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A study of childhood febrile convulsions with particular reference to HHV-6 infection: pathogenic considerations

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Abstract Most febrile convulsions (FC) in infants occur during a viral infection, particularly in children of less than 3 years of age; human herpesvirus 6 (HHV-6) has an important pathogenic role. To evaluate the link between this and other viruses and FC, a group of 65 children (mean age 18.46 months, SD±9.19) with a first episode of simple FC (G1) was compared with 24 children (mean age 19.29 months, SD±13.17) with a febrile syndrome but without FC (G2). Virological study showed the following infections: HHV-6 in 23/65 of G1 and in 12/24 of G2, adenoviruses (ADV) in 9/65 of G1 and in 0/24 of G2, syncytial respiratory virus (SRV) in 3/28 of G1 and in 0/2 of G2, HSV-1 in 6/65 of G1 and in 1/24 of G2, cytomegalovirus (CMV) in 2/65 of G1 and in 0/24 of G2 and HHV-7 in 1/42 of G1 and in 1/13 of G2. Children in G1, statistically compared with G2, were significantly more likely to have a family history of FC and circulating granulocytes, while IgM and α2-globulin were less probable. Some cytokines (IL1β, TNFβ and GM-CSF) were found in 24 children in G1 and 12 in G2; no differences were found between the two groups. In the light of our data and of the recent literature, the possibility that the cytokines may act on the nervous system cannot be excluded. Among the HHV-6-infected children, those suffering from convulsions were statistically more likely to have a family history of FC and IgM, while IgA were less likely. In G1, 57 cases were followed up over 2 years: 9 of them had a second episode of FC. Virological diagnosis at the first episode of FC revealed HHV-6 infection in 3 cases, 2 of these being due to viral reactivation. We underline the important role of HHV-6 infection in FC and postulate a relationship between family history and the immunity of the patient; this is confirmed by the loss of statistical significance in the reduction of IgM in G1 compared with G2 with no family history of FC. The reactivation of FC by HHV-6 is a possibility to be borne in mind; an increased number of cases would be needed to confirm this hypothesis.

Key words Febrile convulsions · Human herpesvirus 6 · Viral infection · Cytokines · Immunity · Childhood

Introduction

During childhood, particularly from 6 months to 3 years of age, 3–5 children in every 100 have at least one episode of febrile convulsions (FC). Most childhood FC may be defined as the simple type (a duration of less than 15 min, no signs of focal activity, no pre-existing neurological pathology), with critical manifestations of the generalized clonic type in most cases. Only a small number can be clas-

sified as the complex type (in general, all cases that do not have the above characteristics) that can lead to a *state* of febrile convulsions; these can be considered rather serious epileptic events [4].

Although the etiopathogenesis of FC has never been defined, many studies have suggested various risk factors: age (the child's brain is more susceptible to irritative stimuli owing to the chemical-structural characteristics of the immature organ), heredity (there is an 8–18% greater chance of FC if they have occurred in other family members) [10, 19] and, to a lesser extent, the degree of fever. A second episode of FC may recur in 30–40% of cases [6].

It is well known that most FC occur with respiratory and digestive symptoms and that 86% of cases may be attributed to viral infections; bacteriemia tests are positive in approx. 5% for *Streptococcus pneumoniae* [5]. They are relatively frequent in the course of exanthem subitum (ES) and shigella infections [8]; in African countries, 50% of FC occur in children with malarial parasitemia [7].

It is thus legitimate to ask whether the etiological agent involved, in particular the type of virus, may play a direct or indirect role in the convulsive phenomena. The viruses most often found in children with FC appear to be the enteroviruses [16], but in the light of more recent studies the human herpesvirus 6 (HHV-6) has attracted attention, having recently been recognized as the etiological agent of ES [1]. This lymphotropic virus is quite diffuse in the environment; it has also been isolated from the saliva and biological fluids of adults as well. It infects humans at an early age (approximately 90% of children are immune at 2 years of age) with a sudden, high fever which has in itself always been considered the cause of the association with FC. In our experience, exanthema appears in about a quarter of the cases, whereas there are aspecific symptoms of upper respiratory tract inflammation in most [2]. The virus has also been isolated in cases of encephalitis [13, 23]. HHV-6 can induce high-level production of some cytokines (powerful proteins responsible for numerous effects, such as induction of pyrogenicity and activation of T-cells and granulocytes), including interleukin-1β (IL1β), tumor necrosis factor (TNF) and interferon-α (INF-α) by circulating monocytes [9, 14], in addition to inhibition of the proliferative response to the mitogen of the circulating mononucleate cells [12]. Owing to these effects on the immune system, HHV-6 – like other herpetic viruses – may persist in the CNS and in other tissues and be reactivated with the onset of other pathologies after marrow transplant and also with recurring FC [3, 15, 17].

