Varicella-Zoster Virus Reactivation Is an Important Cause of Acute Peripheral Facial Paralysis in Children

Yasushi Furuta, MD, Fumio Ohtani, MD,* Hiroshi Aizawa, MD,* Satoshi Fukuda, MD,* Hiroki Kawabata, PhD,† and Tomas Bergström, MD‡*

Background: Reactivation of herpes simplex virus type 1 is thought to be a major cause of adult idiopathic peripheral facial paralysis or Bell's palsy. However, few studies have examined the pathogenesis of this condition in children. Serologic assays and polymerase chain reaction (PCR) analysis of paired sera and saliva samples were used here to investigate the causes of acute peripheral facial paralysis in pediatric patients.

Methods: A total of 30 children with acute peripheral facial paralysis were recruited. Paired sera were assayed for evidence of herpesvirus, mumps virus or *Borrelia* infection. PCR was used to detect herpes simplex virus type 1 and varicella-zoster virus (VZV) DNA in saliva samples.

Results: Ramsay Hunt syndrome with accompanying zoster lesions was diagnosed clinically in 2 patients, and VZV reactivation was confirmed serologically. VZV reactivation in the absence of zoster (zoster sine herpete) was diagnosed in 9 patients with either serologic assays or PCR. Thus VZV reactivation was demonstrated in 11 of 30 (37%) patients. The prevalence of VZV reactivation among patients between 6 and 15 years of age was significantly higher than in those younger than 5 years of age (53% versus 9%, $P = 0.023$).

Conclusions: Our data indicate that VZV reactivation is an important cause of acute peripheral facial paralysis in children, especially those between 6 and 15 years of age.

Key Words: acute peripheral facial paralysis, Bell's palsy, Ramsay Hunt syndrome, varicella-zoster virus, zoster sine herpete

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Peripheral facial paralysis in children can be caused by a range of disorders, including congenital anomaly, trauma, otitis media, Lyme borreliosis and neoplastic lesions of the temporal bone or parotid gland. Viral infections might also be associated with facial paralysis. For example, reactivation of varicella-zoster virus (VZV) causes Ramsay Hunt syndrome with characteristic acute peripheral facial paralysis, accompanied by zoster around the auricle or in the oropharynx, and dysfunction of the eighth cranial nerve. Herpes simplex virus type 1 (HSV-1),[1] Epstein-Barr virus (EBV),[2] cytomegalovirus (CMV),[3] human herpesvirus 6 (HHV-6)[4] and mumps virus[5,6] have all been reported to cause acute peripheral facial paralysis in children. However, in the majority of patients with this condition, the cause remains unknown and a diagnosis of "idiopathic" peripheral facial paralysis or Bell's palsy is made. Bell's palsy accounts for 24–61% of all cases of facial paralysis and is the most common form in children.[7] The majority of children with Bell's palsy recover uneventfully; however, in ~4% of patients recovery is incomplete and sequelae occur including synkinesis.[8]

Reactivation of HSV-1 has been reported most frequently and is one of the most likely causes of the condition in adults.[9,10] VZV reactivation can also cause acute peripheral facial paralysis in the absence of zoster, which is a condition termed zoster sine herpete.[2,11] We showed in a previous study that zoster sine herpete is an underlying cause of Bell's palsy in adults.[12] This form of paralysis should be confirmed as VZV-associated by appropriate serologic and/or molecular assays.[13] There have been only a few studies to date where the virologic causes of acute peripheral facial paralysis in children have been analyzed.[7] Hence in the present study we examined paired sera and saliva samples from such patients for herpesviruses and mumps virus infections as well as *Borrelia* infection.

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From the *Department of Otolaryngology-Head and Neck Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan; the †Department of Bacteriology, National Institute of Infectious Diseases, Tokyo, Japan; and the ‡Department of Clinical Virology, Göteborg University, Göteborg, Sweden

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Address for reprints: Dr Yasushi Furuta, Department of Otolaryngology-Head and Neck Surgery, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7, Kita-Ku, Sapporo 060-8638, Japan. Fax 81-11-717-7566; E-mail yfuruta@med.hokudai.ac.jp.

