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Virology of Infantile Chronic Recurrent Parotitis in Santiago de Chile

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Infantile chronic recurrent parotitis (ICRP) has been attributed to multiple causes, including viral infections, and therefore its treatment remains empirical. Our aim was to evaluate the involvement of respiratory and oropharyngeal viruses in acute episodes of ICRP. Seventy children were studied, 50 patients and 20 age-matched controls, in a 2-year follow-up study. Saliva samples were taken from the parotid duct and analyzed by viral isolation and immunofluorescence for adenovirus (Ad), respiratory sincitial virus (RSV), parainfluenza virus (PI), influenza virus (Flu), Cytomegalovirus (CMV), and herpes simplex virus (HSV). Paired sera samples were tested by ELISA for anti-Epstein-Barr virus (EBV) IgG and anti-mumps IgM and IgG. Viral infections were detected in 7/50 (14%) cases of the ICRP group: one CMV; 2 Enteroviruses isolated in human embryonic lung fibroblast cells; 1 Flu A; and 3 mumps virus. No EBV seroconversions were detected. In the control group, 2 out of the 20 children had an asymptomatic mumps positive IgM titer. Our data indicate that the main respiratory and oropharyngeal viruses are not the cause of acute episodes of ICRP in Chilean children. ***J. Med. Virol. 70:459–462, 2003.***

KEY WORDS: infantile recurrent parotitis; viral ICRP; Santiago, Chile

INTRODUCTION

Infantile chronic recurrent parotitis (ICRP) is the second most common cause of inflammatory salivary gland swelling in children, after mumps [Kaban et al., 1978]. Acute episodes are characterized by painful, tender, unilateral, or bilateral parotid gland swelling, which may last from a few days to more than two weeks. The swelling typically appears suddenly over a period of a few hours and may be accompanied by systemic symptoms, including fever and general malaise [Jones, 1953].

The disease usually begins in a child between 3 and 6 years of age, but earlier or later initiation of symptoms has been observed [Blatt, 1966; Konno and Ito, 1979]. Exacerbations may occur over many years, usually at 3- to 4-month intervals, with great individual variations [Galli and Yitzhak, 1985; Geterud et al., 1988]. When the child reaches puberty, the symptoms usually subside. Although the disease may resolve completely, persistent cases have been observed [Galli and Yitzhak, 1986; Watkin and Hobsley, 1986].

The histopathologic condition of the affected gland in ICPR reveals areas with massive infiltration of lymphocytes and lymph follicle formation [Kaban et al., 1978; Ericson et al., 1991]. There are cystically dilated irregular ducts, which correspond to small spherical collections of contrast medium in the sialographic image, called sialectases. Whether these changes are the cause or the result of the recurrent exacerbations of parotitis is still under discussion. A variety of etiological factors have been proposed for ICRP, including allergy [Mandel and Kaynar, 1995], ascending bacterial infection [Giglio et al., 1997], viral infection [Akaboshi et al., 1983], autoimmunity [Friis et al., 1983], and congenital structural defects [Smith, 1953]. There is no satisfactory theory that explains its etiopathogenesis. This study was undertaken to test the hypothesis that acute episodes of ICRP are the consequence of oropharyngeal viral infections.

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MATERIALS AND METHODS

The study group was comprised of 70 children: 50 patients with ICRP and 20 controls. The patients were admitted to the children's Maxillofacial Surgery Department of San Juan de Dios Hospital, a reference center for this pathology in Santiago and were followed for two years. Diagnosis of ICRP was based on clinical criteria and confirmed by conventional sialography. The criteria for including a patient in the study were: (1) development of symptoms before 10 years of age; (2) at least 2 episodes involving the same gland; (3) duration of each episode from 2 to 10 days; (4) sialography showing characteristic stippling; and (5) absence of antibiotic therapy for at least 30 days before obtaining the sample. Of the 20 children included as controls, 12 were attending outpatient clinics for immunization programs and presented no past history of parotid swelling, and 8 presented other salivary gland pathology, such as mucocele or fibrosis.

Parotid duct saliva and serum samples from the ICRP patients and the control group were used for viral studies.

