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Abstract

Purpose: Human herpesvirus-6 (HHV-6) is reportedly associated with various chronic neurological diseases; however, no study has analyzed the association between HHV-6 infection and antiphospholipid syndrome (APS). This study aimed to establish a relationship between primary HHV-6 infection and APS.

Methods: The prevalence of antiphospholipid antibodies (aPLs), including anticardiolipin-IgG (aCL-IgG), aCL-IgM, and anti-β2 glycoprotein-1 (anti-β2GP1) were investigated according to age in 85 preschool children aged 3–6 months, 7–11 months, and 1, 2, 3, 4, 5, and 6 years, who were immunocompetent and asymptomatic for cerebrovascular and cardiovascular disease. A second study was conducted with 62 infants (7–23 months of age) suspected of primary HHV-6 infection on the basis of symptoms of exanthem subitum. Serum analyses of aPLs and antibodies to HHV-6 were performed within 1 week of symptoms appearance and 2 weeks later to test whether HHV-6 infection induces aPL.

Results: All children aged under 6 months tested negative for aPL, whereas those aged between 7 months–3 years tested highly positive for anticardiolipin-IgG (aCL-IgG). Positivity rates of aCL-IgG were significantly higher (p value < 0.05) in the primary-infected group (59.4%, 19/32) than those in the uninfected group (27.8%, 5/18).

Conclusion: This study clearly indicated that the occurrence of aCL-IgG coincided with the period when maternal antibodies decline and infants contract various infectious diseases, and aCL-IgG induction is associated with primary HHV-6 infection.

Key Words: Digital subtraction angiography, Iodine, Gadolinium, Carbon dioxide

Introduction

Human herpesvirus-6 (HHV-6) is a lymphotropic virus that was first isolated in 1986 from immunosuppressed patients[1]. HHV-6 species are divided into HHV-6A (order *Herpesvirales,* family *Herpesviridae,* subfamily *Betaherpesvirinae, genus Roseololvirus,* species *Human herpesvirus 6A*) and HHV-6B (order *Herpesvirales,* family *Herpesviridae,* subfamily *Betaherpesvirinae, genus Roseololvirus,* species *Human herpesvirus 6B*). Whereas HHV-6A is most commonly isolated from patients with human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome[2], HHV-6B causes exanthema subitum during infancy[3]. Both strains infect mature $CD4^+$ T cells[4] and interfere with the host immune system through a variety of mechanisms, including dysregulation of cellular cytokine production, modulation of natural killer cell function, and modification of cell surface receptor expression[5]. These viruses can persist in a latent form after primary infection and then recur in peripheral blood, saliva, and cerebrospinal fluid at various times to cause chronic neurological diseases, including Guillain–Barré syndrome[6], multiple sclerosis[7], chronic fatigue syndrome[8], mesial temporal lobe epilepsy[9].

Several patients with primary HHV-6 infection have been demonstrated to develop cerebral infarction[10] or thrombocytopenic purpura[11]. However, the underlying mechanism has not been elucidated. Incidentally, we recently reported a case of cerebral infarction caused by antiphospholipid syndrome (APS) following primary HHV-6 infection[12]. APS is an autoimmune disease characterized by thrombosis, thrombocytopenia, or pregnancy loss in the persisting presence of antiphospholipid antibodies (aPLs) such as anticardiolipin (aCL) and anti-β2 glycoprotein-1 (anti-β2GP1) [13]. Similar to most chronic diseases, the multifactorial etiology of APS combines genetic susceptibility and environmental factors[14]. For instance, unexpected production of aPLs during childhood is caused by infection with viruses such as cytomegalovirus[15, 16], Epstein–Barr virus[17], and varicella-zoster virus[18, 19]. Many infections have been found to be associated with aPLs[20-22], however, excluding a case report[12], no study has analyzed the association between HHV-6 infection and APS.

This study aimed to establish a relationship between primary HHV-6 infection and APS. First, we investigated the prevalence of aPLs according to age, particularly in preschool children. Second, we compared the prevalence of aPLs among 7- to 23-month-old infants according to the presence of HHV-6 infection. The results confirmed that primary HHV-6 infection induces aCL-IgG.