Accordingly, we set out to identify which viruses are mainly involved in FC and to discover whether there are elements differentiating children who develop FC from those who do not during viral infections in general and in the case of HHV-6 infection in particular, whether different amounts of cytokines are present in children with FC than in other, nonconvulsive, children, and finally, whether different types of viruses pose different levels of risk of recurrent FC.

Patients and methods

The study group consisted of 89 children (38 boys, 58.5%, and 27 girls, 41.5%) with high fever associated with respiratory and/or digestive symptoms, 65 (73%) of whom had been affected by a first simple FC (G1). Of these, 36 (55.4%) were admitted to the Section of Pediatrics in Modena and 29 (44.6%) to the Section of Pediatrics at the Civil Hospital in Sassuolo. Ages ranged from 2 to 48 months (mean=18.6, SD±9.19). Most of these patients (57 children, 87.7%) were followed up for at least 12 months.

The control group consisted of 24 subjects (12 boys and 12 girls) with ages ranging from 4 to 48 months (mean=19.29, SD±13.17) who were admitted to the Section of Pediatrics in Modena following an episode of fever without FC (G2).

Virological study was conducted in all the patients by various methods. The following tests were performed on a peripheral blood sample with the addition of heparin and on an oropharyngeal culture swab, taken within 24 h of the FC or time of admission.

Isolation of lymphotropic viral agents

The lymphocytes were separated from the peripheral blood samples by centrifugation with Fycoll-Hypaque gradients. The mononucleate cells, stimulated with phytohemagglutinin, were placed in a culture with RPMI 1640 medium supplemented with inactivated bovine serum and a 5% IL_2 solution, in incubation at 37°C in CO_2. The oropharyngeal secretions on the swab were diluted in RPMI 1640 medium to which antimicrobial and antifungal solutions had been added. Each preparation was inoculated into umbilical cord blood lymphocyte cultures prepared in the same way as peripheral blood lymphocyte cultures. The cultures, provided with fresh medium, were observed daily under a microscope for 30–40 days to test for any cytopathic effect. The cytopathogenic agents isolated were recognized as HHV-6 and human herpesvirus 7 (HHV-7) if there was specific reactivity with the monoclonal antibody to HHV-6 protein 41 and to a HHV-7 human hyperimmune serum in an indirect immunofluorescent assay (IFA).

Isolation of nonlymphotropic viral agents

Every oropharyngeal secretion was inoculated on a single layer of VERO cells and human fibroblasts. The cell cultures were observed daily under a microscope for 30–40 days to detect any cytopathic effect. The isolated cytopathogenic agents were recognized as belonging to the adenovirus (ADV) group if there was specific reactivity to the rabbit serum immunized against the ADV group antigen in an IFA reaction.

The following tests were performed on acute and convalescent sera, the former collected on the first or second day of illness, the latter from a minimum of 5 to a maximum of 10 days thereafter.

Serological studies

The acute and convalescent sera of each patient were tested for the presence of antibodies for the following viruses: HHV-6, HHV-7, ADV, herpes simplex virus 1 (HSV-1), cytomegalovirus (CMV) and syncytial respiratory virus (SRV). With the exception of the HHV-6 and HHV-7 antigens, consisting of strains which we have isolated [21], the other antigens were supplied by commercial sources (Pasteur Diagnostics). The following immunological reactions were applied: IFA for HHV-6 and HHV-7 antibody testing, enzyme-linked immunosorbent assay (ELISA) for CMV antibodies, complement fixation test for HSV-1 antibodies and the ADV group antigen.