Saliva Collection and Virus Identification

After decontamination of the opening of the Stenson's duct with iodophor for 1 min, a sterile plastic tube was inserted 2 to 3 cm in the duct and the secretion of saliva was stimulated by massaging the gland. Saliva obtained (2.5 ml) was transported in 0.5-ml phosphate buffer saline (PBS) on wet ice to the laboratory, within 1 hr and processed for immediate viral detection by an indirect immunofluorescence assay (IFA) and for viral isolation in cell culture. One aliquot was kept at −70°C. A total of 86 parotid duct aspirates were analyzed. Sixty-eight were obtained from the 50 ICRP patients, 9 of whom had one or more recurrences during the study period.

Each saliva specimen was processed as described elsewhere [Avendaño et al., 1991; Martínez et al., 1998]. Briefly, the samples were inoculated into HEp-2, MDCK, CV-1, and human embryonic lung fibroblast cells. Cultures were observed every other day for cytopathic effect (CPE). The presence of viruses was confirmed by DFA or IFA, either upon detection of CPE or after 10 days of incubation for RSV, Ad, PI 1-3, Flu A-B, HSV, and 30 days for CMV.

IFA was performed for detection of RSV, Ad, Flu A-B, PI 1-3, and CMV, and DFA for HSV [Martínez et al., 1998]. Standard indirect immunofluorescent staining was done as described elsewhere [Ballew et al., 1984; Larrañaga et al., 1990; Avendaño et al., 1991], using monoclonal antibodies for RSV, Ad, PI 1, and PI 2, kindly provided by Dr. L. Anderson (CDC, Atlanta, GA), monoclonal antibodies for PI 3 and Flu A and Flu B provided by Dr. Pothier (Dijon, France), and rabbit polyclonal antibodies for Ad, supplied by Dr. G. Wadell (Sweden). For HSV and CMV, a commercial (Imagen Dako™) antibody was used [Martínez et al., 1998]. Positive immunofluorescence cells were documented by phase-contrast light microscopy (Nikon™).

A total of 113 blood samples were collected for detection of antibodies to EBV and mumps. Sera samples were stored at −20°C until studied for IgG levels to EBV and IgM-IgG levels to mumps virus. Eighty-four were from ICPR patients, with paired samples obtained from 35 patients. Twenty-nine sera samples were collected from the age-matched control group, with 11 children giving paired samples.

Determination of Antibodies to EBV and to Mumps Virus

SIA™ Epstein-Barr VCA IgG assay (SIGMA™) is an indirect enzyme-labeled immunosorbent assay (ELISA) for the determination of IgG antibodies to Epstein-Barr viral capsid antigen (VCA) using antigen-coated multiwells as a solid phase. Melotest Parotitis IgG and Melotest Parotitis IgM (MELOTEC Biotechnology™) are enzyme immunoassays (EIA) for the detection of specific antibodies against mumps virus antigens in human sera. All assays were performed according to manufacturer's instructions.

RESULTS

Clinical Features

Of the 50 patients with ICRP, 29 were boys (58%) and 21 girls (42%). Ages ranged from 1 to 12 years, with a mean of 5.6 years. In all 50 patients, unilateral or bilateral parotid swelling was associated with pain and malaise, and in 36 patients (72%), fever was present. Clinical observation of the parotid duct saliva revealed purulent discharge in 66% of the ICRP patients and a normal or filamentous saliva appearance in the rest. At the onset of parotitis, all patients had symptoms of an upper respiratory tract infection; i.e., common cold, pharyngitis, or bronchitis. Patients' records revealed that 30% suffered from allergies and 18% had evidence of at least 1 family member with ICRP history.

The control group consisted of 11 boys (55%) and 9 girls (45%). Ages ranged from 2 to 14 years old (average 5.6 years). None of them had fever or upper respiratory tract symptoms when the samples were taken. All saliva samples obtained from the parotid duct had a normal clear appearance. Only one child had a record of allergies and none of them had a family member with ICRP.