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PATIENTS AND METHODS

Patients. The study included 30 pediatric patients younger than 15 years of age who visited the Hokkaido University Hospital, Japan, or its associated hospitals between September 1996 and January 2003. All were recruited within 10 days of the onset of acute peripheral facial paralysis. Paired sera were taken from the patients at their initial visit and 2 to 3 weeks later (convalescent phase). Between 1 and 5 saliva samples were collected from each of 23 patients when they attended the hospital. Two children showed recurrent facial paralysis. One child had recurrent paralysis of the left side, and paired sera were drawn during the first episode. Another child had 3 episodes of paralysis, alternating on the right and left sides and then recurring on the left. Paired sera were drawn on the second and third episodes. Informed consent was obtained from the children's parents by the format approved by the Institutional Review Board. Pediatric patients with congenital paralysis (n = 4), otitis media (n = 2) and those from whom paired sera were not obtained (n = 15) were excluded from the study.

Serologic Analysis. Anti-HSV type-common and anti-VZV antibody titers were measured with enzyme-linked immunosorbent assay (ELISA) kits (Enzygnost Anti-HSV/IgG and IgM, anti-VZV/IgG and IgM; Dade Behring Marburg, Marburg, Germany) and an automatic ELISA processor (Processor III; Dade Behring Marburg). The antibody ELISA values were quantified in international units (mIU/mL) by calculations performed with the α method. Significant changes (>2-fold) in IgG antibody values or the presence of IgM antibodies were considered an indication of recent VZV and HSV infection (in accordance with the manufacturer's instructions). Anti-VZV antibodies were also assayed by the complement fixation test (CF). The HSV type was determined with an HSV type-specific ELISA and an HSV type-specific Western blot analysis, as described previously.[12] Confluent monolayers of human fibroblast cells were infected with VZV strain 992045 isolated in Göteborg, Sweden. The VZV antigen was prepared, and Western blot analysis was performed as before.[12]

Anti-EBV and CMV IgM antibodies were assayed by immunofluorescence, and IgG antibodies by ELISA.[14] Anti-HHV-6 IgG antibodies were measured by immunofluorescence.[15] Antimumps IgG and IgM levels were assayed by ELISA (Enzygnost Antimumps/IgG and IgM; Dade Behring Marburg). Western blot analysis for anti-*Borrelia* antibodies was performed using *Borrelia garinii* strain HP1 and *Borrelia afzelii* strain P/Gau as the antigens.[16]

Polymerase Chain Reaction (PCR). DNA was extracted from 100-μL saliva samples with the use of a DNA extraction kit (SepaGene; Sanko Pure Chemicals, Tokyo, Japan). VZV and HSV-1 DNA in the saliva samples were detected by a previously described nested PCR assay.[13,17]

Diagnosis. Ramsay Hunt syndrome was diagnosed if acute peripheral facial paralysis occurred together with typical zoster lesions around the auricle or in the oral epithelium. Zoster sine herpete was diagnosed if VZV DNA was detected in saliva samples by PCR or if serologic assays indicated recent VZV infection. Bell's palsy was diagnosed in all other patients.

RESULTS

Clinical Diagnosis. At the time of the first hospital visits of 30 pediatric patients with acute peripheral facial paralysis, only 1 patient had typical zoster lesions at the auricle in addition to facial paralysis. Zoster lesions appeared 9 days after the onset of paralysis in 1 child, who was initially diagnosed with Bell's palsy. VZV reactivation was confirmed in these 2 patients with serologic assays of paired sera, and a diagnosis of Ramsay Hunt syndrome was made (2 of 30 = 7%; Table 1, cases 1 and 2). None of the patients had typical

TABLE 1. Diagnosis of VZV Reactivation

Patient	Age (yr)	Zoster	Serologic Assays			Saliva PCR	Diagnosis
			IgM	IgG	CF Titer		
1	9	Present	4.3→2.7*	133→79*	x16→x16	Neg.	RHS
2	9	Present	Neg.→1.0	21→51	×8→×16	Neg.	RHS
3	11	None	Neg.→1.6	3.2→32	×8→×16	Pos.	ZSH
4	13	None	2.1→4.6	24→240	×16→×32	Pos.	ZSH
5	13	None	Neg.→Neg.	12→630	<4→×4	Pos.	ZSH
6	14	None	Neg.→Neg.	23→46	×8→×16	Neg.	ZSH
7	7	None	Neg.→1.2	26→93	×8→×16	Neg.	ZSH
8	9	None	2.2→2.0	61→46	×16→×16	Neg.	ZSH
9	5	None	2.5→2.1	120→82	×16→×16	Neg.	ZSH
10	10	None	1.4→1.3	65→70	×128→×64	Neg.	ZSH
11	7	None	2.1→2.6	29→29	×8→×16	Neg.	Bell
12	3	None	3.1→2.6	2.8→2.1	<4→<4	Neg.	Bell
13	14	None	Neg.→Neg.	27→41	×16→×16	Pos.	ZSH