Some of the acute sera of FC and nonconvulsive cases were tested for serum cytokines IL1β, TNF1β and granulocyte-macrophage

Table 1 Comparison of viral infections in children with and without convulsions with statistical significance of differences, and in children with recurrent and nonrecurrent disease (*G1* children with, *G2* children without convulsions, *G1R* children with recurrent disease, *G1NR* children with nonrecurrent disease)

	G1 (65 cases)	G2 (24 cases)	*P*	G1R (9 cases)	G1NR (48 cases)
HHV-6	23/65 (35.4%)	13/24 (54.2%)	0.452	3/9 (33.3%)	16/48 (33.3%)
HHV-6 reactivation	5/65 (7.7%)	4/24 (16.7%)	0.472	2/9 (22.2%)	3/48 (6.2%)
ADV	9/65 (13.8%)	0/24	0.166	2/9 (22.2%)	7/48 (14.6%)
RSV	3/28 (10.7%)	0/2	–	1/5 (20%)	1/22 (4.5%)
HSV-1	6/65 (9.2%)	1/24 (4.2%)	0.773	1/9 (11.1%)	5/48 (10.4%)
CMV	2/65 (3.1%)	0/24	0.964	1/9 (11.1%)	1/48 (2.1%)
HHV-7	1/42 (2.4%)	1/13 (7.7%)	0.988	1/7 (14.3%)	0/31 (0%)

Table 2 Comparison of the characteristics, clinical signs and symptoms in G1 and G2 overall and in G1 and G2 children infected with human herpesvirus 6 (*G1HHV-6* and *G2HHV-6*) with statistical significance of differences, and in G1R and G1NR

	G1 (65 cases)	G2 (24 cases)	*P*	G1HHV-6 (23 cases)	G2HHV-6 (13 cases)	*P*	G1R (9 cases)	G2NR (48 cases)
Male	38 (58.5%)	12 (50%)	0.856	15 (65.2%)	7 (53.8%)	0.961	7 (77.8%)	29 (60.4%)
Female	27 (41.5%)	12 (50%)	0.820	8 (34.8%)	6 (46.2%)	0.907	2 (22.2%)	19 (39.6%)
Age (months)	18.5 ± 9.2	19.3 ± 13.2	0.739	16.6 ± ±7.5	18.4 ± 12.4	0.605	15.3 ± 4.4	18.9 ± 9.8
FC family history	47 (62.6%)	1 (4.2%)	*0.000*	15 (65.2%)	1 (7.7%)	0.057	8 (88.9%)	32 (66.7%)
FC 1st degree	16 (24.6%)	1 (4.2%)	–	–	–	–	4 (44.4%)	11 (22.9%)
Fever (°C)	38.9 ± 0.8	38.9 ± 0.6	0.733	38.9 ± 0.9	39.1 ± 0.5	0.796	38.5 ± 0.9	38.9 ± 0.7
Exanthema	9 (13.8%)	9 (37.5%)	0.099	5 (21.7%)	8 (61.5%)	0.207	1 (11.1%)	4 (8.3%)
ES diagnosis	4 (6.1%)	2 (8.3%)	0.893	3 (13%)	2 (15.4%)	0.744	1 (11.1%)	2 (4.2%)
High respiratory symptomatology	56 (86.1%)	14 (58.3%)	0.404	20 (87%)	6 (46.2%)	0.413	7 (77.8%)	41 (85.4%)
Low respiratory symptomatology	4 (6.1%)	8 (33.3%)	*0.015*	0	3 (23.1%)	0.121	1 (11.1%)	3 (6.3%)
Digestive symptomatology	7 (10.8%)	7 (29.2%)	0.152	2 (8.7%)	3 (23.1%)	0.591	0	5 (10.4%)

colony-stimulating factor (GM-CSF) with an ELISA test using commercially supplied kits, viz. Endogen, Dupont and RD systems, respectively.

Clinical and case-history data were used to analyze: a family history of FC, body temperature immediately before the FC in G1 and the maximum fever in G2, presence of exanthema, clinical diagnosis of ES, presence of respiratory symptoms compatible with high- or low-tract inflammation and digestive symptoms.

The following hematological tests were also evaluated: leukocytes/mm^3, neutrophils/mm^3, lymphocytes/mm^3, immunoglobulins mg/dl (IgG, IgA, IgM), erythrocyte sedimentation rate (ERS), α2-globulin%, C-reactive protein (CRP).

The results obtained were processed statistically using the Student's *t*-test and Chi-square test, with significance set at $P \leq 0.05$.

