③髄液検査：髄液中のアミロイドβ42タンパクが低下し，リン酸化タウタンパクが増加している．

(3) 治　療

現在，アルツハイマー病の治療としては，薬物療法と非薬物療法が行われている．薬物療法としては，アルツハイマー病では神経系のアセチルコリン活性が低下していることから，アセチルコリン濃度を高める塩酸ドネペジル（アリセプト®）が治療の中核となっている．進行とともに現れる周辺症状に対する治療法としては，不穏・興奮には非定型抗精神病薬，抑うつには選択的セロトニン再取り込み阻害薬などが投与されている．非薬物療法としては，回想法，リアリティ・オリエンテーション（見当識訓練）法，音楽療法，芸術療法，記憶訓練，レクリエーション療法などがある．

プラスα

リアリティ・オリエンテーション

患者に対して氏名・場所・時間など基本的な情報の質問を繰り返すことで，対人関係や協調性，認知能力を高める療法である．

3　ナーシングチェックポイント

認知症を正しく理解し，適切なケアをすることが大切である．認知症患者では，環境の変化や不適切なケアによる精神的ストレスにより不眠や不穏，徘徊，暴言などの周辺症状が出現する．症状の背景となる原因を検討して不安を少しでも和らげ，その人らしい生活を送ることができるように援助することが認知症ケアの第一原則である．さらに，全身状態の悪化や薬物の有害反応が症状の進行や周辺症状の出現に影響することがあるため，栄養状態や排尿・排便の状態，水分バランスなどを把握しておくことも大切である．

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2）平井俊策ほか．アルツハイマー病．日本臨牀，2003.

重要用語

認知症　　**周辺症状**

中核症状

Case Report

Neuromyelitis Optica Preceded by Brain Demyelinating Episode

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ABSTRACT

Neuromyelitis optica (NMO) is considered a distinct disease from multiple sclerosis (MS) because of its pathogenesis. It is well accepted that NMO selectively affects the spinal cord and optic nerve and is not associated with brain lesions at the onset of the disease, unlike MS. We present a unique case where the patient's initial lesion was in the brain, and optic neuritis and myelitis were revealed 6 years after the brain lesion. In addition, the patient's serum antiaquaporin 4 (AQP4) antibody was positive. We consider the brain lesion to precede abnormal lesion of NMO, and the AQP4 measurement is important for diagnostics, even if it occurs with brain lesions.

Keywords: Neuromyelitis optica, aquaporin 4, brain lesion, MRI.

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Introduction

Neuromyelitis optica (NMO) is an inflammatory demyelinating disease of the central nervous system that most commonly disturbs the spinal cord and optic nerves, selectively. A highly specific serum antibody (NMO-IgG) has recently been found in NMO patients,[1] and NMO-IgG reacts specifically with the water channel protein aquaporin 4 (AQP4), which is concentrated in astrocytic foot processes at the blood-brain barrier.[2] In addition, a high rate of anti-AQP4 antibody was detected in Asian patients with multiple sclerosis (MS). This was characterized by the selective involvement of the optic nerve and long spinal cord lesions extending over three vertebral segments.[3]

Unlike MS, NMO is not associated in most patients with brain lesions at disease onset. However, brain lesions do occur over time in the majority of NMO patients. Until now, there has been no report of an NMO case where brain lesions presented before the onset of optic neuritis and myelitis. We present here a unique NMO case where brain lesions were revealed 6 years before the onset of optic neuritis and myelitis.

Case report

A 21-year-old woman was admitted to our hospital because of her transient mild neurological symptoms, such as gait disturbance and dizziness, which continued for several days. Her medical history revealed that she had experienced aseptic meningitis on three occasions as a teenager. She did not reveal any symptoms that would suggest spinal cord or optic nerve disturbance. Magnetic resonance imaging (MRI) of her brain revealed several T2 hyperintense lesions in her corpus callosum (genu, splenium), left internal capsule, and left corona radiata (Fig 1). Her cerebrospinal fluid (CSF) revealed normal findings. She was retrospectively classified with acute disseminated encephalomyelitis (ADEM) or the initial episode of MS. For the next 6 years without medication, she did not present any neurological symptoms.

At age 27, she was admitted to our hospital again because of neurological symptoms gradually developed between about a week. She had bilateral poor eyesight, visual field disturbance, severe paraplegia with difficult walking, bilateral extensor plantar responses, severe disturbance of all sensory modalities of her trunk and bilateral legs below the T4 level, and urinary retention. She had no erythema or arthritis. The laboratory tests revealed high levels of serum antinuclear antibody, anti-Ro antibody, and antithyroid antibodies. The Schirmer test was positive (right 2 mm, left 2 mm); however, her minor salivary gland biopsy showed no inflammatory infiltration. Her CSF on admission revealed marked pleocytosis (482/ul, 60% polymorphonuclear leukocytes), high protein (220 mg/dl), and IgG (45.7 mg/dl) concentrations, however, negative for oligoclonal IgG bands. Her serum collected in the acute phase was examined by the method previously described [3] and was found to be positive for anti-AQP4 antibody. An MRI of her brain presented similar findings to 6 years earlier (Fig 2) and that of the cervical and thoracic spinal cord revealed a T2 hyperintense lesion within the central area of the cord extending from C6 to T8 without contrast enhancing (Fig 3). We diagnosed her as NMO. She did not meet the criteria of any collagen disease

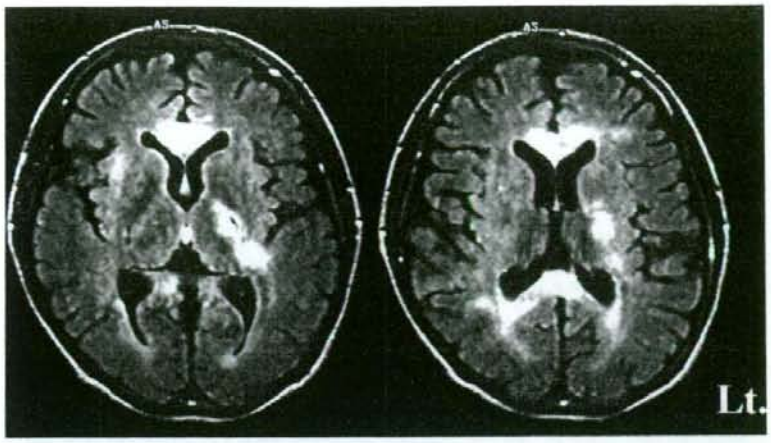

Fig 1. Brain MRI (fluid attenuated inversion recovery images) at age 21 revealed several T2 hyperintense lesions in her corpus callosum (genu, splenium), left internal capsule, and left corona radiata.

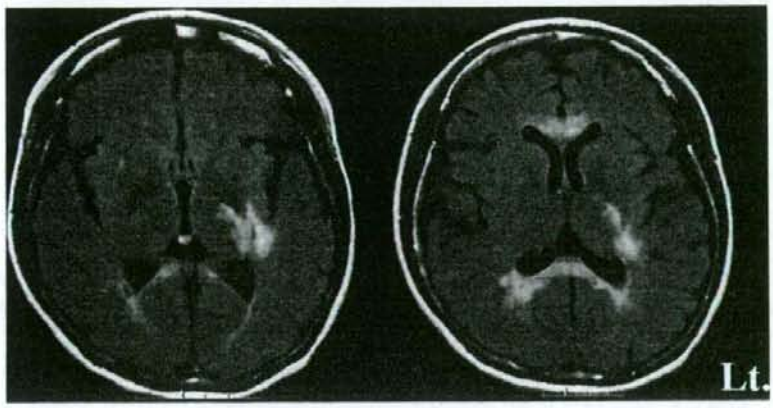

Fig 2. Brain MRI (fluid attenuated inversion recovery images) at age 27 revealed presented similar findings to 6 years before.

such as Sjogren syndrome or systematic lupus erythematosus. A 3-day course of 1 mg/day intravenous methylprednisolone followed by oral prednisolone was administered immediately after admission. On the 14th day of admission she was able to walk unassisted, and her eyesight and visual field disturbance significantly improved. Her spinal cord MRI showed a reduction in the T2 hyperintense area, and CSF findings were normalized.

She was treated with low-dose oral prednisolone after discharge and no relapse was noted over the subsequent 18 months.

