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Parvovirus B19 associated autoantibodies upregulation in women and children in Southern China

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Abstract

Objectives: Human parvovirus B19, the cause of fifth disease in children and transient arthropathy in adults, could induce autoimmunity and the production of autoantibodies. The aim of this study is to explore the relationship between B19 infection and autoantibodies upregulation in women and children.

Methods: Of 512 women and children in our hospital between 2016 and 2018, all cases simultaneously test anti-B19 IgM and autoantibodies like anti-nuclear antibody, anti-Sm and anti-double stranded DNA antibody were included in this study.

Results: Parvovirus B19 infection could significantly upregulate anti-nuclear antibody and anti-Sm, but not anti-double stranded DNA, the titer of autoantibodies is associated with the content of anti-B19 IgM, and the infection in children is accompanied with more obvious autoantibodies upregulation.

Conclusions: Our data shows that parvovirus B19 infection is related to autoantibodies production in both women and children, and the status of infection may associate with the titer of autoantibodies in parvovirus B19 infected patients.

Keywords: autoantibodies; children; parvovirus B19 serology; women.

Introduction

Human parvovirus B19, a single-stranded DNA virus, preferentially targets the red blood cell precursors in the bone marrow. The virus is widespread, especially in children, causing erythema infectiosum, a childhood exanthem characterized by slapped cheek rash. In adults, infection is occasionally associated with symmetric polyarthropathy that mimic rheumatoid arthritis. B19V is an immunomodulating virus and has been frequently detected in children and young people, and therefore 60–80% of adults have antibodies against B19V. After primary infection, B19V can remain in the body and persists in many different tissues, including skin, bone marrow, synovium, and liver, and it is believed that this is a lifelong phenomenon.

Parvovirus B19 infection, like many viral infections, could trigger the production of a variety of autoantibodies, many of which have been shown to be key to the pathogenesis of particular disease [1]. Parvovirus B19 infection has also been demonstrated to induce autoimmunity and mimic the manifestation of autoimmune disease, like systemic lupus erythematosus (SLE) [2–5]. In children, it has been reported that parvovirus B19 may be associated with childhood idiopathic thrombocytopenic purpura (ITP) [6]. But whether parvovirus B19 infection causes autoimmune diseases or just clinical mimicry deserves further investigation.

In the present study, we analyzed the results of anti-B19 IgM and autoimmune antibodies in women and children in our hospital, we demonstrated that B19 infection could promote the production of anti-nuclear antibody (ANA) and anti-Sm antibody, but not anti-double stranded DNA antibody (anti-dsDNA), and the titer of autoantibodies was associated with the content of anti-B19 IgM, which means that the status of infection may associate with the titer of autoantibodies in parvovirus B19 infected patients.

Materials and methods

Study population

Data of ANA and Parvovirus B19 IgM of 512 patients were obtained retrospectively from the laboratory information system during 2016–

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2018 in our hospital (Southern Medical University Affiliated Maternal & Child Health Hospital of Foshan, Foshan, China), only subjects who have simultaneous tested ANA and Parvovirus B19 IgM can be selected. Patients who have already been diagnosed with autoimmune disease but Parvovirus B19 IgM was negative were included as control group.

Laboratory analysis

Venous blood was collected using separation gel coagulation promoting tubes, then centrifugation at 4,000 g for 5 min. Detection of serum parvovirus B19 IgM was performed utilizing SERION ELISA classic Parvovirus IgM kit (ESR122M, SERION, Germany) according to the manufacturer's protocol. For ANA, anti-dsDNA and anti-Sm detection, we used semi-quantitative ELISA method by UNION Immunoassay Analyzer (YHLO, China).

Statistical analysis

GraphPad Prism was used for the statistical analysis. All data were presented as the mean \pm SEM. The differences in the means between two groups were analyzed using two-tailed t-tests. A one-way ANOVA, followed by Turkey's multiple comparisons test, was used to compare multiple data sets.

Results

Information of included patients

A total of 593 patients were included in this study, among which 118 were children, the remaining were women of childbearing age. Patients who have already been diagnosed with autoimmune disease but without B19V infection were included as control group.