*Antibody values ($\times 10^2$ mIU/ml) of the first serum→convalescent serum.
Neg., negative; Pos., positive; RHS, Ramsay Hunt syndrome; ZSH, zoster sine herpete.

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herpes labialis at the onset of paralysis or could recall experiencing a tick bite. Therefore we considered the remaining 28 children to have Bell's palsy clinically.

Diagnosis of VZV Reactivation. Among the 28 pediatric patients with a clinical diagnosis of Bell's palsy, 10 patients had either a significant increase in anti-VZV IgG antibody values or IgM antibodies detected by ELISA (Table 1, cases 3–12). By CF, none of the patients showed a significant increase (4-fold or above) in anti-VZV antibody titer (Table 1). VZV DNA was detected by PCR in 3 of the 10 children's saliva samples on at least 1 occasion during the acute phase of paralysis. Thus zoster sine herpete was confirmed in these 3 cases (cases 3–5). Of the remaining 7 VZV DNA-negative children, 2 children (cases 6 and 7) had 2-fold and 3.6-fold increases in anti-VZV IgG antibody values, respectively. The increase in anti-VZV IgG antibody values was marginal, and anti-IgM antibody was negative in case 6; therefore we examined this patient's sera by Western blot analysis. Significant increases in antibody responses to VZV glycoprotein E were confirmed. Three other children (cases 8–10) had both IgM antibodies and high values of anti-VZV IgG antibodies [ELISA value more than the mean + 3SD of the healthy controls ($\geq 50 \times 10^2$ mIU/mL)] in the absence of significant increases in the second of their paired sera. A diagnosis of zoster sine herpete was made for these 5 VZV DNA-negative children (cases 6–10). The remaining 2 children (cases 11 and 12) had positive IgM antibodies, but their sera showed neither significant increases in anti-VZV IgG antibody values nor high anti-VZV IgG antibody. Therefore a diagnosis of zoster sine herpete was not made in these 2 cases. VZV DNA was detected in the saliva of 1 further child (case 13) whose sera showed a 1.5-fold increase in anti-VZV IgG antibody values. Because VZV DNA is not detectable in healthy people,[13] we diagnosed this child as having zoster sine herpete. Consequently zoster sine herpete was confirmed in 9 of the 28 children (32%) who were previously given a clinical diagnosis of Bell's palsy. In total, facial paralysis caused by VZV reactivation (Ramsay Hunt syndrome and zoster sine herpete) accounted for the symptoms in 11 of 30 (37%) children with acute peripheral facial paralysis.

Age-Related Prevalence of VZV-Induced Facial Paralysis. We next examined the prevalence of Ramsay Hunt syndrome or zoster sine herpete (VZV-induced facial paralysis) in relation to patient age. The prevalence of VZV-induced facial paralysis in 6- to 15-year-old patients was significantly higher than among the group younger than 5 years of age (53% versus 9%; $P = 0.023$, Fisher's exact test).

Diagnosis of HSV-1 Reactivation. An HSV type-common ELISA showed that 13 of the 30 children (43%) were positive for anti-HSV IgG antibodies. All 13 had anti-HSV-1 antibodies, but none had anti-HSV-2 antibodies by type-specific assays. One child, who was diagnosed as having zoster sine herpete, showed a significant increase in both anti-HSV IgG antibody values and a positive IgM antibody response. Western blot analysis confirmed significant increases in the immunoreactivity of the serum for HSV-1 glycoprotein B and D. Therefore dual reactivation of HSV-1 and VZV was suggested in this child. A total of 12 other HSV-seropositive children did not show significant increases in anti-HSV IgG or IgM antibody values. Saliva samples were obtained for 12 of the 13 HSV-1-seropositive children within 6 days of the onset of paralysis. HSV-1 DNA was detected in 2 children during the acute phase (day 4 in both cases). HSV-1 DNA was not detected in any HSV-seronegative children. Consequently 3 of the 30 children (10%) showed evidence of HSV-1 reactivation around the onset of facial paralysis.