Results

Virological studies revealed a viral etiology in 44 out of 65 (67.7%) cases with FC (G1) and in 14 out of 24 (58.3%) without FC (G2). HHV6 was found in 23 (35.4%) cases in G1 and in 13 (54.2%) in G2 (P=0.425), including 5 (7.7%) in G1 and 4 (16.7%) in G2 who were diagnosed as having viral reactivation (P=0.472). The HHV-6 reactivations have an incidence of 5/23 (21.7%) in G1 and of 4/13 (30.8%) in G2 (P=0.939). The incidence of other viruses was: ADV in 9/65 (13.8%) in G1 and 0/24 in G2 (P=0.166); RSV in 3/28 (10.7%) in G1 and 0/2 in G2; HSV-1 in 6/65 (9.2%) in G1 and 1/24 (4.2%) in G2 (P=0.773); CMV in 2/65 (3.1%) in G1 and 0/24 in G2 (P=0.964); HHV-7 in 1/42 (2.4%) in G1 and 1/13 (7.7%) in G2 (Table 1). The convulsion risk for each virus, calculated as the number of FC attributable to a virus out of the total number of diagnoses for that infection, was: 9/9 ADV infections (100%), 2/2 CMV (100%), 6/7 HSV-1 (85.7%), 23/35 HHV-6 (65.7%), 18/26 (69.2%) being first infections and 5/9 (55.5%), reactivations, 5/9 HHV-7 (50%).

The ages in G1 and G2 were similar (P=0.739) (Table 2). In G1, a family history of first-degree FC was seen in 16/65 (24.6%) of cases and of first- and second-degree FC combined in 47/65 (62.6%); in G2, a family history was present only in 1/24 (4.2%), FC being of the first degree; the difference was highly significant (P=0.000). Clinical signs and symptoms evaluated in the two groups are reported in Table 2, and the statistical processing showed no difference between febrile levels (P=0.733), exanthem (P=0.099), diagnosis of ES (P=0.893), infection of the upper respiratory (P=0.404) and digestive (P=0.152) tracts; a significant difference was seen in the signs and symptoms of lower respiratory tract infection (P=0.015).

Hematological tests (Table 3) showed the following statistical differences between G1 and G2: leukocytes P=0.031, neutrophils P=0.011 (higher levels in G1), lymphocytes P=0.418, IgG P=0.649, IgA P=0.389, IgM

Table 3 Statistical comparison of hematological values (mean±SD) between G1 and G2 and various subgroups (*G1wf, G2wf* G1, G2 without a family history of febrile convulsions)

	G1 (65 cases)	G2 (24 cases)	*P*	G1HHV-6 (23 cases)	G2HHV-6 (13 cases)	*P*	G1wf (18 cases)	G2wf (23 cases)	*P*	G1R (9 cases)	G1NR (48 cases)
Leukocytes	12930±6973.6	9655.8±3489.8	*0.031*	12461.7±6929.4	10503.1±3709.4	0.353	13532.8±7380.8	9566.9±3540.3	*0.029*	12864.4±7610.5	13381.7±7061.9
Neutrophils	7701.3±5769.6	4440.2±3432.3	*0.011*	7427.6±5349.9	5126.8±4145.6	0.205	7926.9±6179.6	4292.5±3430.5	*0.022*	7751.3±6720.4	8264.9±5648.4
Lymphocytes	4010.4±1790.3	3667.8±1644.7	0.418	4108.5±2007.6	3807.8±1296.7	0.633	4516.9±1956.1	3710.3±1668.1	0.162	4091.3±1328.7	3967.7±1764.3
IgG	866.0±294.2	904.3±292.9	0.649	886±239.4	977.4±283.4	0.354	970.5±298.1	904.3±292.9	0.562	663.7±106.6	847.8±280.3
IgA	75.5±50.5	87.4±42.6	0.389	58.8±24.0	94.5±48.3	*0.011*	65±22.8	87.4±42.6	0.121	44.7±16.3	67.2±29.3
IgM	148.2±64.8	188.3±56.5	*0.028*	150.3±55.2	192.4±58.5	0.059	160.4±67.7	188.3±56.5	0.242	93.7±88.1	141.7±54.8
ESR	25.9±17.9	30.1±23.1	0.380	24.7±17.4	33.5±20.8	0.188	26.1±17.8	30.4±23.6	0.536	24.3±11.4	26.1±17.9
α2-Globulin	13.2±2.4	15.0±2.4	*0.003*	13.5±1.9	14.8±2.6	0.134	12.4±3.3	15.2±2.4	*0.006*	14.1±2.5	12.8±2.7
CRP	3.3±3.6	2.7±2.7	0.651	2.9±3.1	2.3±2.5	0.660	3.3±3.8	2.8±2.9	0.744	3.6±3.7	3.5±3.9

P=0.028 (lower levels in G1), ERS *P*=0.380, α2-globulin *P*=0.003 (lower levels in G1), CRP *P*=0.651.