Materials and Methods

The prevalence of aPLs according to age in preschool children

This prospective study was designed to investigate the prevalence of aPLs in immunocompetent preschool children who were asymptomatic for cerebrovascular or cardiovascular diseases or for APS. The exclusion criteria included apparent febrile illness, history of blood or immunoglobulin transfusion, and intake of immunosuppressive agents. Serum samples were obtained from children who visited Kagoshima University Hospital or our collaborating research hospitals between January 2008 and May 2011 for routine blood analysis for various diseases. The age groups were 3–6 months, 7–11 months, 1 year, 2 years, 3 years, 4 years, 5 years, and 6 years, with a minimum of 10 children per group. Serum was also obtained from 15-year-old adolescents (n = 10) and adults in their 40s (n = 10) with no history of cerebrovascular or cardiovascular diseases or APS as healthy controls. We tested the impact of age on the prevalence of seropositivity for aCL-IgG, aCL-IgM, and anti-β2-GP1. The following clinical data were recorded: age, gender, underlying disease, and family history of autoimmune disease.

The prevalence of aPLs according to the presence of HHV-6 infection

This prospective study was designed to investigate the prevalence of aPLs following primary HHV-6 infection. Accordingly, we selected a new group of 7- to 23-month-old preschool children with clinically suspected exanthema subitum (primary HHV-6B infection) on the basis of high fever and/or rash. Subjects with HIV or enlarged lymph nodes were excluded to avoid cases of HHV-6A infection. In addition, subjects who had a history of blood or immunoglobulin transfusion, intake of immunosuppressive agents, and autoimmune, cerebrovascular, or cardiovascular diseases were excluded. The serum samples were obtained twice. The first collection was performed within 1 week after the onset of symptoms, and the second collection occurred approximately 2 weeks later to detect HHV-6 seroconversion. Both samples were tested for aPLs and anti-HHV-6 antibodies. The subjects were into an HHV-6 uninfected group, a primary-infected group, and a post-infected group on the basis of seroconversion of anti-HHV-6 antibodies, and aPLs positivity

rates were compared among these groups.

aPL assay

aCL-IgG and aCL-IgM levels were measured by Bio Medical Laboratories (BML), Inc. (Tokyo, Japan) using a standardized enzyme-linked immunosorbent assay kit (MESACUP Cardiolipin Test®; MBL Co., Ltd., Nagano, Japan), as described previously[23]. Anti-β2-GP1 (isotype IgG) was also measured by BML using an anti-CL β2-GP1 kit® (Yamasa Corp., Chiba, Japan). The assay was fully validated by BML. The cut-off values provided by the assay manufacturer were >10, >8, and >3.5 U/ml for aCL-IgG, aCL-IgM, and anti-β2-GP1, respectively.

Antibodies for the HHV-6 assay

Blood analysis for HHV-6 infection was also performed by indirect immunofluorescence by BML. Serum samples were tested to detect HHV-6-infected lymphocytes fixed on teflon-coated slides using an antibody that recognizes the virus. Serum samples were tested in parallel dilutions. IgG and IgM antibodies were detected using fluorescein isothiocyanate-conjugated goat anti-human IgG and IgM (DAKO Japan Co., Ltd., Kyoto, Japan).

Statistical analysis

The two-sided Fisher's exact test was used to determine statistically significant differences between the groups. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS statistics 17.0 for Windows (SPSS, Inc., Chicago, IL, USA).

Ethics

The ethics committee of Kagoshima University approved the study (registration number; 19-41). All parents of the children who were selected as subjects were personally informed about the research sample, and written informed consent was obtained prior to enrollment from the parents of patients and controls in accordance with the declaration of Helsinki.