Prevalence of Anti-HSV Antibody in Children With Bell's Palsy. By means of serologic assays and PCR, 19 children who lacked VZV reactivation were diagnosed as having Bell's palsy. Anti-HSV IgG antibodies were positive in 9 of 19 (47%) pediatric patients with Bell's palsy and in 4 of 11 (36%) of those with VZV reactivation. The difference in the prevalence of anti-HSV antibodies between the 2 groups was not statistically significant ($P > 0.05$, Fisher's exact test).

Diagnosis of Other Infectious Agents. To investigate other infectious causes of acute peripheral facial paralysis in these children, their sera were analyzed for antibodies to EBV, CMV, HHV-6, mumps virus and *Borrelia* (Table 2). Samples from 1 child (1 year old) were positive for IgM antibodies to CMV, EBV and mumps virus, suggesting recent infections by these viruses. This child had had recurrent facial paralysis 1 year after the first episode. In addition, we identified 2 children whose samples were positive in an IgM-antibody test for mumps virus: 1 of the 2 children had parotitis and fever 7 days before the onset of facial paralysis. One child had IgM antibodies to CMV. Seroconversion to HHV-6 was not detected in any of the children. Two patients had IgM antibod-

TABLE 2. Diagnosis and Virologic Data for 30 Children With Acute Peripheral Facial Paralysis

Diagnosis and Virologic Data	No. of Patients
Bell's palsy	19 (63)*
HSV-1 (PCR)†	2
Mumps (parotitis + IgM)	1
Mumps (IgM)	1
CMV + EBV + mumps (IgM)	1
CMV (IgM)	1
None	13
Zoster sine herpete	9 (30)
VZV (IgM/IgG + PCR)	3
VZV (IgM/IgG)	4
VZV (PCR)	1
VZV (IgM/IgG) + HSV-1 (IgM/IgG)	1
Ramsay Hunt syndrome	2 (7)
VZV (zoster + IgM/IgG)	2
Total	30

*Numbers in parentheses, percent.
†Positive virologic data are indicated in parentheses.

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ies against either *B. garinii* or *B. afzelii*, which were confirmed by Western blot analysis according to the Centers for Disease Control and Prevention criteria for the serologic diagnosis of Lyme disease.[18] However, they did not have IgG antibodies against *B. garinii* or *B. afzelii*. Neither of the 2 patients had erythema migrans typical of Lyme borreliosis, nor could they recall a history of a tick bite. Therefore no cases of acute peripheral facial paralysis caused by Lyme borreliosis were detected among the 30 children. No evidence of these infectious agents was detected in the single child with 3 episodes of alternating paralysis.

Recovery From Facial Paralysis. Steroids (usually 1 mg/kg prednisolone) were administered to 25 of the 30 pediatric patients. Eleven patients were given additional acyclovir. All 19 children with Bell's palsy recovered completely to the grade I level (House-Brackmann grading system).[19] Recovery was complete in 8 of the 11 children (73%) with VZV reactivation, whereas the remaining 3 children with VZV reactivation recovered to grade II, with sequelae including slight asymmetry of facial movement or mild synkinesis. Six children with VZV reactivation received acyclovir at the recommended dosage for VZV infection and steroids, and 4 of the 6 (67%) recovered completely. The remaining 5 children with VZV reactivation received steroid therapy alone, and recovery was complete in 4 of the 5 cases (80%). The difference in the cure rate between the 2 treatment groups was not statistically significant ($P > 0.05$, Fisher's exact test).