Discussion

Wingerchuk et al. proposed diagnostic criteria for defining NMO that require optic neuritis, myelitis, and at least two of three supporting criteria as follows: MRI evidence of a contiguous spinal cord lesion three or more segments in length, onset brain MRI non-diagnostic for MS, or NMO-IgG.[4] Especially concerning the brain MRI, patients with NMO present normal or few non-specific minor subcortical white matter changes at the onset of the disease, and they usually do not fulfill Barkhof radiological criteria for MS.[5] Pittock et al. showed brain MRI lesions in 36 patients among 60 reviewed NMO patients. Most lesions were non-specific, but 6 patients had MS-like lesions without symptoms, and 5 patients had diencephalic, brainstem, or cerebral lesions atypical for MS. It should be noted that half of the patients in this study with a normal initial brain MRI developed abnormalities on a subsequent MRI.[6] Nakashima et al. also reported that brain lesions were seen in 71% of the patients with NMO-IgG, but most were medullary lesions as an extension of cervical myelitis or non-specific cerebral white matter lesions.[7] Brain lesions are no longer an exclusionary criterion in the most recently proposed diagnostic criteria for NMO.[4] In these reported cases, brain lesions did not precede optic nerve

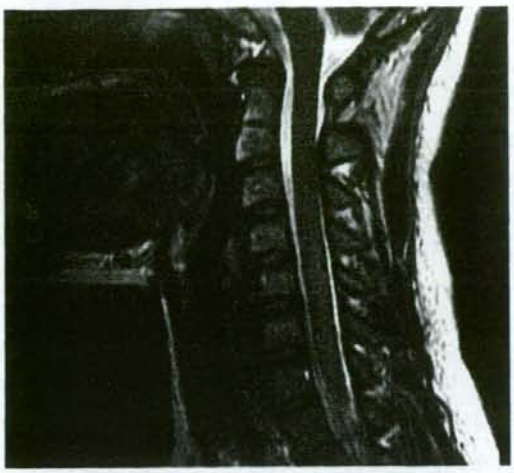

Fig 3. Cervical and thoracic spinal cord MRI (T2-weighted images) at age 27 revealed T2 hyperintense lesion within the central area of cord extending from C6 to T8.

or spinal cord lesions. This makes our case unique because the patient showed brain lesions before optic nerve and spinal cord lesions. It indicates brain lesions can precede the abnormality of later diagnosed NMO.

There is strong evidence that immunomodulatory therapy such as interferon beta is effective for MS patients to prevent recurrence. However, Warabi et al. reported interferon beta-1b treatment was not successful for MS with genetic and clinical characteristics mimicking NMO.[8] In addition, Matsuoka et al. reported that anti-AQP4 antibody-positive MS patients fulfilling definite NMO criteria showed less frequent responses to interferon beta-1b than anti-AQP4 antibody-negative opticospinal MS patients with longitudinally extensive spinal cord lesions.[9] In fact, immunosuppressive treatment is currently the most commonly used drug for the acute and long-term treatment of NMO patients.[10-12] These findings are consistent with findings that NMO is an autoantibody-mediated disease. Accordingly, intravenous corticosteroids and oral prednisolone therapy were very effective for our patient, and she has maintained without relapse using low-dose oral prednisolone. NMO prognosis is generally poorer than MS prognosis because most attacks are moderate or severe and usually follow a relapsing course. Therefore, it is important to discriminate between NMO and MS at the early stage of the disease to select an appropriate treatment, especially in the case present chronologically or spatially atypical brain lesions.

In conclusion, we consider the measurement of anti-AQP4 antibody provides not only the additional diagnostic certainty but also the best therapy and prognostic conclusion in cases with clinically atypical presentation.

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Cytokine levels in sputum of patients with tracheostomy and profound multiple disabilities

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Abstract

Background. Airway immunopathogenesis is unclear in patients with profound multiple disabilities (PMD) who undergo tracheostomy. *Methods.* The levels of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, IL-8, IL-10, and IL-12p70 cytokines were determined in sputum of 28 patients with PMD who underwent tracheostomy and in 14 healthy subjects, using a cytometric bead array. *Results.* The concentrations of IL-1β, IL-6 and IL-8 in the patients were significantly higher than those in controls ($p < 0.001$). IL-6, and IL-8 levels in eight PMD patients in the febrile period were significantly higher than those in the afebrile period ($p < 0.01$ and $p < 0.05$, respectively). Serum CRP levels were slightly elevated in 12 of the 28 patients (43%) in the afebrile period, but there were no significant differences in the level of any cytokine between patients with normal and elevated serum CRP. *Conclusion.* PMD patients with tracheostomy have chronic airway inflammation.

Keywords: Airway inflammation; Profound multiple disabilities; Sputum; Tracheostomy

1. Introduction

Patients with profound multiple disabilities (PMD) frequently have respiratory problems which affect their quality of life. Such problems commonly stem from central nervous system dysfunctions and/or severe motor disabilities. Complications include dysmyotonia, thoracic deformation, structural disorder of the respiratory tract (laryngomalacia, tracheal stenosis, subglottic stenosis), dysphagia, and gastro-esophageal reflex disease, and these often influence each other and result in respiratory insufficiency [1]. These patients may require tracheostomy, after which some are able to breathe non-physiologically, whereas others require mechanical ventilation. Respiratory infection may also recur in some cases [2,3], and chronic inflammation can occur in the lower respiratory tract of children with tracheostomy [4].

To examine the hypothesis that patients with PMD have chronic airway inflammation, we measured cytokine concentrations in sputum, which are useful for local evaluation of airway cells and cytokines levels [5]. The levels of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, and IL-8, which are proinflammatory cytokines [6–8]; IL-10, an anti-inflammatory cytokine [6,9]; and IL-12p70, a cytokine required for induction of Th1 immune responses [10] in the sputum of PMD patients with tracheostomy were compared with those in healthy subjects. We also investigated the relationship between cytokines and serum C-reactive protein (CRP) levels [11] in patients with PMD in the afebrile period.

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2. Patients and methods

2.1. Subjects

Sputum was obtained from all 28 patients with PMD who received tracheostomy (18 males and 10 females; mean age, 21 years old; range, 3–48 years old) after admission to the National Hospital Organization Sanyo Hospital and Tsuzumigaura Child Medical Welfare Center, and from 14 healthy subjects (11 males and 3 females; mean age, 29 years old; range, 22–37 years old) from April 2005 to February 2007 (Table 1). Informed consent was obtained from the parents of patients and from control subjects. The protocol was approved by the Institutional Review Board of Yamaguchi University Hospital (H17-13).

Of the 28 PMD patients with tracheostomy, 15 required mechanical ventilation: 9 were ventilated in volume-control mode, with a positive end-expiratory pressure (PEEP) of 0–4 cm H_2O (mean, 2 cm H_2O) and a tidal volume of 6–12 ml/kg (mean, 8.5 ml/kg), and 6 were ventilated in pressure control mode, with a PEEP of 2–5 cm H_2O (mean, 4.1 cm H_2O), a peak inspiratory pressure (PIP) of 10–20 cm H_2O (mean, 15.8 cm H_2O), and a tidal volume of approximately 4–9 ml/kg (mean, 6.4 ml/kg). The comorbid conditions of the patients included cerebral palsy ($n = 13$), near-drowning ($n = 6$), encephalitis/encephalopathy ($n = 3$), a car accident ($n = 1$), holoprosencephaly ($n = 1$), Lennox–Gastaut syndrome ($n = 1$), near-miss sudden infant death syndrome ($n = 1$), Rett syndrome ($n = 1$), and trisomy 13 ($n = 1$). The causes of cerebral palsy in 13 patients were hypoxic ischemic encephalopathy ($n = 4$), asphyxia at birth ($n = 3$), meconium aspiration syndrome ($n = 1$), hydrops fetalis ($n = 1$), birth trauma ($n = 1$), and unspecified causes ($n = 3$).

The control subjects were 14 healthy volunteers who were non-smokers and did not have acute or chronic respiratory diseases. There was no significant difference in age between the PMD patients and healthy controls by Mann–Whitney U test.

Table 1
Clinical characteristics of PMD patients with tracheostomy and control subjects

	PMD patients with tracheostomy ($n = 28$)	Control subjects ($n = 14$)
Age (mean, range)	21 year, 3–48 year	29 year, 22–37 year
Sex (male:female)	18:10	11:3
Comorbid conditions	Cerebral palsy ($n = 13$) Lennox–Gastaut syndrome ($n = 1$) Near-drowning ($n =$) Encephalitis/encephalopathy ($n = 3$) Car accident ($n = 1$) Holoprosencephaly ($n = 1$) Near-miss sudden infant death syndrome ($n = 1$) Rett syndrome ($n = 1$) Trisomy 13 ($n = 1$)	

2.2. Sputum induction and processing

Sputum samples were obtained from the 28 PMD patients with tracheostomy in the afebrile period, using an endotracheal suction catheter set to which a 10-ml syringe was connected. The catheter was inserted into the lower lung lobe via the tracheal cannula, and sputum samples were aspirated into the syringe manually via the catheter. Sputum samples from the patients were also obtained in the febrile period (within the first 72 h of fever, which was defined as a temperature of $\geqslant 38.0$ °C or 1.0 °C higher than normal body temperature [12]). Coughed up samples were collected from the 14 control subjects. Control subjects did not cough up sputum spontaneously all day, but were able to cough up a sufficient amount after getting up in the morning. After collection, sputum samples were immediately placed on ice. They were treated with 0.2% bromhexine hydrochloride (Bisolvon; Boehringer Ingelheim, Tokyo, Japan) at a ratio of 1:4 (w/v) to homogenize the samples, briefly vortexed, rocked for 15 min at room temperature, and centrifuged at 1500 rpm for 5 min. The supernatants were stored frozen at −80 °C until the assay was performed.