Viral Study

Acute viral infections were detected in 7 of the 50 ICRP patients studied (Table I). CMV was obtained from the saliva sample of a 3-year-old boy with painful parotid swelling, purulent saliva, and history of 3 similar previous episodes. Two Enteroviruses were isolated in human embryonic lung fibroblast cells and confirmed by monoclonal antibodies (CMV-negative and Coxsackie B–positive); one was obtained from a 1-year-old boy with painful parotid swelling, normal clear saliva, fever, and history of 4 previous ICRP episodes, and the other

TABLE I. Viruses Detected and Characteristics of the Infants With ICRP

Virus	No. (%)	Patient	Clinical features	No. of ICRP episodes
CMV	1 (2)	3-year boy	Painful parotid swelling and purulent saliva	3
Enterovirus	2 (4)	1-year boy	Painful parotid swelling and fever	4
		3-year girl	Painful parotid swelling, purulent saliva, and fever	2
Influenza A	1 (2)	4-year girl	Painful parotid swelling	3
Mumps virus	3 (6)	4-year girl	Purulent saliva	3
		10-year boy	Parotid swelling	>6
		10-year boy	Parotid swelling	>6
Total	7 (14)			

corresponded to a 3-year-old girl with painful parotid swelling, purulent saliva, fever, and history of 2 ICRP episodes. An influenza A virus was isolated from the saliva of a 4-year-old girl with painful parotid swelling, normal saliva, history of 3 previous ICRP episodes and also family history of ICRP. The other 3 cases were patients with positive serology (IgM) for mumps virus; a 4 year old girl with purulent saliva and history of 3 previous episodes of ICRP as well as allergy symptoms; and two 10-year-old boys with atopia history and more than 6 previous ICRP episodes. EBV-IgG was positive in 97% of the patients and no titer changes were observed in paired sera samples.

In the control group, 2 out of the 20 children presented positive IgM levels for mumps virus. Ten of eleven were EBV-IgG positive and no seroconvertions were detected. All IFA and viral isolation assays were negative.

DISCUSSION

Since the initiation of mumps vaccination in Chilean children, ICRP is one of the major inflammatory parotid gland swelling without an accepted treatment strategy.

In this study, we found out that acute viral infections were detected in only 14% of the patients with ICRP. In addition, 3 of the 4 positive viral isolation cases (2 with Enteroviruses and 1 with influenza A) were obtained during periods when these viruses typically cause epidemics in Chile (September and May, respectively) [Larrañaga et al., 2000]. This situation makes a specific viral etiological for ICRP very unlikely. Similarly, the isolation of CMV from a very young child with ICRP probably indicates a coincident shedding rather than causal relationship to the development of the parotid swelling.

Remarkable is the fact that no respiratory virus (except one Flu A virus) was obtained from the cases studied, even though all the patients showed symptoms of an upper respiratory tract infection. We do not believe that this is the result of a delayed sampling, since our patients come to the hospital at the onset of symptoms due to the parotid swelling and intense pain observed in ICRP, and because they receive periodic controls in our Maxillofacial Surgery Department. Nevertheless, infection of the upper respiratory tract might be a first step in a sequence of events triggering the reactivation of the disease through dehydration of the child, with reduced salivary secretion and mucosa inflammation, so providing a ground for secondary infections [Ericson et al., 1991]. Future studies could focus on other upper respiratory tract viruses, such as rhinoviruses and coronaviruses.

Mumps infection was found in similar proportion in the ICRP and control groups, again conferring no support to the possibility that the onset of ICRP might be a consequence of mumps infection in our children. Previous studies in other countries have found similar results [Konno and Ito, 1979; Akaboshi et al., 1983; Ericson et al., 1991].

It is noteworthy that a high proportion of patients and children from the control group presented positive levels of anti-VCA-IgG. These values are similar to the ones obtained by Akaboshi et al. [1983], who found that 85% in the ICRP group and 80% in the control group were VCA IgG(+). Previous studies have shown that infectious EBV can be obtained from parotid duct aspirates in seropositive subjects [Morgan et al., 1979], indicating that the parotid salivary gland is a local site of virus production. It seems plausible that ICRP might be caused by an acute exacerbation or inflammation of the parotid gland due to bouts of local multiplication in EBV carriers [Akaboshi et al., 1983].

Our results exclude the main known respiratory viruses as the principal etiologic agents in ICRP in Chilean children and show no differences in the rate of mumps infection between controls and ICRP patients. Human herpes viruses (CMV, HSV, and EBV) seem not to have a significant participation, although the possibility that EBV could be replicating locally in the parotid gland cannot be ruled out. These data clarify the spectrum of viral agents that might be implicated in the etiology of ICRP and redirect the approach for viral research in our children.

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