DISCUSSION

The findings presented here indicate that VZV reactivation (Ramsay Hunt syndrome or zoster sine herpete) is an important cause of acute peripheral facial paralysis in children, especially those between 6 and 15 years of age. Only a few studies to date have analyzed paired sera for evidence of VZV reactivation in pediatric patients with facial paralysis. Hato et al[20] reported data from a large-scale study including 311 children. Their results indicated that VZV reactivation leading to Ramsay Hunt syndrome or zoster sine herpete was the cause of facial paralysis in 16.7% (52 out of 311) of cases, compared with 37% in the present study. This discrepancy might be a result of the use of different serologic assays. Hato et al[20] used CF to diagnose zoster sine herpete. They described the appearance of herpetic vesicles in 42 of 52 pediatric patients with Ramsay Hunt syndrome, including zoster sine herpete; thus 10 of 311 cases (3.2%) received this diagnosis by CF alone. In the present study, we used ELISA in combination with PCR analysis of saliva samples, and we excluded patients from whom paired sera were not obtained. Our data indicated zoster sine herpete in 30% of the pediatric patients. VZV reactivation, as indicated by CF, was not diagnosed in any of our patients with Ramsay Hunt syndrome or zoster sine herpete, indicating a lower sensitivity for CF than for ELISA. In addition, facial paralysis in Ramsay Hunt syndrome can occur at different times from the early phase to the regression phase of VZV reactivation.[21] Therefore some patients with Ramsay Hunt syndrome or zoster sine herpete have a high anti-VZV IgG value at the initial visit but show no significant increase in the antibody value in paired sera, as demonstrated in our case 1 and cases 8–10. These findings suggest that analyses of anti-VZV IgG and IgM antibodies with the use of paired sera by ELISA should be performed routinely for the laboratory diagnosis of pediatric patients with acute peripheral facial paralysis.

The effectiveness of steroid treatment of children with Bell's palsy is controversial because the majority of patients recover completely, regardless of treatment.[22] The rate of complete cure for adult facial paralysis in patients with VZV reactivation is lower than for Bell's palsy patients.[23] In the present study, pediatric patients with VZV reactivation showed a lower recovery rate than those with Bell's palsy (73% versus 100%). The early administration of antiviral agents and steroids after the onset of paralysis caused by VZV reactivation has been recommended.[24,25] Antiviral agents might inhibit the replication and spread of VZV in the facial nerve, and steroids might reduce its inflammation and edema when paralysis has occurred. Antiviral agents were not shown to benefit children with VZV reactivation in the present study, although the number of patients included was small. Further large clinical studies are needed to prove the effectiveness of combination therapy comprising steroids and antiviral agents, for pediatric patients with VZV reactivation.

HSV-1 DNA was detected in the saliva of 2 patients during the acute phase of facial paralysis. Because HSV-1 can be shed asymptomatically in the saliva and tears of healthy people,[26] the detection of HSV-1 DNA in clinical samples from patients with Bell's palsy does not indicate that this virus is a direct cause of facial paralysis. Several serologic studies[12,27,28] have shown that the prevalence of antibody to HSV among patients with Bell's palsy is higher than among control subjects. These findings provide indirect evidence of an association between HSV-1 and Bell's palsy. By contrast, our data show a relatively low prevalence of anti-HSV-1 antibody in pediatric patients with Bell's palsy (47%). Furthermore no significant difference was observed between the prevalence of anti-HSV-1 antibody in pediatric patients with Bell's palsy and those with VZV reactivation. These findings suggest that HSV-1 is not a major cause of facial paralysis in children.

Among our cohort of 30 patients, the incidence of VZV reactivation was higher in older children (6–15 years old) with facial paralysis than in younger children (0–5 years old). Hato et al[20] also reported a higher incidence of Ramsay Hunt syndrome, including zoster sine herpete, in older children (7–15 years old) than in preschool children. There might be additional unknown causes of acute facial paralysis in younger children, because most children younger than 5 years

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of age were HSV-seronegative and lacked VZV reactivation. Interestingly 3 of 11 (27%) patients younger than 5 years of age had antimumps IgM antibodies, although only 1 child had a recent episode of mumps parotitis. Reinfection by mumps virus with the absence of parotitis has been reported to constitute another form of mumps-induced facial paralysis.[6,29] Further large scale controlled studies will be necessary to demonstrate any association between acute peripheral facial paralysis and mumps virus infection. Lyme borreliosis has also been implicated in the pathogenesis of acute peripheral facial paralysis in children.[30] Although Hokkaido Island, where our Institute is located, is an area with endemic Lyme disease in Japan, acute peripheral facial paralysis caused by Lyme borreliosis appears to be uncommon in this area.

In conclusion, this study indicates that VZV reactivation is an important cause of acute peripheral facial paralysis in children, especially those 6–15 years of age. Conversely HSV-1 reactivation is not a significant factor underlying Bell's palsy in childhood. The appropriate diagnosis of VZV reactivation should be facilitated by ELISA testing of paired sera from pediatric patients with acute peripheral facial paralysis.

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