Results

The prevalence of aPLs according to age in preschool children

The objective of this first project was to test whether childhood APS targets a specific class of aPLs among the most likely candidates: aCL-IgG, aCL-IgM, and anti-β2-GP1. Serum samples were obtained from 85 immunocompetent children between 3 months and 6 years of age who were asymptomatic for cerebrovascular or cardiovascular diseases or for APS. Table 1 demonstrates the prevalence of aPLs according to age in these children. Although the overall prevalence of aCL-IgG positivity was relatively high at 22.4%

Table 1. The prevalence of antiphospholipid antibodies according to age in preschool children

Ages	Subjects tested		Subjects positive for antibodies		
			aCL-IgG*	aCL-IgM†	anti-β2-GP1‡
	n	males:females	n (%)	n (%)	n (%)
3–6 months	10	8:2	0 (0%)	0 (0%)	0 (0%)
7–11 months	10	7:3	5 (50.0%)	0 (0%)	0 (0%)
1 year	11	6:5	6 (54.5%)	0 (0%)	0 (0%)
2 years	13	5:8	4 (30.8%)	0 (0%)	0 (0%)
3 years	10	7:3	3 (30.0%)	0 (0%)	0 (0%)
4 years	10	7:3	1 (10.0%)	0 (0%)	0 (0%)
5 years	10	3:7	0 (0%)	1 (10.0%)	0 (0%)
6 years	11	5:6	0 (0%)	0 (0%)	0 (0%)
Total	85	48:37	19 (22.4%)	1 (1.2%)	0 (0%)
Controls					
15 years	10	3:7	0 (0%)	0 (0%)	0 (0%)
Adults in forties	10	5:5	0 (0%)	0 (0%)	0 (0%)

*anticardiolipin-IgG, †anticardiolipin-IgM, ‡anti-β2 glycoprotein-1.

(19/85), that of aCL-IgM positivity was low at 1.2% (1/85), and none of the tested children were positive for anti-β2-GP1. All healthy 15-year-old adolescents and adults were negative for all examined antibodies. Closer examination revealed that aCL-IgG positivity rates were within 30.0%–54.5% among children between the ages of 7 months and 3 years. Figure 1 demonstrates the absolute values of aCL-IgG according to age. The aCL-IgG titer ranged from 1 to 28 U/ml, and relatively high values were observed in children aged between 7 months and 3 years. Collectively, these data indicate that childhood aPLs are detected primarily by an increase in aCL-IgG production in children between the ages of 7 months and 3 years.

Detailed examination of the subjects' characteristics suggests that aCL-IgG positivity is statistically unrelated to gender or a family history of autoimmune disease (Table 2). In addition, subjects were diagnosed with a variety of underlying diseases, none of which resulted in aCL-IgG positivity rates exceeding 30%. None of the children developed any clinical symptoms of cerebrovascular or cardiovascular diseases or APS during the study.

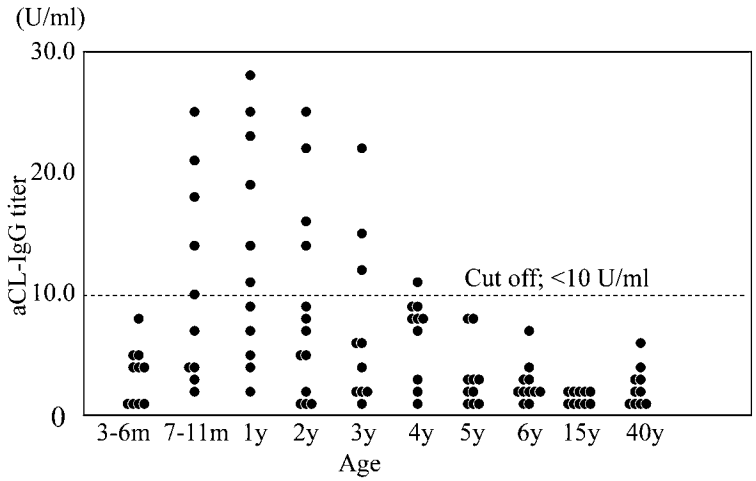
The prevalence of aPLs according to the presence of HHV-6 infection