2.3. Collection of serum samples

Serum CRP levels (normal: $\leqslant 0.30$ mg/dl) were measured in the 28 patients with PMD in the afebrile period.

2.4. Determination of cytokine levels in sputum

The concentrations of TNF-α, IL-1β, IL-6, IL-8, IL-10, and IL-12p70 were measured with a cytometric bead array (CBA) kit (BD PharMingen, San Diego, CA) according to the manufacturer's instructions and as described previously [13–16]. Data analysis was performed using Prism (GraphPad Software, San Diego, CA). Briefly, a CBA comprises a series of beads exhibiting discrete fluorescence intensities at 670 nm. Each series of beads is coated with a monoclonal antibody against a single cytokine, and a mixture of six series of beads can detect six cytokines in one sample. A secondary phycoerythrin-conjugated monoclonal antibody is used to stain the beads proportionally to the amount of bound cytokine. After fluorescence intensity calibration and electronic color compensation procedures, standard and test samples were analyzed with a FACScan flow cytometer equipped with CellQuest software (BD PharMingen). Data were transferred to GraphPad Prism for transformation and analysis. Starting with standard dilutions, the software performed log transformation of the data and then fitted a curve to 10 discrete points using a four-parameter logistic model. A calibration curve generated for each cytokine was used to determine the cytokine concentrations in the samples. The lower detection limits for TNF-α, IL-1β, IL-6, IL-8, IL-10, and IL-12p70 were 2.8 pg/ml, 7.2 pg/ml, 2.5 pg/ml, 3.6 pg/ml, 2.8 pg/ml, and 1.9 pg/ml, respectively.

2.5. Statistical analysis

All data were log transformed to obtain an approximately normal distribution. Differences in the results between groups were analyzed by T test, and those with $p < 0.05$ were considered significant. Correlations were analyzed using Pearson's correlation coefficient. All values are shown as geometric means, and all calculations were performed using SPSS 12.0 (SPSS, Inc., Chicago, IL, USA).

Table 2
Cytokine levels in sputum of PMD patients with tracheostomy in the afebrile period, and levels in controls

Cytokine (pg/ml)	PMD patients with tracheostomy ($n = 28$)	Controls ($n = 14$)
TNF-α	4.7 (<2.8–125)	2.6 (<2.8–65.2)
IL-1β	1017 (103–21,316)***	31.3 (<7.2–243)
IL-6	164 (20–1016)***	9.0 (<2.5–476)
IL-8	10,658 (754–50,108)***	384 (<3.6–8076)
IL-10	2.7 (<2.8–77.6)	2.9 (<2.8–40.1)
IL-12p70	2.9 (<1.9–271)	3.1 (<1.9–175)

Results are expressed as geometric means (and ranges).
*** $p < 0.001$ vs. controls.

3. Results

Cytokine levels in sputum of PMD patients and controls are shown in Table 2. The concentrations of IL-1β, IL-6, and IL-8 in PMD patients with tracheostomy were significantly higher than those in controls (all $p < 0.001$) (Fig. 1). The concentrations of IL-1β were correlated with those of IL-8 in sputum of the patients ($p < 0.001$) (Fig. 2), but IL-6 levels did not correlate with IL-1β or IL-8 levels. There were no significant differences in the concentrations of TNF-α, IL-10, and IL-12p70 between the patients and controls, and there were no significant differences in cytokine levels between PMD patients with and without mechanical ventilation (data not shown).

Eight PMD patients with tracheostomy had fever during the study period: seven were diagnosed with respiratory infection based on clinical manifestations, and one with respiratory infection based on clinical manifestations and chest computed tomography. The concentrations of IL-6 and IL-8 in the eight patients in the febrile period were significantly higher than those in the afebrile period ($p < 0.01$ and $p < 0.05$, respectively), but there was no significant difference in IL-1β levels between the febrile and afebrile periods (Fig. 3).

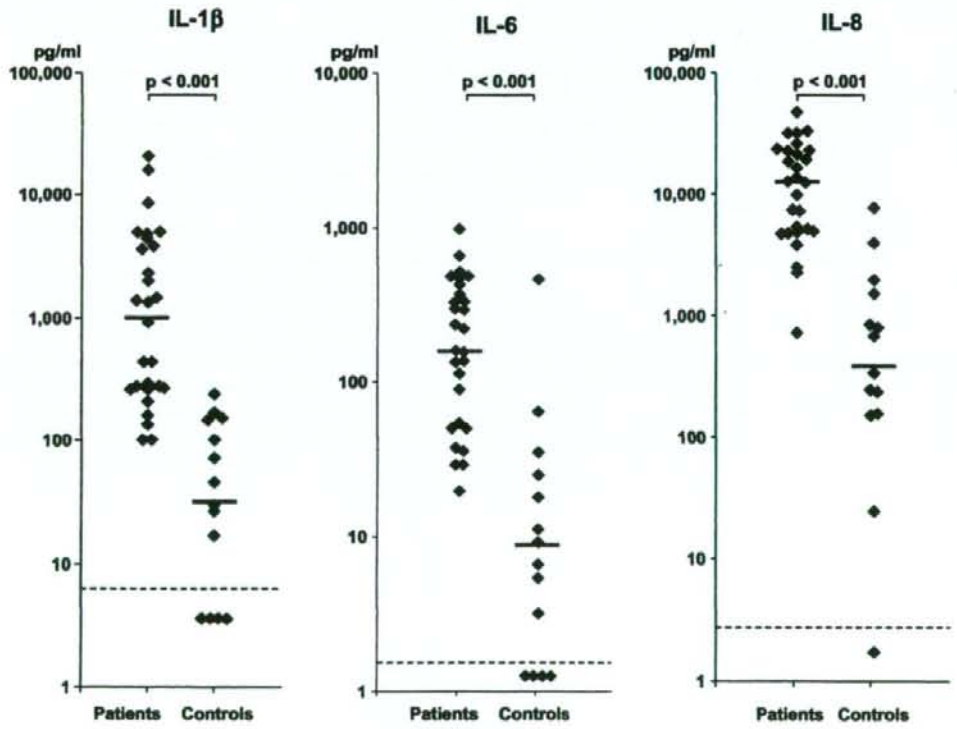

Fig. 1. Concentrations of IL-1β, IL-6, and IL-8 in sputum of PMD patients with tracheostomy in the afebrile period, and levels in controls. Horizontal lines indicate geometric means. Dotted lines indicate lower detection limits.

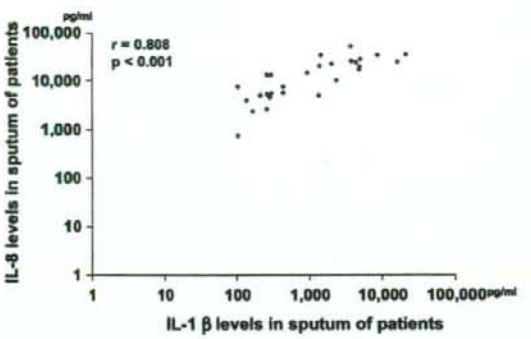

Fig. 2. Relationship between IL-1β and IL-8 levels in sputum of PMD patients with tracheostomy. *r*, Pearson's coefficient.

Serum CRP levels were elevated in 12 of the 28 patients (43%) with PMD (mean, 1.33 mg/dl; range, 0.37–2.96 mg/dl) in the afebrile period. Serum CRP levels showed no correlation with IL-1β, IL-6 or IL-8, and there were no significant differences in IL-1β, IL-6 or IL-8 levels between patients with normal ($n = 16$) and elevated ($n = 12$) serum CRP (Fig. 4).

4. Discussion

Our results show that the concentrations of IL-1β, IL-6, and IL-8 in sputum of PMD patients with tracheostomy were significantly higher than the respective levels in controls, and that IL-1β levels were correlated with IL-8 levels. Mechanical ventilation did not affect the cytokine levels in sputum of patients. IL-1β is a proinflammatory cytokine that is produced mainly by monocytes and macrophages at sites of local inflammation [5,6]. IL-8 is a chemoattractant for neutrophils and is produced by various cells, including monocytes, T lymphocytes, neutrophils, fibroblasts, endothelial cells and epithelial cells [8], and IL-8 in bronchoalveolar lavage fluid has been proposed as a marker for intense airway inflammation [17–19]. IL-1β, IL-6, and IL-8 were all produced at higher levels in PMD patients with tracheostomy, suggesting that such patients have chronic airway inflammation, and IL-6 and IL-8 levels in sputum of patients with respiratory infections were significantly higher in the febrile period than in the afebrile period. Serum CRP levels were also slightly elevated in 43% of patients with PMD in the afebrile period, but there were no significant differences in IL-1β, IL-6 or IL-8 levels between patients with normal and elevated serum CRP. This suggests that the increased IL-1β, IL-6 or IL-8 levels in sputum of PMD patients in the afebrile period were not responsible for infection, since elevated serum CRP often indicates the presence of infection [11].