One hundred three patients were parvovirus B19 IgM positive, among which 84 were women of childbearing age. The clinical manifestations of parvovirus B19 infection were not specific, in women, parvovirus B19 antibodies were tested due to infertility and recurrent miscarriage. In children, the most common symptom of parvovirus B19 IgM positive patients was thrombocytopenia. Age information of included patients is shown in Table 1.

Parvovirus B19 associated autoantibodies upregulation in women

To clarify if autoantibodies would be upregulated in parvovirus B19 infected patients as it has been reported, the relationship between the level of autoantibodies and parvovirus B19 IgM was analyzed.

In women of childbearing age, the B19 virus detection is very important for its close relationship with recurrent miscarriage, and it may pose a potential hazard to the fetus. Here the relationship between autoantibodies and B19 IgM in women was analyzed, 475 women were included, among which 51 were parvovirus B19 IgM positive, 33 were weakly positive. The results shows that positive B19 IgM was associated with ANA and anti-Sm upregulation, while no significant difference was found in anti-dsDNA (Table 2).

Parvovirus B19 could induce the production of autoantibodies, but whether the level of autoantibodies was associated with the titer of B19 virus was not reported. Here in our hospital, we did not have the DNA results of B19 virus, we use IgM to reflect the infection status of Parvovirus B19. And we found out that in B19 IgM positive group, the ANA level was much higher than the weakly positive group (60.80 ± 15.25 vs. 33.77 ± 5.93), but compared to the control group, the ANA level was much lower. Suggesting that the level of autoantibodies increased in the acute phase of Parvovirus B19 infection, but did not reach the level in autoimmune disease.

Parvovirus B19 infection in children

Children are more susceptible to B19 virus, the clinical manifestation of whom are also more serious.

Among 97 children who were simultaneously tested B19 IgM and autoantibodies, 19 were B19 IgM positive, 78

Table 1: Age information of included patients.

Parvovirus B19 IgM	-	\pm	+	Control
Age of women, years	28, 3 \pm 5.0	29, 4 \pm 4.6	29, 6 \pm 5.3	30, 7 \pm 4.8
Age of children, years	3, 7 \pm 1.2	3, 1 \pm 1.0	3, 5 \pm 1.4	3, 0 \pm 0.9

All information is presented as mean \pm SD.

Table 2: The level of autoantibodies in Parvovirus B19 infected women.

Parvovirus B19 IgM	ANA	anti-dsDNA	anti-Sm
- (n=331)	25.61 \pm 1.55	12.42 \pm 0.81	1.72 \pm 0.05
\pm (n=33)	35.51 \pm 7.93 ^b	9.82 \pm 1.31	2.93 \pm 0.37 ^b
+ (n=51)	47.13 \pm 9.69 ^a	12.82 \pm 1.43	2.98 \pm 0.26 ^b
Control (n=60)	113.1 \pm 13.15 ^a	29.82 \pm 4.53 ^a	2.94 \pm 0.13 ^b

"-" is negative, "+" is positive. All results are presented as mean \pm SD. ^ap<0.01, compared with the negative group, ^bp<0.05, compared with the negative group.

were negative. As there were only 19 positive cases, we didn't divide them into positive and weakly positive group as above. Comparing autoantibodies of the two groups, patients in positive B19 IgM group have significantly higher ANA and anti-Sm but not obvious in anti-dsDNA (Table 3).

Comparing data in Tables 2 and 3, ANA level was higher in children than adult women, and this was more obvious after B19 infection ($p < 0.05$), suggesting that in the group of children there are more acute infection cases.

Discussion

The role of parvovirus B19 in the pathogenesis of autoimmune disease has garnered significant interest. Here, we found that parvovirus B19 infection robustly increases the production of ANA and anti-Sm, especially in children, the increase of autoantibodies is more obvious. Taking together, these data indicate the close relationship between parvovirus B19 and autoantibodies upregulation in women and children.