Because we detected high serum levels of aCL-IgG in 22.4% of the preschool children, the objective of the second project was to test whether aCL-IgG production is related to primary HHV-6B infection. To test this hypothesis, a different group of infants aged 7–23 months old suspected of exanthema subitum were tested for serum levels of HHV-6 antibodies and aPLs. Serum samples were obtained from 62 infants (36 males and 26 females). Forty-seven infants had no underlying disease, whereas the following diseases were present among the remaining 15 patients: cryptogenic epilepsy (n = 2), hydronephrosis (n = 2), neonatal asphyxia (n = 2), psychomotor delay (n = 2), congenital arthrogryposis (n = 1), congenital duodenal atresia (n = 1), congenital vertebral anomaly (n = 1), inguinal hernia (n = 1), iron deficiency anemia (n = 1), Robertson type dislocation (n = 1), and Rubinstein–Taybi syndrome (n = 1).

The seroconversion to HHV-6 was defined as at least a 4-fold increase in the anti-HHV-6 IgG titer in 2 weeks. The subjects were separated into three groups regarding HHV-6 infection: uninfected infants with two seronegative samples; primary-infected infants with a seronegative first sample but seropositive second sample; and post-infected infants with two seropositive samples. If even one positive for aPLs for either of the paired sera, we determined that aPL-positive.

Table 3 shows that 7- to 23-month-old children with symptoms of skin rash and/or high fever had an increased prevalence of aCL-IgG positivity of 46.8%. The positive aCL-IgG concentrations were within the range of 10–48 U/ml. Furthermore, primary-infected and post-infected infants were relatively high for aCL-IgG compared with uninfected infants, with prevalence in the range of 41.7%–59.4%. The aCL-IgG positivity rate was significantly higher in the primary-infected

Figure 1: Absolute anticardiolipin-IgG (aCL-IgG) values according to age.



The cut-off value for aCL-IgG was >10 U/ml. Relatively high values of aCL-IgG were also observed in children between 7 months and 3 years of age in addition to high positivity rates.
m; months of age, y; years of age.

Table 2. Clinical features of participants of the study of a prevalence of antiphospholipid antibodies according to age in preschool children

	Subjects tested n	**Subjects positive for aCL-IgG*** n (%)
male	48	11 (22.9%)
female	37	8 (21.6%)
family history of autoimmune disease		
positive	8	3 (37.5%)
negative	77	14 (18.2%)
underlying diseases		
convulsive diseases	21	4 (19.0%)
cryptogenic epilepsy	16	3
past history of febrile convulsion	5	1
iron deficiency anemia	14	3 (21.4%)
endocrine and metabolic diseases	13	2 (15.4%)
congenital hypothyroidism	7	1
short stature	3	0
idiopathic hypertension	1	1
rickets	1	0
suspected diabetes mellitus	1	0
minor surgical diseases	7	2 (28.6%)
hypospadias	2	0
cataract	1	1
cleft palate	1	1
congenital blepharoptosis	1	0
micromelia	1	0
strabismus	1	0
congenital metabolic diseases	7	1 (14.3%)
congenital lactic acidosis	2	1
Pompe disease	1	0
Farber disease	1	0
Gaucher disease	1	0
Beta-ketothiolase deficiency	1	0
PKAN†	1	0
neurocutaneous syndromes	4	1 (25.0%)
neurofibromatosis type 1	3	1
tuberous sclerosis	1	0
others	19	4 (21.1%)
psychomotor delay (etiology unknown)	9	1
healthy volunteer	3	1
liver dysfunction	2	0
Duchenne muscular dystrophy	1	1
general fatigue	1	1
spastic paraplegia	1	0
suspected deafness	1	0
suspected arrhythmia	1	0
total	85	19 (22.4%)