Patients with PMD may experience stress due to motor paralysis, bed rest, dysmyotonia, and tracheostomy. Immobilization stress induces TNF-α and IL-1β in experimental animal models [20,21], and stress also induces activation of nuclear factor-κB (NF-κB) [22]. NF-κB is a ubiquitous

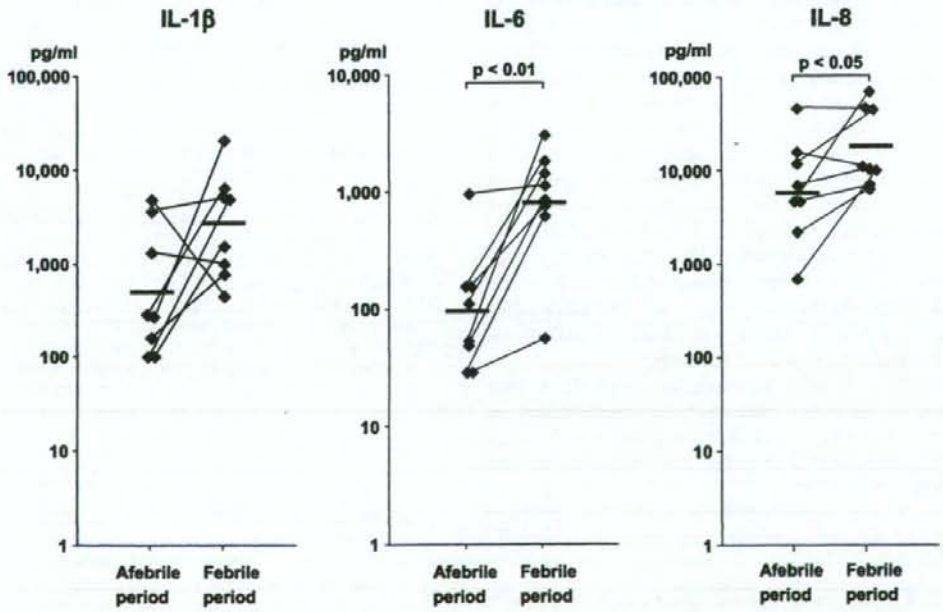

Fig. 3. Concentrations of IL-1β, IL-6, and IL-8 in eight PMD patients with tracheostomy in the febrile and afebrile periods. Horizontal lines indicate geometric means.

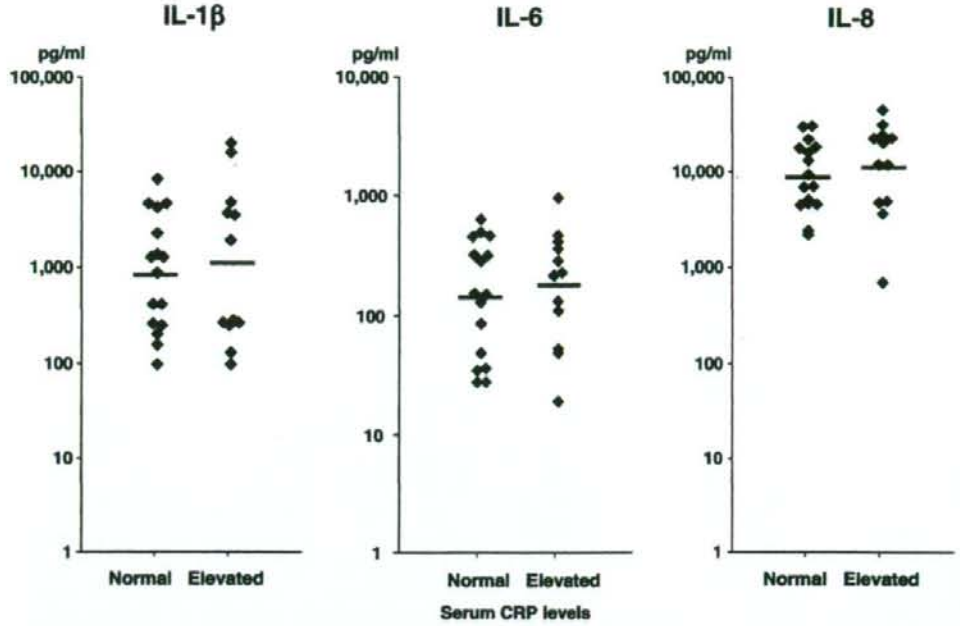

Fig. 4. Concentrations of IL-1β, IL-6, and IL-8 in sputum of PMD patients with normal ($n = 16$) and elevated ($n = 12$) serum CRP levels. Horizontal lines indicate geometric means.

transcription factor for genes that encode proinflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α [23], and our results suggest that stress-induced NF-κB may produce proinflammatory cytokines. We have reported NF-κB activation in several diseases in childhood, including Kawasaki disease; neonatal asphyxia; meningitis; influenza-associated encephalopathy; chronic infantile neurologic, cutaneous, articular syndrome; and sepsis [16,24–28]. Alternatively, since PMD patients with tracheostomy easily aspirate saliva and gastric juice into the lower airway, aspiration may induce production of proinflammatory cytokines in these patients, since acid aspiration has been shown to induce TNF-α and IL-8 in bronchoalveolar lavage fluid in an experimental animal model [29,30]. Physical stimulation by the tracheal cannula and endotracheal suction catheter may also damage airway endothelial cells and induce production of proinflammatory cytokines. Further studies are needed to clarify the mechanism of airway inflammation in PMD patients with tracheostomy.

In conclusion, the concentrations of IL-1β, IL-6, and IL-8 in sputum of PMD patients with tracheostomy in the afebrile period were significantly higher than those of controls, suggesting that these patients have chronic airway inflammation.

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Main Article

Unilateral associated laryngeal paralysis due to varicella-zoster virus: virus antibody testing and videofluoroscopic findings

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Abstract

The relationship between varicella-zoster virus and idiopathic associated laryngeal paralysis was examined in five patients, using complement fixation or enzyme immunoassay testing. In all cases, significant changes in serum levels of varicella-zoster virus antibody were observed. Videofluoroscopy was useful in assessing the severity of the dysphagia and in making an accurate diagnosis; both laryngeal elevation and weakness of pharyngeal wall contraction were also observed. In two cases in which antiviral therapy was delayed, the outcome was poor, with increased levels of varicella-zoster virus immunoglobulin M found on enzyme immunoassay. The outcome of the condition may thus depend both on the speed of antiviral therapy commencement following onset of symptoms, and on the levels of varicella-zoster virus immunoglobulin M antibody (measured by enzyme immunoassay). Our study suggests that varicella-zoster virus should be considered in the differential diagnosis of patients with idiopathic associated laryngeal paralysis, and rapid antiviral therapy should be initiated when necessary.

Key words: Herpes Virus 3, Human; Laryngeal Nerves; Paralysis; Glossopharyngeal Nerve Diseases; Photofluorography

Introduction

Varicella-zoster virus persists, in its latent phase, in the ganglia of the spinal cord and cranial nerves, and its reactivation may cause various types of cranial nerve palsy. Ramsay Hunt syndrome[1] is well known, presenting with facial palsy, with or without auditory or vestibular involvement. Sometimes, it may be followed by glossopharyngeal nerve (IX) and/or vagal nerve (X) palsies.[2–11] However, similar palsies due to varicella-zoster virus, but without facial nerve palsy, have so far been reported only rarely, and the diagnosis in such cases is not always easy to make.[12–16] Generally, varicella-zoster virus mediated IXth and Xth cranial nerve palsies are included in the aetiology of associated laryngeal paralysis. However, if no other abnormalities are observed except for mild dysphagia and vocal fold paralysis, then a correct diagnosis may be overlooked and the condition mistaken for idiopathic recurrent nerve paralysis.

In this study, the relationship between acute, unilateral associated laryngeal paralysis (i.e. cranial nerve IX and/or X palsies) and varicella-zoster virus reactivation was serologically examined, and unilateral associated laryngeal paralysis was evaluated by videofluoroscopy.

Patients and methods

We examined cases of patients with acute associated laryngeal paralysis, but without any organic or abnormal findings on head and neck imaging, who were treated at our otolaryngology clinic from 2002 to 2004. Among the 15 cases demonstrating unilateral associated laryngeal paralysis, five cases with a serologically positive response for varicella-zoster virus were identified and analysed.

Each case was examined, and the presence of herpetic eruptions on the skin, pharyngeal mucosa or laryngeal mucosa was identified. An inspection of the lower cranial nerve findings was performed, including assessment of tongue mobility and fasciculation, and the presence of the curtain sign (i.e. a right or left shift in the pharyngeal wall on phonation). Tactile sensation was examined using a cotton swab, and taste sensation was evaluated using a paper filter disc technique. The presence of any abnormal mobility in the sternocleidomastoid and trapezius muscles was also

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tested, and vocal fold paralysis was identified by laryngofibre-optic examination.

