニウムによる造影効果は乏しく，脳浮腫や水頭症，mass effect の所見は認めなかった（図 1-a-c）．

入院時診断：脳幹部グリオーマの疑い

入院後経過①：入院後両上下肢の筋力低下は更に進行し，水平・上方向への眼振も出現した．入院 4 日目には呼吸状態が悪化し人工呼吸管理を開始した．頭部 MRI では腫瘤影の増大傾向を認めた．急性の経過が脳幹部腫瘍の臨床像と異なるため，入院 5 日目，診断目的に開頭生検術が施行された．

病理所見：グリオーマを含めた腫瘍性病変は認めなかった．泡沫状の細胞質を有する組織球が多数出現し，血管周囲に炎症細胞浸潤を伴っている点は炎症や脱髄，梗塞などの組織崩壊病変を疑わせた（図 2）．

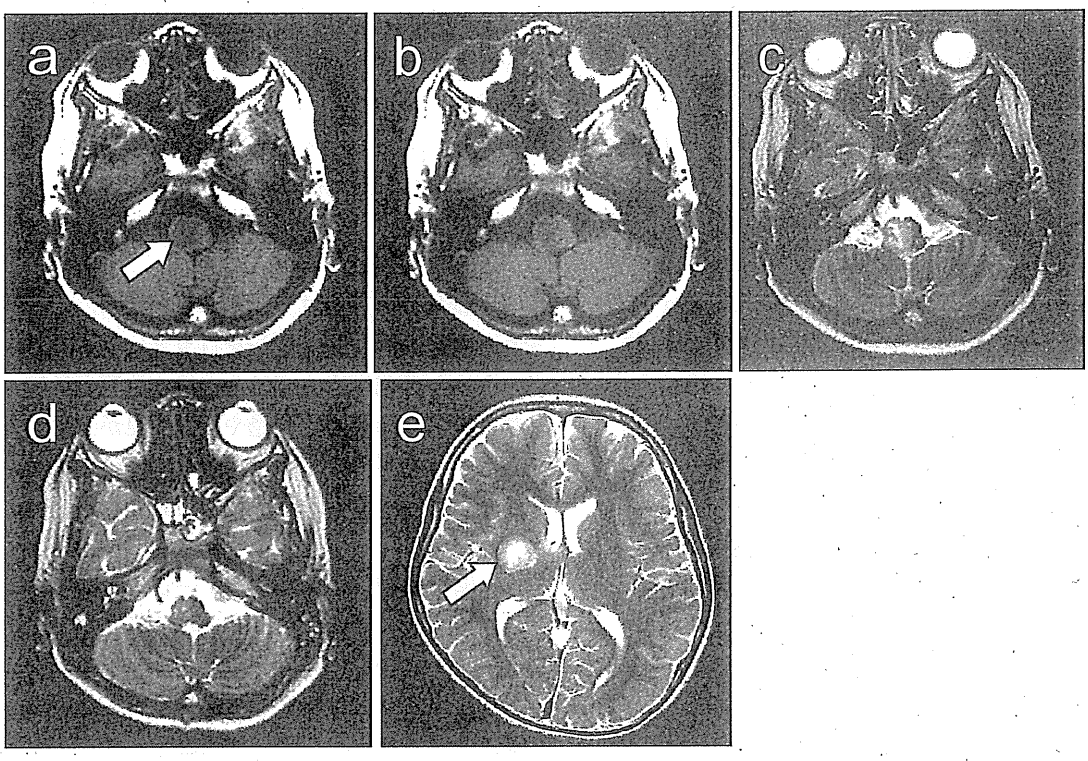

図 1　頭部 MRI 所見.
a, b, c.　入院時．延髄右腹側に正中を超えて，T1 低信号，T2 高信号の 1.3×1.5×2.4 cm 大の腫瘤影を認める．境界明瞭で造影効果はほとんどみられない．a：T1 強調画像，軸位断，b：造影 T1 強調画像，軸位断，c：T2 強調画像，軸位断
d.　ステロイドパルス治療 3 クール施行後．T2 強調画像，軸位断．治療前と比べ腫瘤は縮小している．
e.　初発から 9 か月後．T2 強調画像，軸位断．右大脳基底核に T2 高信号の 22×18×27 mm の大の腫瘤性病変を認める．