*anticardiolipin-IgG, †pantothenate kinase-associated neurodegeneration

Table 3. Prevalence of antiphospholipid antibodies among the human herpesvirus-6 uninfected, primary-infected and post-infected groups

	n	age (month)	Subjects positive for antibodies aCL-IgG†	aCL-IgM‡	anti-β2-GP1§
uninfected¶	18	10.3 ± 4.1	5 (27.8%) ┐*	3 (16.7%)	0 (0%)
primary-infected‖	32	11.9 ± 4.5	19 (59.4%)┘	5 (15.6%)	3 (9.4%)
post-infected**	12	15.3 ± 4.9	5 (41.7%)	1 (8.3%)	0 (0%)
total	62	12.2 ± 4.7	29 (46.8%)	9 (14.5%)	3 (4.8%)

If even one positive for aPLs for either of the paired sera, we determined that aPL-positive.
p values were obtained by the two-sided Fisher's exact test.
* $p < 0.05$
†anticardiolipin-IgG, ‡anticardiolipin-IgM, §anti-β2 glycoprotein-1, ¶HHV-6 uninfected group, ‖HHV-6 primary-infected group,
**HHV-6 post-infected group.

group than in the uninfected group ($p < 0.05$). Altogether, these data suggest that HHV-6B infection induces the production of aCL-IgG at the time of primary infection. By contrast, the three subject groups did not differ significantly in terms of aCL-IgM and anti-β2-GP1 prevalence, suggesting that primary HHV-6B infection does not affect the production of these aPLs in infants.

We examined the change in aCL-IgG positivity in paired sera for each child. Among the 19 aCL-IgG-positive children in the primary-infected group, four children who tested negative in the first blood sample tested positive during the convalescent period, whereas the remaining 15 who tested positive in the first blood sample remained positive during the convalescent period. No patient with aCL-IgG positivity in the first blood sample demonstrated negativity in the second. Among the five aCL-IgG-positive children in the uninfected group, one child demonstrated the seroconversion to aCL-IgG from the acute phase to the convalescent phase. Among the five aCL-IgG-positive children in the post-infected group, all children were positive in both samples.

None of the children demonstrated any clinical symptoms of cerebrovascular or cardiovascular diseases or APS during the study.

Discussion

As we reported a case of cerebral infarction caused by APS following primary HHV-6 infection[12], we tested the hypothesis that primary HHV-6 infection induces APS. The present study revealed that the serum levels of aCL-IgG were below the cut-off value until the age of 6 months, after which they increased from 7 months to 3 years of age. Interestingly, the positive rates of HHV-6 antibody from 6 to 12 months increased from 14% (6 months) to 83% (12 months), and almost all children after 13 months of age had the antibody[24]. The occurrence of aCL-IgG coincides with the time when maternal antibodies decline and infants contract various infectious diseases, including HHV-6.

Our study supports a relationship between primary HHV-6 infection and aCL-IgG production. First, positivity rates of aCL-IgG were significantly higher in the primary-infected group than those in the uninfected group. Second, four children who tested negative in the first blood sample tested positive during the convalescent period among the 19 aCL-IgG-positive children in the primary-infected group. It is not entirely clear whether the HHV-6 primary infection that induced aCL-IgG in 15 children in the primary-infected group tested positive for aCL-IgG during the acute phase. However, it is possible that the aCL antibody was induced about 1 week after fever onset because the incubation period for HHV-6 is about 10 days and the virus-neutralizing antibodies had already been induced during the febrile period[25]. Some HHV-6 uninfected children are positive for aCL-IgG at a relatively low rate, suggesting that aCL-IgG induction in infancy is multifactorial. This study is limited with regard to the elucidation of other factors because no data concerning history of other infections were collected. Altogether, these data suggest that primary HHV-6 infection induces aCL-IgG

in Japanese preschool infants.

Many studies have reported the presence of aCL-IgG as a risk factor for cerebrovascular[26,27] or cardiovascular[28] disease in young people, and infection-induced aPLs are closely associated with thrombosis in many instances[12,16–19]. However, none of the participants in our study demonstrated any clinical symptoms of cerebrovascular or cardiovascular disease or APS during the study period. According to the so-called two-hit hypothesis[29], the occurrence of thrombosis is often triggered by additional factors such as smoking, hypertension, diabetes, obesity, hyperlipidemia, oral contraceptive use, or atherosclerotic vascular disease. The lack of other prothrombotic conditions may be one of the reasons why no infant developed cerebrovascular or cardiovascular disease in this study. Although the pathogenicity of aCL associated with infections is obscure at this time, physicians should remember that primary HHV-6 infection is associated with a high rate of aCL-IgG positivity.