Virus antibody assay

Complement fixation and enzyme immunoassay testing were performed, and immunoglobulin (Ig) G and IgM antibody titres for varicella-zoster virus were serially measured.

In addition, complement fixation and enzyme immunoassay testing was also undertaken for herpes simplex virus IgG and IgM, because herpes simplex virus can also produce lower cranial nerve palsies.

In principle, changes in the complement fixation test and IgG and IgM enzyme immunoassay antibody titre results were divided into three stages: an early stage, one week after onset; a late stage, two to three weeks after onset; and a recovery stage, more than four weeks after onset.

The complement fixation test titre was expressed at the largest dilution magnification which showed a positive finding, and a greater than four-fold increase (two tube differences) in the measurements at two different stages was considered to be a significantly positive result.

Enzyme immunoassay measurements were made using a commercially available analyser (Denka Seiken Co., Tokyo, Japan). An IgG value twice the normal level and an IgM value increase of over 0.8 were considered to be significantly positive.

The cerebrospinal fluid (CSF) cell count and protein, glucose and IgG levels were examined only for case one. In this case, varicella-zoster virus deoxyribonucleic acid (DNA) in the CSF was also examined by polymerase chain reaction.

Evaluation of swallowing

Using videofluoroscopy, pharyngeal wall contraction, laryngeal elevation and aspiration were evaluated by means of a 3 ml barium swallow.

Treatment and outcome

Acyclovir (4000 mg/day) and prednisolone (30 mg/day) were administered for 12 days in all cases except for case three, as soon as a herpetic infection was suspected. We clearly recorded the date of the first examination following onset of associated laryngeal paralysis, and the date of antiviral therapy commencement.

The associated laryngeal paralysis was assessed, based on the laryngofibre-optic and videofluoroscopic findings, from the initial hospital visit to six months after presentation. The outcome of each case was evaluated as follows: 'excellent' for cases showing rapid recovery without therapy; 'good' for recovery within several weeks of onset; 'fair' for delayed recovery within six months of onset; and 'poor' for palsy remaining after six months.

Results

Five cases of unilateral associated laryngeal paralysis showing significant results for varicella-zoster virus testing were identified (Table I). Patients' mean age was 61 years (range: 53–72); they comprised four men and one woman. The chief symptom in all cases was either hoarseness or dysphagia.

No case showed skin eruptions (i.e. redness or blisters) in the auricle, external auditory canal or oral cavity, or on the limbs or trunk (either side). However, in case two, diffuse redness with white spots on the palsied side was recognised on the left mucous membrane from the epiglottis to the arytenoids, for one week. In all other cases, no abnormality was observed in the pharyngeal or laryngeal regions.

On examining lower cranial nerve function, all cases showed good tongue mobility without fasciculation. The curtain sign in all cases was positive, but the shift was slight in cases three and four. All cases except for case four showed a reduction in both pharyngeal tactile sensation and taste sensation in the posterior one-third on the palsy side. Bilateral mobility of the sternocleidomastoid and trapezius muscles was good in all cases. All cases demonstrated paramedian fixation of the unilateral vocal fold. As a result, cases one to three and five were determined to have unilateral palsy of the IXth and Xth cranial

TABLE I

CLINICAL CHARACTERISTICS OF FIVE UNILATERAL LARYNGEAL PALSY CASES

Pt no	Age (yrs)/sex	Symptoms	Herpetic eruption	Nerve palsies	Curtain sign	Pharyngeal sensation	Vocal fold fixation
1	53/F	Hoarseness Severe dysphagia	–	L IX, X	+	↓	+
2	72/M	Sore throat Hoarseness Dysphagia	+	L IX, X	+	↓	+
3	61/M	Hoarseness Mild dysphagia	–	L IX, X	±	↓	+
4	64/M	Hoarseness Mild dysphagia	–	R X	±	Normal	+
5	54/M	Sore throat Hoarseness Severe dysphagia	–	L IX, X	+	↓	+

Pt no = patient number; yrs = years; F = female; M = male; L = left; R = right; IX = glossopharyngeal nerve; X = vagal nerve; ± = unremarkable

nerves, while case four demonstrated only palsy of the Xth cranial nerve.

Varicella-zoster virus serology

In case one, the serum complement fixation result for varicella-zoster virus decreased from 1:64 to 1:16, comparing the acute to the recovery stage, and the enzyme immunoassay result for varicella-zoster virus IgG increased from 39.2 to 81.9.

In case two, the serum complement fixation result for varicella-zoster virus decreased from 1:128 to 1:32, and the enzyme immunoassay result for varicella-zoster virus IgG increased from 36.1 to ≥128.

In case three, the serum complement fixation result for varicella-zoster virus also decreased from 1:128 to 1:16, but the enzyme immunoassay result for varicella-zoster virus IgG showed high values of 128 and 101 at both the late acute and the recovery stages, respectively (Figure 1a and 1b).

In the late acute stage in cases four and five, the enzyme immunoassay result for varicella-zoster virus IgM showed high values of 1.35 and 2.76, respectively (Figure 1c). In all cases positive for varicella-zoster virus infection, a significant change in complement fixation result and enzyme immunoassay IgG result, or the presence of IgM on enzyme immunoassay, were found. In all cases, enzyme immunoassay for herpes simplex virus IgG was positive. However, no significant increases were observed. These responses seemed to indicate a cross-reaction for varicella-zoster virus, and enzyme immunoassay for herpes simplex virus IgM was negative in all cases.

In case one, CSF analysis revealed: 24 cells per mm^3 (normal finding: less than five cells); protein 41 mg/dl; glucose 70 mg/dl; and IgG 4.4 mg/dl. In addition, varicella-zoster virus DNA was not detected in the CSF, using polymerase chain reaction.

Videofluoroscopic findings

Videofluoroscopy findings are shown in Table II. In all cases, no abnormality of the oral preparatory and oral propulsive phases was found, and the tongue was pushed backwards and downwards into the pharynx.

Cases one and five showed absence of the normal pharyngeal wall contraction on the palsy side and delayed laryngeal elevation of a half vertebra width during swallowing. As a result, not all 3 ml of the barium passed through the oesophagus aditus but instead remained in the bilateral piriform sinus, and some of the barium was thus aspirated.

In case two, weak pharyngeal wall contraction and delayed laryngeal elevation caused aspiration during swallowing. Such aspiration was observed during laryngeal descent (Figure 2).

Cases three and four demonstrated weakness of unilateral pharyngeal wall contraction during swallowing (Figure 3), and a small amount of barium remained in the piriform sinus on the paralysed side after swallowing.

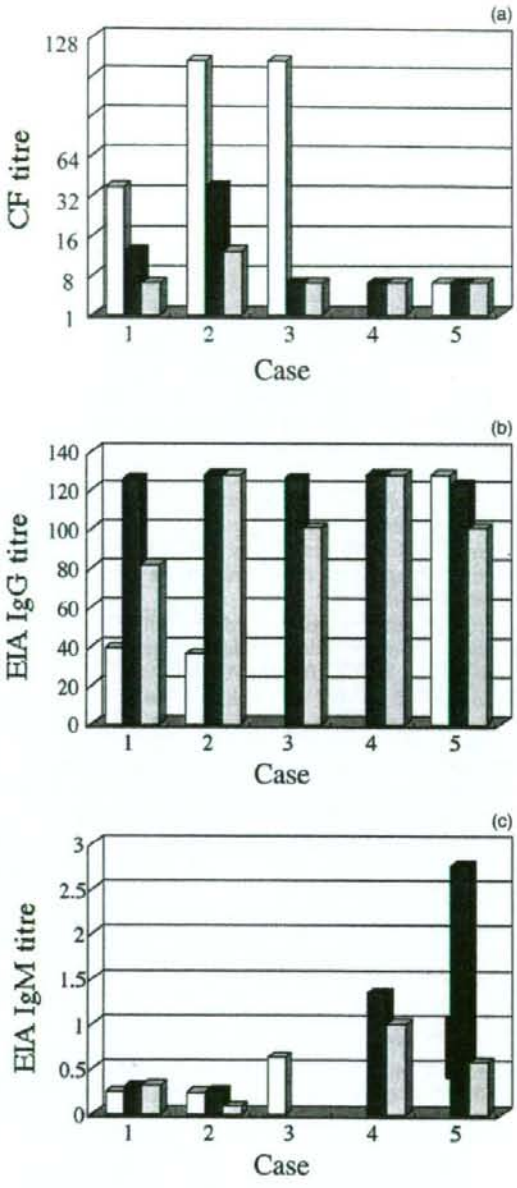

FIG. 1

Changes in varicella-zoster virus serology results. White bar = early acute stage (<1 week after onset); dark grey bar = late acute stage (<2–3 weeks after onset); light grey bar = recovery stage (>4 weeks after onset). (a) Varicella-zoster virus complement fixation (CF) test (cases 1, 2 and 3 show significant decreases over time, comparing the acute and recovery stages); (b) enzyme immunoassay varicella-zoster virus immunoglobulin (Ig) G test (cases 1 and 2 show significant increases over time); (c) enzyme immunoassay varicella-zoster virus IgM test (cases 4 and 5 show high values in the late acute stage, of 1.35 and 2.76, respectively).