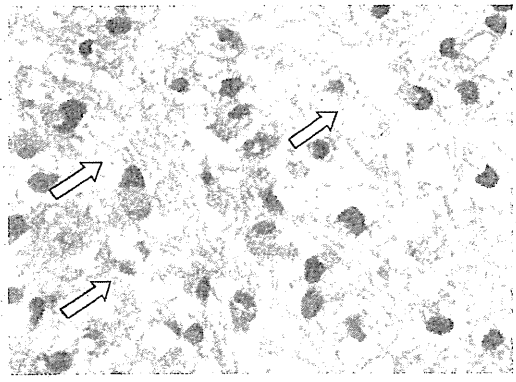

図 2　延髄病理所見（HE 染色，400 倍）
泡沫状の細胞質を有する組織球が多数出現しており，脱髄や炎症，梗塞などの組織崩壊病変と考えられた．

入院後経過②：組織診断は困難であったが，臨床所見と合わせ，脱髄や炎症性病変の可能性が高いと考え，入院 21 日目よりステロイドパルス療法（メチルプレドニゾロン 30 mg/kg/日を 3 日間静脈注射）を開始した．

ステロイドパルス療法開始後，筋力と呼吸器症状は著明に改善し，1 クール終了後 1 週間で人工呼吸管理を終了した．一方で，右斜め上方共同偏視，眼振，注視麻痺が目立つようになったが，ステロイドパルス療法 3 クール施行後には徐々に改善傾向を認めた．治療開始後 2 か月で若干の眼振を認めるのみで，自力歩行も可能な状態となり，退院となった．画像上も著明な改善を認めた（図 1-d）．

退院後，発症から 9 か月で，眼振と左顔面神経麻痺が出現，右内包後脚，大脳基底核に病変を認め（図 1-e），時間的，空間的多発性から最終的に MS と診断した．

考　察

脳幹部グリオーマとの鑑別が初発時には極めて困難であったが，組織生検により診断的治療に結びついた多発性硬化症の小児例を経験した．

MS は通常臨床経過と脳・脊髄 MRI 検査および髄液検査（オリゴクローナルバンド，IgG index などを含む）から，2010 年に改定された McDonald 基準を用いて診断される[1]．また，小児においては感度が低いことが指摘されていたが[5]，McDonald 基準を改定することで 85％の感度で他疾患との鑑

別が可能であるとの報告がある[6]．しかし，特にMS初回発症の脱髄性病変と考えられているCISにおいて，腫瘍と極めて類似した画像を呈する場合は，tumefactive MSと呼ばれ，診断が困難となる場合がある．稀な病態であるがその報告が散見され[2]，小児例の報告もある[7]．Tumefactive MSの基準は，2 cm以上の病巣，mass effect，浮腫，open ring enhancementなどを特徴とする[2]．特にopen ring enhancementは脱髄病変に対して84.4%～93.8%の特異度を示すと言われているが，open ring enhancementを示すものは22～39%にとどまると報告されている．本症例ではmass effectやopen ring enhancementなどは認めなかった．

Bickerstaff型脳幹脳炎は4週間以内に進行する外眼筋麻痺，運動失調を主要症状とし，意識障害や深部腱反射の亢進を特徴とするGuillain-Barré症候群の亜型と考えられている疾患である．MRIの異常は約30%に，抗ガングリオシドGQ-1b抗体の上昇は66%に認められるとの報告がある[8]．本症例では，抗ガングリオシドGQ-1b抗体は陰性で，最初は四肢麻痺と球麻痺が主症状であったが，その後眼球運動障害が強まったことからBickerstaff型脳幹脳炎の可能性も当初は考えられた．治療は免疫グロブリン大量療法が第一選択となる．

一方，小児脳幹部グリオーマは小児脳腫瘍の10～20%を占め，その80～90%は予後不良な浸潤性腫瘍であるとされている[9]．本症例ではT1低信号，T2高信号を呈し，境界明瞭で造影効果は認めなかった．これらの所見はグリオーマに矛盾しない所見であった．脳幹部グリオーマは予後不良の疾患であるが放射線療法が治療選択となる．

腫瘍とMSの鑑別に，組織生検を行うかの是非については議論の決着はついていない[3,4]．非侵襲的診断方法として，MR spectroscopyが鑑別診断に有効であるとの報告もある[10]．