Statistical processing showed no difference between convulsive (G1HHV-6) and non-convulsive (G2HHV-6) HHV-6 infected children in age (*P*=0.605), family history (*P*=0.057), degree of fever (*P*=0.796), exanthema (*P*=0.207) or diagnosis of exanthem subitum (*P*=0.744), or in the signs and symptoms of infection of the upper (*P*=0.413) and the lower respiratory tracts (*P*=0.121) or of the digestive tract (*P*=0.591) (Table 2). Hematological tests (mean values are reported in Table 3) revealed the following statistical differences: leukocytes *P*=0.353, neutrophils *P*=0.205, lymphocytes *P*=0.633, IgG *P*=0.354, IgA *P*=0.011 (with lower levels in G1HHV-6), IgM *P*=0.059, ERS *P*=0.188, α2-globulin *P*=0.134, CRP *P*=0.660.

Statistical processing of data obtained from children without a family history (wf) of FC showed no difference between G1wf and G2wf as regards age (21 months – SD±8.49 – in G1wf and 19.57 months – SD±13.39 in G2wf; *P*=0.695) or hematological tests (Table 3), except for leukocytes and neutrophils (higher levels in G1wf) and α2-globulin (lower levels in G1wf).

Of the 57 children followed up for 2 years, 9 (15.8%) suffered a second episode 5–20 months (mean 13.89, SD±5.4) after the first FC. The diagnoses of viral infection at the time of the first episode in the two groups of children with recurrent (R) and with nonrecurrent (NR) convulsions are reported in Table 1. In particular, the incidence of HHV-6 reactivations is 2/3 (66.6%) in R and 3/16 (18.75%) in NR (*P*=0.083). In R, a family history of first-degree FC is present in 4/9 cases (44.4%) and of first- plus second-degree FC in 8/9 (88.8%); in NR, there is a family history of first-degree FC in 11/48 children (22.9%) and of first- plus second-degree FC in 32/48 (66.7%). The other characteristics of the first episode of FC in these children are reported in Tables 2 and 3.

The following cytokines were tested for in 24 children in G1 and in 12 children in G2, and found in measurable quantities: IL1β in 0/24 in G1 and 1/12 (8.3%) of control cases, TNF1β in 5/24 (20.8%) in G1 and 2/12 (16.7%) of control cases; GM-CSF was not found in any child in either of the two groups. No statistical processing was carried out given the small number of cases.

Discussion

The children in our study group were affected by simple FC; in particular, no signs of serious neurological disorders or paroxysmal EEG alterations were detected.

The most recent clinical studies have confirmed that childhood FC occur during a viral infection in most cases (67.7% according to our study group), although tests for isolating the virus in various biological fluids are not always positive. The virus most frequently responsible is cer-

tainly HHV-6 (35.4% of the cases included in this study, although only 17% presented the typical exanthema). Other viruses are obviously capable of inducing a febrile process in which convulsions are generated; in particular, ADVs, which are less infective than HHV-6, seem closely correlated to FC (100% of the subjects found to be infected), followed by CMV, HSV-1 and HHV-7. An etiological study extended to other viruses, such as the enteroviruses [16], could further increase the number of diagnoses of viral infection, leaving less room for other types of etiology. As such, HHV-6 seems numerically important, while a greater risk of FC exists for the ADVs. HHV-6 could be acting directly, as demonstrated by the presence of viral DNA in the cerebrospinal fluid, especially in complex FC, or indirectly. The latter mechanism could represent a mechanism common to other convulsive events in the course of different infections, such as bacterial infections without meningitis or malaria.

As suggested by this study, one factor distinguishing children who develop FC from those in the control group proves to be a family history of FC. These data are confirmed in the most homogeneous group of children infected by HHV-6. But the precise mechanism implicated in the family history is not clear even today. Is the CNS more susceptible to infective or metabolic stimuli? Is it a question of an irregular immune system response to infection?