Outcomes

For each case except for case three, antiviral therapy was administered. In cases one to five, following onset of unilateral associated laryngeal paralysis,

examination occurred after: one day, three days, one week, two weeks, and two weeks, respectively. Following onset, antiviral therapy was commenced in cases one, two, four and five after: seven days, 10 days, three weeks and four weeks, respectively. In case five, antiviral therapy was delayed due to initial suspicion of a brainstem infarction.

In case one, vocal fold paralysis resolved following rapid recovery of pharyngeal swallowing over a four-week period; the outcome was thus judged to be good. Case two showed an improvement in vocal fold paralysis symptoms over an eight-week period, following rapid recovery from aspiration; this outcome was thus also classified as good. In case three, vocal fold paralysis (comprising weak pharyngeal wall contraction) rapidly recovered over a three-week period before varicella-zoster virus was diagnosed, and thus the outcome was considered to be excellent. In case four, weak pharyngeal wall contraction gradually recovered, but vocal fold paralysis persisted for longer than six months; this outcome was thus classified as poor. In case five, vocal fold paralysis recovered, following rapid recovery of pharyngeal swallowing, over a six-month period; the outcome was thus judged to be fair.

Discussion

Our study analysed five cases of associated laryngeal paralysis due to varicella-zoster virus. Associated laryngeal paralysis is noted to involve various combinations of palsy of the IXth and Xth cranial nerves, and also other types of palsy of the lower cranial nerves. However, our five cases showed unilateral palsy of the IXth and Xth cranial nerves. In our first, second and fifth cases, either a brainstem infarction or Guillain–Barre syndrome was initially suspected. Serological analysis indicated a varicella-zoster virus infection, and dysphagia was evaluated by either laryngeal fibrescope or videofluoroscopy.

To our knowledge, unilateral palsy of the IXth and Xth cranial nerves due to varicella-zoster virus has only been reported in a few cases.[12–16] Engström and Wohlfart[11] have reported two cases of unilateral palsy in the IXth and Xth cranial nerves, together with Ramsay Hunt syndrome. Since then, several cases of associated laryngeal paralysis due to varicella-zoster virus, with or without Ramsay Hunt syndrome, have been reported by other authors.

In Ramsay Hunt syndrome, palsy of the VIIIth cranial nerve is often accompanied by spread of inflammation due to varicella-zoster virus reactivated in the geniculate ganglia,[9,12] as well as in the cochlea or vestibular ganglia.[2] Since, anatomically, the geniculate ganglia lies far from the IXth and Xth cranial nerves, our cases of varicella-zoster virus induced IXth and Xth cranial nerve palsy are thought to have been caused by the vagal varicella-zoster virus focus of the IXth and Xth cranial nerves, rather than by a geniculate focus, as in Ramsay Hunt syndrome. In addition, cranial magnetic resonance imaging revealed gadolinium enhancement of the jugular foramen[17] or the IXth and Xth ganglia.[18] On the other hand, Parker[19] reported that bilateral cranial nerve palsy due to varicella-zoster virus sometimes occurs. He considered such palsy might be caused by local meningitis, being followed by infection of the nerve root or more extensive neural involvement.

Five cases of IXth and Xth cranial nerve palsy due to varicella-zoster virus have been reported to involve pharyngolaryngeal herpetic eruptions.[12–14,16] In case two of our series, since the region of white spots was considered to be related to the dominant region of the internal branch of the superior laryngeal nerve, such lesions would seem to represent herpetic eruptions. Aitken and Brain[20] have reported Ramsay Hunt syndrome without any herpetic eruptions. Muroi *et al.*[21] have reported that herpetic eruptions in the pharyngolarynx disappear quickly, compared with those occurring on the skin. This would indicate that, in case 1, 3, 4, 5 without herpetic eruptions of Table 1, such lesions could not have appeared from the onset, or they might have already disappeared before the first examination. It therefore seems difficult to diagnose reactivation of varicella-zoster virus and to identify resultant cases of cranial nerve palsy, in the absence of active eruptions.

The significant changes in the serum complement fixation test and enzyme immunoassay IgG test for varicella-zoster virus in cases one, two and three, and the high value of the enzyme immunoassay result for varicella-zoster virus IgM in cases four and five, led us to diagnose a varicella-zoster virus infection. Aizawa *et al.*[22] reported variable patterns of varicella-zoster virus antibody in patients with Ramsay Hunt syndrome. In one case, the varicella-zoster virus antibody level was increased at the initial hospital visit. In a case of paralysis, the

TABLE II

VIDEOFLUOROSCOPIC FINDINGS AND OUTCOME IN FIVE UNILATERAL LARYNGEAL PALSY CASES

Pt no	Videofluoroscopic findings			1st examination*	Therapy begun*	Outcome (palsy duration)
	Contraction	Elevation	Aspiration			
1	Absent	Half	+	1 day	7 days	Good (4 wks)
2	Weak	Delayed	+	3 days	10 days	Good (8 wks)
3	Weak	Normal	−	1 wk	No therapy	Excellent (3 wks)
4	Weak	Normal	−	2 wks	3 wks	Poor (>6 mths)
5	Absent	Half	+	2 wks	4 wks	Fair (6 mths)

*Time delay from onset of laryngeal palsy. Pt no = patient number; contraction = pharyngeal wall contraction on palsy side; elevation = laryngeal elevation; half = laryngeal elevation of a half vertebra width; wk = week; mth = month

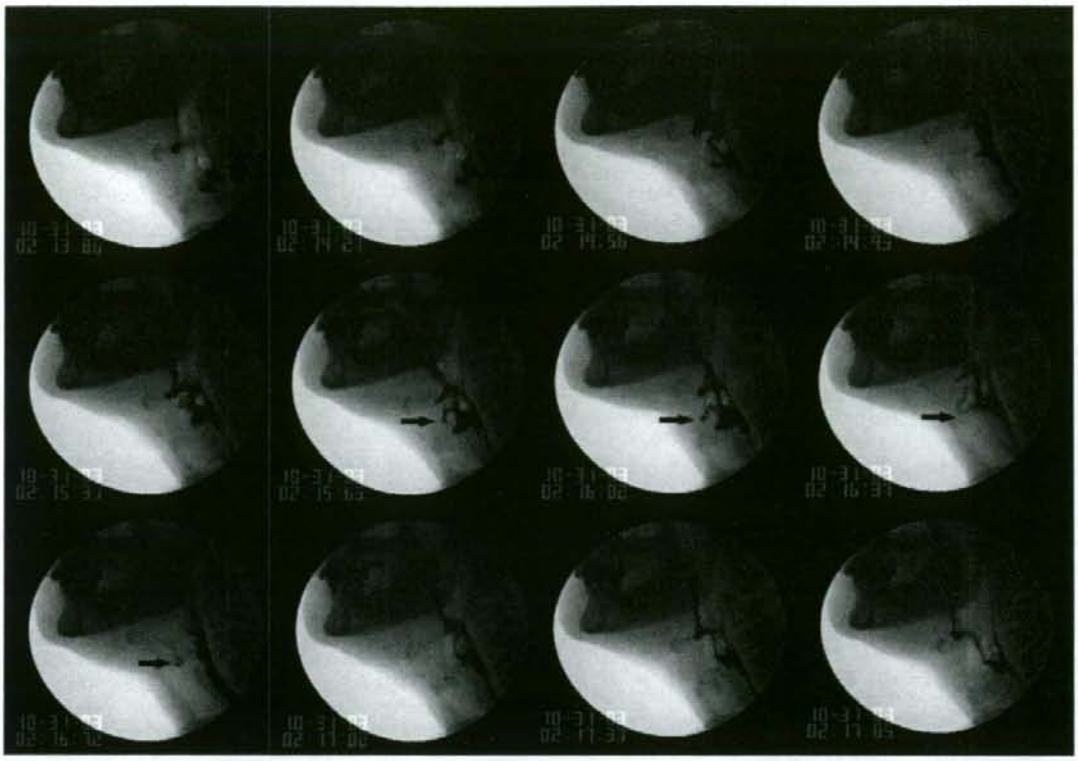

FIG. 2
Videofluoroscopy, lateral views, for case 2. Aspiration (arrow) is observed during laryngeal downward movement on the swallowing.

varicella-zoster virus antibody level at the onset of paralysis was low, but had increased by the time the paired serum was tested. Our cases one, two and three showed the former pattern, while cases four and five showed the latter pattern.