As it has been reported, parvovirus B19 infection could stimulate the production of autoantibodies, include ANA, anti-dsDNA, and other anti-nuclear soluble antigen antibodies [7]. Here we observed that along with a high-level parvovirus B19 IgM titer, the content of autoantibodies will also increase, but we did not found a correlation between anti-dsDNA and parvovirus B19 IgM. Anti-Sm antibody was also analyzed, as SLE is the most reported autoimmune disease associated with parvovirus B19 infection. We observed that anti-Sm was also higher in parvovirus B19 IgM positive group, but the antibody titer was much lower than the upper limit of the normal reference range. Prompt that the increase of anti-Sm may not be clinically meaningful.

Researchers have observed that some patients with parvovirus B19 infection have the similar manifestation of

autoimmune diseases [8, 9], chronic infection induces the production of anti-virus antibodies with autoantigen binding properties [4]. Until now, many autoimmune diseases have been proved to be associated with this virus [1, 10], but whether B19 infection could induce autoimmune disease did not come to a conclusion yet. Most of the patients infected by parvovirus B19 did not develop into classic SLE or other autoimmune diseases [9], thus many researchers believe that parvovirus B19 associated autoimmune disease like symptomatology may just clinical mimicry [5, 11].

Besides, Patients with autoimmune disease often have an abnormal immune function, and more susceptible to parvovirus B19 infection. Milda Naciute et al. [12, 13] reported that B19 virus could modulate the levels of cytokines in the plasma of rheumatoid arthritis (RA) patients and regulatory T-cells, thus to lower antiviral clearance of B19 and leads to activation of persistent human parvovirus B19 infection. It is rather complicated to say whether parvovirus B19 infection induced autoimmune diseases, or patients with autoimmune disease have a higher parvovirus B19 infection rates. And further research is needed to clarify if chronic parvovirus B19 infection could induce the occurrence of autoimmune diseases.

Here we compared the autoantibodies level between parvovirus B19 IgM positive and weakly positive groups, we observed that that the elevated level of autoantibodies is related to parvovirus B19 IgM level. This result prompt that in the acute phase of infection, the level of autoantibodies is higher, may partially support the view that autoantibodies transiently increase during parvovirus B19 infection.

In children, it has been reported that parvovirus B19 infection could induce ITP [6], and patients suffered from ITP has a higher parvovirus B19 infection incidence [14]. Here, in our hospital, in B19 virus-infected children, ANA level was significantly higher than that in B19 IgM negative group. Meanwhile comparing with female patients, ANA upregulation in children was much more obvious, thus we speculate that children are more susceptible to B19 virus and there are more acute infection cases in children. As only 19 positive cases of children were included, more data are needed to support our results. As shown in Tables 2 and 3, the ANA level in B19 IgM negative group in children was higher than that in women, we speculate that this is because most of the 97 children were diagnosed as allergic purpura or thrombocytopenia, which could also be caused by cytomegalovirus, Epstein-Barr virus and other viruses [15, 16]. As only 19 positive and 78 negative cases of children were included, more data are needed to support our results.

Table 3: Upregulation of autoantibodies in Parvovirus B19 infected children.

Parvovirus B19 IgM	ANA	Anti-dsDNA	Anti-Sm
- (n=78)	46.85 ± 7.10	13.09 ± 0.97	1.91 ± 0.08
+ (n=19)	86.15 ± 25.30 ^a	13.12 ± 1.88	2.26 ± 0.45
Control (n=21)	127.94 ± 15.85 ^b	28.882 ± 4.01 ^b	2.71 ± 0.15 ^b

“-” stands for negative, “+” is positive. All results are presented as mean ± SD. ^a $p < 0.05$, compared with the negative group. ^b $p < 0.01$, compared with the negative group.

Conclusions

In summary, our results show that Parvovirus B19 infection is related to autoantibodies production in both women and children, and the status of infection may associate with the titer of autoantibodies in parvovirus B19 infected patients.

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Ethical approval: The study was approved by the Ethics Committee of Southern Medical University Affiliated Maternal & Child Health Hospital, Foshan (China), and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013). All participants gave their written informed consent forms.

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