Of the clinical and hematological data taken into account in our study (Tables 2, 3), few afforded significant results worthy of interest; in particular, the level of body temperature seemed to play no role in FC. Children with FC have higher numbers of leukocytes and circulating neutrophils. Regarding HHV-6, there is a marked, though statistically nonsignificant, level of granulocytosis in the convulsive children, the lack of significance probably being due to the small sample size; inflammation tests reveal no differences. More indicative are the levels of immunoglobulins, which are lower in the children with FC, although statistical analysis is significant for IgM only. In the HHV6-infected group, the children who develop FC have lower total Immunoglobulins but, above all, significantly lower IgA and IgM at the limit of significance. The nonsignificance of lower IgA and IgM in children without a family history of FC demonstrates a certain correlation between family history and immunological factors, while leukocytosis, granulocytosis and $\alpha 2$-globulin remain different. Children with recurrent FC have lower IgG, IgA and IgM values at the first episode than those with nonrecurrent FC. IgA and IgM play an important role at the onset of a viral infection. The lowered response of these antibodies could favor viral diffusion, probably extending to the CNS. This may be interpreted as an impaired immune system response, which may even be hereditary, in subjects who develop FC. It is well known that these phenomena are partly modulated by cytokines and are correlated with CNS diseases [18]. An increase in IL1β production, obtained by culturing mononucleate blood cells of children with FC, has been observed with the normalization of cell function after the FC episode [11]. However IL1β, TNFα and INF-α are induced by HHV-6 in peripheral blood lymphocyte cultures [9, 14]. In our experience, IL1β and TNFβ were measurable only in a few cases of convulsive children and GM-CSF was not found in any of their serum samples. Given the extreme difficulty in demonstrating these cytokines, it may be useful to test for them at different times, particularly during the convulsive crisis, or in the cerebrospinal fluid. In our opinion, cytokines could be involved through an unregulated secretion by producer cells and/or an anomalous distribution or functioning of the appropriate receptors on the membrane of the neural target cells.

Some (15%) of the patients followed up over a long period suffered a second FC episode. In these patients, the incidence of family history for FC in general, and of first-degree FC in particular, increased considerably. Regarding recurrent FC, a recent multi-center study [20] stresses the importance of age less than 18 months at the first seizure crisis, a family history of FC and nonfebrile convulsions. In our experience, age does not seem to be a significant factor; the importance of a family history of FC is, however, confirmed.

All the children with recurrent FC had undergone virological diagnosis at the time of the first FC. In all but 3 cases, the diagnosis was infection by a herpetic virus. We feel we must point out that HHV-6 reactivations (at the first FC) are three times more frequent in the children with recurrent FC in our study. However, given the limited number of cases reviewed, we do not feel justified in confirming the hypothesis of other authors, who emphasize the role of HHV-6 reactivation in the recurrence of FC [15]. Unfortunately, it was not possible to carry out a virological study at the time of the second FC episode.

On the basis of our observations, a speculative hypothesis may be advanced: several viruses, in particular HHV-6, may act at the time of the first infection, or may remain latent (typical of herpetic viruses) and be reactivated to induce seizures. Indeed, the presence of viral DNA, detected with a polymerase chain reaction technique, has been reported in the cerebrospinal fluid of approximately half the children with ES and FC (of both simple and complex types) [22]. The presence of HHV-6 DNA does not, however, correspond to the cerebrospinal fluid alterations typical of an encephalic inflammatory process [22]. The positive PCR is known to be as sensitive as seroconversion, which confirms the validity of the techniques utilized by us for the diagnosis of HHV-6 infection. Moreover, HHV-6 DNA has been more frequently demonstrated in children with recurrent FC [15]; the virus could therefore be reactivated at the time of further FC episodes. The pathogenic role of the virus remains uncertain, however.

In conclusion, the existence of a relationship between viruses and FC seems to be confirmed by our study, as is the role of heredity both in the first FC and in recurring

episodes. Children who develop FC during the course of an HHV-6 infection differ from those who do not in their marked granulocytosis and reduced levels of IgA and IgM. The heredity factor could be represented by a reduced immune response to the viral infection. HHV-6 could also influence the CNS through reactivation, even some time after the original infection, thus fostering certain types of recurring seizures. Finally, we cannot exclude the possibility of an indirect mechanism involving high cytokine production or enhanced receptor sensitivity. Further virological and immunological studies are necessary to confirm these hypotheses.

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