- **This was a study of varicella-zoster infection in patients presenting with glossopharyngeal and vagal palsies**
- **The authors present the pathological and clinical presentations, and argue for the use of antiviral therapy in such cases**

Based on the results from the serum complement fixation test and the enzyme immunoassay varicella-zoster virus IgG test, the laryngeal paralysis in cases one, two and three was diagnosed as being of varicella-zoster virus origin. These results indicate the necessity of serial serological testing in patients with idiopathic vocal fold paralysis. The high IgM values in cases four and five may suggest an increased varicella-zoster viral load. In addition, a serological response indicating no antibody titre fluctuation due to varicella-zoster virus reactivation can occur, as seen in our case three. It therefore appears important to evaluate the presence of varicella-zoster virus DNA, by polymerase chain reaction,[23–25] in saliva, blisters, CSF etc, before making a diagnosis.

In order to more precisely evaluate a palsy of the IXth and Xth cranial nerves, we employed videofluoroscopy[26] and examined pharyngeal wall contraction, laryngeal elevation and aspiration. Cases three and four seemed to show only unilateral recurrent laryngeal nerve paralysis, judging from an unremarkable curtain sign. However, videofluoroscopy demonstrated the existence of Xth cranial nerve palsy, based on the finding of weak unilateral pharyngeal wall contraction. In cases one, two and five, vocal fold mobility recovered more slowly than pharyngeal wall contraction and laryngeal elevation, while cases three and four showed no remarkable findings except for vocal fold paralysis. The recurrent nerve is thus considered to be the most vulnerable of all the pharyngolaryngeal branches of the Xth cranial nerve, because the recurrent laryngeal nerve travels a long distance from the Xth cranial nerve ganglion to the pharyngolaryngeal region.

Although the duration of laryngeal palsy in cases four and five was longer than that in the other

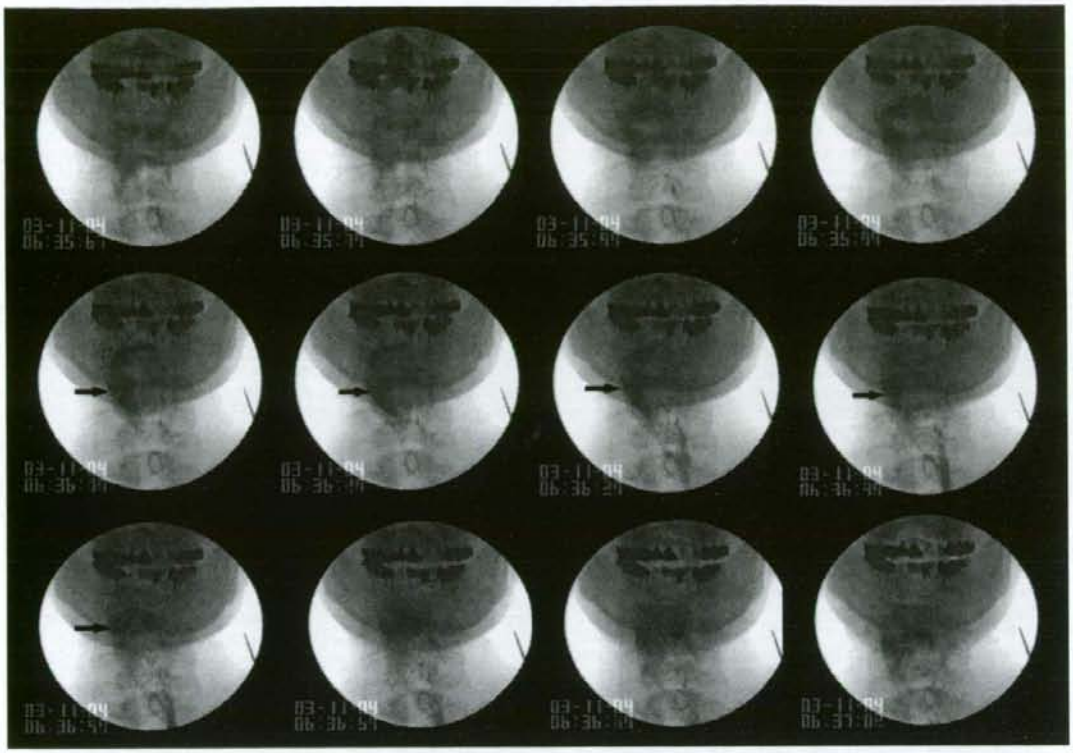

FIG. 3

Videofluoroscopy, anteroposterior views, for case 4. Weak pharyngeal wall contraction is observed for the right lateral wall (black arrow indicates right lateral wall).

cases, the primary symptoms in these cases were less severe than those of other cases, and the degree of the palsy was conversely milder (based on objective evaluation). In addition, in cases four and five, the period from onset of illness to start of therapy was longer than that of other cases, and the serum enzyme immunoassay varicella-zoster virus IgM titres on the first examination were higher than standard values. Therefore, the outcome of associated laryngeal paralysis may depend on both the timing of antiviral therapy commencement, and the enzyme immunoassay varicella-zoster virus IgM antibody level.

Conclusion

In cases of varicella-zoster virus cranial palsy in the earlier stages, it is necessary to suppress the spread of varicella-zoster virus and also to reduce the vicious cycle of oedema, constriction and ischaemia, by administering antiviral therapy and steroids.[27,28] Associated laryngeal paralysis may be due to various aetiologies, including demyelinating disorders, vascular disease and viral infection. An accurate diagnosis of varicella-zoster virus palsy may sometimes be missed due to the absence of skin eruptions, or to a stroke-like onset. When patients show unilateral palsy of the IXth and Xth cranial nerves with associated laryngeal paralysis, varicella-zoster virus should be considered in the differential diagnosis. Moreover, our study indicates that varicella-zoster virus serological tests and videofluoroscopy are useful, both in making an accurate diagnosis and in elucidating the pathophysiology of associated laryngeal paralysis due to varicella-zoster virus.

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FULL-LENGTH ORIGINAL RESEARCH

Electroclinical features of epilepsy in patients with juvenile type dentatorubral-pallidoluysian atrophy

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SUMMARY

Purpose: To clarify the electroclinical characteristics of epileptic seizures in patients with juvenile type dentatorubral-pallidoluysian atrophy (DRPLA).

Methods: Seventeen patients with juvenile type DRPLA confirmed by genetic analysis were studied retrospectively. The clinical records of all 17 patients and the ictal video electroencephalography (EEG) recordings from 12 of the 17 patients were reviewed.

Results: Electroclinical studies in 12 patients identified 11 habitual seizures in 6 patients as partial seizures on ictal video EEG recordings. Clinical manifestations composed mainly of versions of the head and loss of consciousness. These partial seizures were persistently recorded throughout the clinical course. Brief generalized seizures (atypical absence and myoclonic seizure) were observed in 6 of 12 patients at the early stage. In contrast, generalized tonic–clonic seizures (GTCS) were recorded in four advanced stage patients who were almost bedridden. Semiological studies in 17 patients showed that the prevalence of partial seizures was significantly higher in patients with younger epilepsy onset (below 10 years of age; χ^2 test, $p < 0.05$) and that the age of epilepsy onset was significantly lower in patients with partial seizures than in those without partial seizures (Mann-Whitney U test, $p = 0.02$). However, the number of CAG repeats and age at clinical onset were not significantly different between two groups.

Discussion: Partial seizure is one of the common epileptic features in juvenile type DRPLA, especially in patients with younger epilepsy onset. Seizure types may be affected in an age-dependent manner and change evolutionally during progression of the clinical stage.

KEY WORDS: Seizure, Progressive myoclonus epilepsy, Semiology, DRPLA.

Dentatorubral-pallidoluysian atrophy (DRPLA) is an autosomal dominant neurodegenerative disorder (Naito & Oyanagi, 1982) caused by expansion of CAG repeat in the DRPLA gene on chromosome 12p (Koide et al., 1994; Nagafuchi et al., 1994). Clinical phenotype varies depending on the degree of unstable expansion of the CAG repeat (Ikeuchi et al., 1995; Komure et al., 1995). Patients with more extensive expansion have earlier onset and present symptoms of progressive myoclonus epilepsies (PME) consisting of epileptic seizures, prominent myoclonus, and progressive mental retardation (PME phenotype). In contrast, patients with smaller expansion have later onset and their main manifestations are ataxia, choreoathetosis, and dementia (non-PME phenotype). Epilepsy may also exist but is much milder than that of the PME phenotype. Naito & Oyanagi (1982) defined such PME phenotype with onset before 20 years of age as "juvenile type" DRPLA. Juvenile type DRPLA usually becomes apparent at an earlier age in successive generations of the same pedigree (anticipation) (Ikeuchi et al., 1995; Komure et al., 1995).