Our observations suggest that postinfectious aPLs tend to disappear according to age. Conversely, one epidemiological study suggested that the infectious environment of infancy influences the likelihood of producing aCL-IgG in adulthood[30], and Uthman et al. speculated that some postinfectious aPLs may be transient but that they may persist in other susceptible individuals[31]. Furthermore, Tung et al. recently reported a case of hypersensitivity syndrome with aCL induction associated with HHV-6 reactivation[32]. Because humans have lifelong exposure to the viral antigen, it appears probable that aCL-IgG is repeatedly induced at different times during childhood and adulthood. This study excluded children with cerebrovascular or cardiovascular diseases or APS; therefore, humans with sustained positivity for aCL-IgG may have been excluded. Further prospective studies are needed to clarify the duration of aCL-IgG induction by HHV-6 during infancy. Moreover, aCL-IgG induction following primary HHV-6 infection may be the beginning of a pathological process that leads to APS.

In conclusion, the occurrence of aCL-IgG coincided with the period when maternal antibodies decline and infants contract various infectious diseases, and aCL-IgG induction is associated with primary HHV-6 infection.

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抗カルジオリピン IgG 抗体の誘導はヒトヘルペスウイルス 6 型の初感染に関連する

豊島光雄 [1)]、奥野壽臣 [2)]、前垣義弘 [3)]、米衛ちひろ [1)]、丸山慎介 [1)]、
根路銘安仁 [1)]、武井修治 [1)]、河野嘉文 [1)]

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目的：ヒトヘルペスウイルス 6 型（Human herpesvirus-6; HHV-6) はこれまでに様々な慢性神経疾患との関連が報告されてきたが、抗リン脂質抗体症候群との関連は検討されていない。本研究は HHV-6 の初感染と抗リン脂質抗体症候群との関連を明らかにすることを目的とした。
方法：第一に、乳幼児期の抗リン脂質抗体（抗カルジオリピン抗体 IgG；aCL-IgG、抗カルジオリピン抗体 IgM；aCL-IgM、anti- β 2 glycoprotein-1；β 2GP1 抗体）の陽性率を年齢ごとに検討した。対象は発熱、脳血管障害、心血管障害のない 85 人の小児であり、生後 3-6 か月、7-11 か月、1 歳、2 歳、3 歳、4 歳、5 歳、6 歳の各群に分けた。第二に、HHV-6 の感染の既往と抗リン脂質抗体の陽性率について検討した。対象は第一の研究とは別の乳幼児であり、発熱や発疹により HHV-6 の初感染（突発性発疹）が疑われた 62 人 (生後 7 ～ 23 か月) とした。発熱から 1 週間以内の急性期とその約 2 週間後に採血を行い、HHV-6 に対する抗体価から未感染群、初感染群、既感染群に分けて抗リン脂質抗体の陽性率を比較した。
結果：生後 6 か月以下の乳児ではすべての抗リン脂質抗体は検出されなかった。生後 7 か月から 3 歳にかけての乳幼児では aCL-IgG が高率に検出された（7 ～ 11 か月群；50%、1 歳群；54.5%、2 歳群；30.8%、3 歳群；30.0%）。4 歳群では aCL-IgG の陽性率は 10%に低下し、5 歳以降に陽性例はなかった。aCL-IgM は 5 歳群の一例でのみ陽性であった。β 2GP1 抗体は全年齢群で陽性例はなかった。aCL-IgG 陽性率は HHV-6 未感染群 (27.8%、5/18 例) よりも初感染群 (59.4%、19/32 例) で有意に高かった (p value < 0.05)。
結語：母体からの移行抗体が減少し、乳幼児が様々な感染症に罹患する時期に aCL-IgG が出現し、HHV-6 の初感染時に aCL-IgG が誘導されることが明らかとなった。