本症例において生検が必要となる根拠は，i）腫瘍を疑わせる画像所見と亜急性の臨床経過が合致せず，鑑別診断が困難であったこと，ii）診断により治療方針や予後が大きく異なることがあげられる．一方危惧される問題点としては，i）脳幹部病変のため，生検自体による症状の悪化や重篤な後遺症の可能性があること，ii）十分な標本が採取できずに確定診断が得られない可能性があることがあげられる．本症例では適切な診断治療を行うため，家族に手術の危険性を十分に行った後，組織生検を行った．組織学的には腫瘍性病変は確認されず，泡沫状の細胞質を有する組織球や血管周囲の炎症細胞浸潤の所見からは脱髄または炎症性疾患を疑った．急性の臨床経過と合わせると，MS関連の脱髄性疾患またはBickestaff型脳幹脳炎などの可能性があると判断し，ステロイドパルス療法を行ったところ著効し，良好な経過をたどった．

脳幹部病変の生検は容易ではないため，組織生検を行わずにステロイド療法を行うという選択肢がある．しかし症例によってはその後の治療方針に大きく影響するため，臨床経過や画像所見が非典型的な場合，手術に伴う危険性を十分に説明した上で，開頭生検術を行う意義は高いものと思われた．

謝　辞：病理診断コンサルテーションに応じて頂きました群馬大学医学部付属病院病理部の平戸純子先生，抗GQ1bガングリオシド抗体を含む抗ガングリオシド抗体の測定をして頂きました近畿大学内科学講座　神経内科部門の楠進教授，アクアポリン4抗体の測定をして頂きました金沢医科大学の田中恵子先生に感謝致します．

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ADORA2A polymorphism predisposes children to encephalopathy with febrile status epilepticus

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Neurology 2013;80;1571; Published online before print March 27, 2013;
DOI 10.1212/WNL.0b013e31828f18d8

ADORA2A polymorphism predisposes children to encephalopathy with febrile status epilepticus

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ABSTRACT

Objective: Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is a childhood encephalopathy following severe febrile seizures, leaving neurologic sequelae in many patients. However, its pathogenesis remains unclear. In this study, we clarified that genetic variation in the adenosine A2A receptor (*ADORA2A*), whose activation is involved in excitotoxicity, may be a predisposing factor of AESD.

Methods: We analyzed 4 *ADORA2A* single nucleotide polymorphisms in 85 patients with AESD. The mRNA expression in brain samples, mRNA and protein expression in lymphoblasts, as well as the production of cyclic adenosine monophosphate (cAMP) by lymphoblasts in response to adenosine were compared among *ADORA2A* diplotypes.

Results: Four single nucleotide polymorphisms were completely linked, which resulted in 2 haplotypes, A and B. Haplotype A (C at rs2298383, T at rs5751876, deletion at rs35320474, and C at rs4822492) frequency in patients was significantly higher than in controls ($p = 0.005$). Homozygous haplotype A (AA diplotype) had a higher risk of developing AESD (odds ratio 2.32, 95% confidence interval 1.32–4.08; $p = 0.003$) via a recessive model. mRNA expression was significantly higher in AA than AB and BB diplotypes, both in the brain ($p = 0.003$ and 0.002, respectively) and lymphoblasts ($p = 0.035$ and 0.003, respectively). In lymphoblasts, ADORA2A protein expression ($p = 0.024$), as well as cellular cAMP production ($p = 0.0006$), was significantly higher in AA than BB diplotype.

Conclusions: AA diplotype of *ADORA2A* is associated with AESD and may alter the intracellular adenosine/cAMP cascade, thereby promoting seizures and excitotoxic brain damage in patients.
Neurology® 2013;80:1571–1576

GLOSSARY

ADORA1 = adenosine A1 receptor; **ADORA2A** = adenosine A2A receptor; **AEIMSE** = acute encephalopathy with inflammation-mediated status epilepticus; **AESD** = acute encephalopathy with biphasic seizures and late reduced diffusion; **cAMP** = cyclic adenosine monophosphate; **CI** = confidence interval; **CPT2** = carnitine palmitoyltransferase II; **G6PDH** = glucose-6-phosphate dehydrogenase; **OR** = odds ratio; **SMRI** = Stanley Medical Research Institute; **SNP** = single nucleotide polymorphism.

During the course of acute febrile diseases, such as influenza and exanthema subitum, some children develop repetitive or prolonged seizures, followed by sustained impairment of consciousness. These conditions are collectively termed acute encephalopathy with inflammation-mediated status epilepticus (AEIMSE).[1] Among AEIMSE, acute encephalopathy with biphasic seizures and late reduced diffusion (AESD)[2] is the most common in Japan, affecting hundreds of children every year.[3] Hemiconvulsion-hemiplegia syndrome, a condition encountered worldwide, often occurs during an infectious disease, and is regarded as a subgroup of AESD.[4] AESD typically shows a biphasic clinical course, consisting of a prolonged febrile seizure

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.