DRPLA is most prevalent in Japan (Nagafuchi et al., 1994), but an increasing number of cases have been reported from other countries with the development of

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molecular methods for diagnosis (Munoz et al., 1999; Licht & Lynch, 2002; Brunetti-Pierri et al., 2006). However, the precise electroclinical features of epilepsy in juvenile DRPLA remain unclear. Only a few case reports evaluated epilepsy in patients with juvenile type DRPLA, and these reports analyzed the seizures usually based on clinical records without ictal electroencephalography (EEG) evaluation. Correct diagnosis of epileptic seizure types is essential to improve the outcome of epileptic seizures. To elucidate the characteristics of epilepsy in juvenile DRPLA, we evaluated the ictal video EEG recordings in 12 patients with juvenile DRPLA and studied the seizure semiology in 17 patients by conducting detailed interview.

METHODS

The clinical records of 17 patients from 14 families (including three pairs of siblings) with genetically confirmed juvenile type DRPLA were reviewed retrospectively. Their clinical profiles are shown in Table 1. Three patients (patients 3, 8, and 10) were already diagnosed of DRPLA by DNA analysis before referral. The remaining patients were diagnosed of DRPLA during follow-up in our hospital by DNA analysis conducted after obtaining informed consent from their parents. Criteria for considering DNA analysis were: (1) the presence of clinical symptoms of PMEs including epilepsy, myoclonus, movement disorder, and developmental delay and (2) no findings indicative of other types of PME. Extending screening to family members of the probands differed from case to case for various reasons. Many families did not agree to the analysis of family members who showed no apparent symptoms, and in several families, the fathers were either dead or unavailable due to divorce. As a result, parental diagnosis was limited to only two families in our hospital. Both familial cases showed paternal transmission, and the fathers did not suffer from epilepsy. No siblings were newly diagnosed with the disease following DNA analysis.

Subjects comprised nine female and eight male patients. All patients were referred to our hospital between 1979 and 2006 because of refractory seizures. The ages at referral ranged from 7 to 28 years (mean, 15.0 years), and follow-up duration ranged from 0.3 to 28 years (mean, 6.8 years). Most of them had no remarkable clinical histories except patient 1 (asphyxia at birth without any subsequent complication) and patient 2 (simple febrile seizure). Brain magnetic resonance imaging (MRI) was conducted at our hospital, and no focal cortical lesion was found in any of the patients.

The clinical profile and seizure semiology of each patient were assessed from interviews with the parents conducted at our outpatient clinic by experienced epileptologists. All patients were evaluated by routine EEG with simultaneous video recording in the outpatient clinic using the standard international 10-20 system during awake and sleep, including activation by intermittent photic stimulation (IPS) with Grass PS22 or PS33 photic stimulator at a flash frequency of 18 Hz. Photoparoxysmal response (PPR) was defined as positive when the response consisted of bilateral diffuse (poly)spikes and slow wave complexes (classical type PPR) (Kasteleijn-Nolst, 1989). Long-term video EEG monitoring (more than 24 h) using the

Table 1. Clinical profiles analyzed from interviews

Patient No.	Sex	Epilepsy onset (year)	Clinical onset (year)	Initial symptom	No. of CAG repeats	Past history	Family history obtained at referral
1	M	4	4	Seizure	65	Asphyxia	Sibling of patient 16
2	M	5	4	Intellectual impairment	76	Simple Fc	n.r.
3	F	6	3	Intellectual impairment	75	n.r.	Grandmother: dementia
4	F	6	2	Intellectual impairment	71	n.r.	n.r.
5	M	6	3	Intellectual impairment	76	n.r.	n.r.
6	M	6	5	Intellectual impairment	69	n.r.	n.r.
7	F	6	6	Seizure	70	n.r.	Sibling of patient 10
8	F	7	5	Intellectual impairment	68	n.r.	n.r.
9	M	8	5	Intellectual impairment	71	n.r.	Sibling of patient 11 Grandmother: dementia
10	F	8	6	Intellectual impairment	70	n.r.	Sibling of patient 7
11	M	9	4	Intellectual impairment	73	n.r.	Sibling of patient 9 Grandmother: dementia
12	M	10	10	Seizure	64	n.r.	n.r.
13	F	11	7	Intellectual impairment	71	n.r.	Aunt: movement disorder
14	M	12	12	Seizure	68	n.r.	Grandfather: movement disorder
15	F	13	9	Intellectual impairment	69	n.r.	n.r.
16	F	18	18	Seizure	67	n.r.	Sibling of patient 1
17	M	18	18	Seizure	65	n.r.	n.r.

No., number; M, male; F, female; n.r., not remarkable; Fc, febrile convulsion.

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international 10-20 system was performed in all except patients 8, 14, and 17. Both routine and long-term EEG recordings were checked by epileptologists in charge of the patients, and video EEG recordings of seizures were stored in the database in our hospital. The authors reviewed the stored video EEG recordings carefully and classified them in line with the International League Against Epilepsy (ILAE) seizure classification (The Commission on Classification and Terminology of the International League Against Epilepsy, 1981).

From the clinical profiles, we evaluated two kinds of onset age in each patient (clinical onset age and epilepsy onset age). The former was the age at which parents noticed initial symptoms related to juvenile type DRPLA, such as mental deficit, learning impairment, or seizures, and the latter was the age of occurrence of the first habitual seizure. To analyze the difference in seizure semiology depending on age at epilepsy onset, patients were divided into two groups: younger epilepsy onset (below 10 years; $n = 11$) and older epilepsy onset (10 years or above; $n = 6$). Statistical analyses were conducted using Spearman's rank correlation test, chi-square (χ^2) test, or Mann–Whitney U test. The level of significance in evaluations was set at $p < 0.05$ in all analyses. All values in the text are presented as mean ± standard deviations (minimum to maximum).

Results

Onset age and CAG repeats

The initial symptom at clinical onset was an epileptic seizure in six patients (35%) and intellectual deficit, such as mental deterioration or learning impairment, in 11 patients (65%). Mean age of clinical onset was 7.1 ± 4.8 (2–18) years and that of epilepsy onset was 9.1 ± 4.1 (4–18) years. Mean number of expanded CAG repeats was 69.9 ± 3.7 (64–76). The correlation between the numbers of CAG repeats and age of clinical or epilepsy onset is shown in Fig. 1. There was a tendency of inverse correlation between the number of CAG repeats and ages at both epilepsy and clinical onset. The number of CAG repeats showed a stronger correlation with age at clinical onset (Spearman's rank correlation test: $n = 17$, $r = -0.691$, $p < 0.002$) than with age at epilepsy onset ($n = 17$, $r = -0.427$, $p = 0.085$). Patients with less CAG repeats tended to have epileptic seizures as the initial symptom, whereas patients with more CAG repeats usually manifested intellectual deficit as the initial symptom. In the latter, epilepsy occurred after several years from the initial symptoms.

Characteristics of epileptic seizures evaluated by ictal video EEG recordings

A total of 33 ictal video EEG recordings were obtained from 12 of 17 patients. The detailed clinical manifestations, EEG findings, and seizure classification of each epileptic seizure are shown in Table 2. The documented seizures were classified into three subgroups: brief generalized seizures (atypical absence, myoclonic seizure), partial seizures, and generalized tonic–clonic seizures (GTCS).

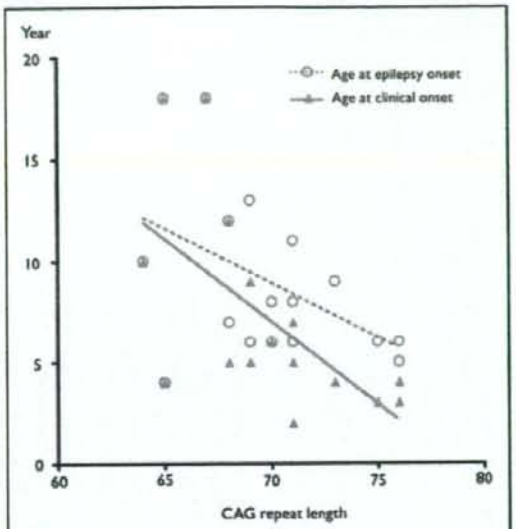

Figure 1.
Correlations between CAG repeat length and onset ages. Open circles and broken line indicates the correlation between CAG repeat length and age of epilepsy onset. Closed triangles and solid line indicates the correlation between the length and age of clinical onset. A significant negative correlation was observed between the repeat length and age of clinical onset.
Epilepsia © ILAE

Brief generalized seizures

Six of 12 patients (50%) had brief generalized seizures. Atypical absence was confirmed in 5 of 12 patients, myoclonic seizure in 4 of 12, and their variants accompanied by atonic component in 1 of 12.

Partial seizures

Eleven partial seizures were identified in 6 of 12 patients. The common initial ictal symptom was version of the head and eyes (sometimes accompanied by version of the body). Six partial seizures in four patients culminated in GTCS (partial seizure evolved to GTC; pGTC) and two seizures in patient 4 showed persistent impairment of consciousness (complex partial seizure; CPS). Two of 11 partial seizures showed tonic posturing (in patient 11), and one seizure included automatism (in patient 7), and these three seizures occurred during sleep. Five seizures were