CASE REPORT

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Congenital cytomegalovirus infection in a preterm infant with 22q11.2 deletion syndrome and immunological abnormalities

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ABSTRACT

The 22q11.2 deletion syndrome has many complications; one of them is immunodeficiency. However, the time of onset and the degree of immunodeficiency can vary. We report a case of a preterm infant with congenital cytomegalovirus infection complicated with 22q11.2 deletion syndrome and immunological abnormalities. Ultrasonography revealed pulmonary atresia, ventricular septal defect, major aortopulmonary collateral artery, and thymic hypoplasia. His serum chemistry tests on admission revealed immunoglobulin G, A, and M levels of 1,547 mg/dL, 70 mg/dL, and 274 mg/dL, respectively. A surface antigen analysis of the peripheral lymphocytes using flow cytometry revealed the following: relatively low CD4-positive T-cell levels (18.1%; 1,767/μL), very high CD8-positive T-cell levels (58.9%; 5,751/μL), and CD4/CD8 ratio of 0.31. The level of T-cell receptor excision circles was relatively low at 17.5 copies/μL. After birth, the CD8-positive T-cell level began to gradually decrease, whereas the CD4/CD8 ratio began to increase. Thrombocytopenia, neutropenia, and skin petechiae were observed on admission. However, the condition improved. Treatment for congenital cytomegalovirus infection was not provided due to the absence of viremia. Unfortunately, the patient died suddenly on the 158th day of life, and the cause of death was unknown. To the best of our knowledge, no association between 22q11 deletion syndrome and cCMV has been described in the recent medical literature. According to the calculation, around one newborn infant who have both 22q11 deletion syndrome and cCMV infection will be born each year in Japan. Healthcare providers should pay more attention to this medical situation in the future.

Keywords: 22q11.2 deletion syndrome, congenital cytomegalovirus infection, immunological abnormalities, surface antigen analysis

Abbreviations:
CMV: cytomegalovirus infection
TRECs: T-cell receptor excision circles

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INTRODUCTION

DiGeorge syndrome, conotruncal anomaly face syndrome, autosomal dominant Opitz G/BBB syndrome, velocardiofacial syndrome (Sphrintzen syndrome), and Cayler cardiofacial syndrome stem from a common genetic cause: a microdeletion on chromosome 22 at band 22q11.2.[1,2] Presently, the common term for all these syndromes is 22q11.2 deletion syndrome.[3] The syndrome has many complications, and one of them is immunodeficiency, which affects up to 75% of pediatric patients with 22q11.2 deletion syndrome. However, the time of onset and the degree of immunodeficiency varies. Congenital cytomegalovirus infection (cCMV) is the most frequent congenital viral infection, and the prevalence of cCMV infection has increased by up to 0.2–6.1% worldwide.[4]

We share our experiences with a preterm patient with cCMV who had 22q11.2 deletion syndrome, his immunological abnormalities, and its chronological change in a few months at birth. Unfortunately, the patient died suddenly on the 158th day of life. This case report may stimulate a discussion about the immunological situation of congenital viral infection in patients with 22q11.2 deletion syndrome.

CASE PRESENTATION

A male infant was delivered naturally at 33 weeks gestation because of early labor contractions. He weighed 1,555 g, and his length was 39.0 cm at birth. Thus, he was symmetrically small for his gestational age. The mother was 33 years old. This was her second pregnancy with natural conception, and the patient's male sibling was 2 years old. Fetal growth restriction and congenital heart disease were detected through ultrasonography at 28 weeks of gestation in our hospital. A pediatric cardiologist performed fetal ultrasonography, which suggested pulmonary atresia with ventricular septal defect and major aortopulmonary collateral artery. Physical examination revealed characteristic facial features such as low-set ears, micrognathia, hepatomegaly (3 cm below the costal margin), and skin petechiae. Ultrasonography revealed pulmonary atresia, a ventricular septal defect, a major aortopulmonary collateral artery, and thymic hypoplasia. Based on these complications, we suspected underlying chromosomal abnormality.

Chromosomal analysis using fluorescence in situ hybridization and G-Banding after birth revealed 22q11.2 deletion syndrome. His serum chemistry tests at birth revealed immunoglobulin G, A, and M levels of 1,547 mg/dL, 70 mg/dL, and 274 mg/dL, respectively, and a C-reactive protein level of 0.33 mg/dL (Table 1). So, we suspected congenital infection or immunological abnormality. His serum antibody levels of immunoglobulin M and immunoglobulin G against the CMV were 24.9 mg/dL and 1.19 mg/dL, respectively. He was diagnosed with cCMV based on the detection of CMV DNA in the urine on a polymerase chain reaction test. A computed tomography scan confirmed thymic hypoplasia.

His serum antibody titers of immunoglobulin M against the herpes simplex virus were 3.79 EIA value, 3.29 EIA value, and 0.28 EIA value on the 7th, 10th, and 33rd day of life, respectively. The polymerase chain reaction test did not detect herpes simplex virus DNA in the serum, and we suspected the results to be false-positive due to the presence of immunological abnormality. A surface antigen analysis of the peripheral lymphocytes by using flow cytometry revealed the following: The percentage and the absolute number of CD4-positive T-cells was 18.1% and 1,767/μL, respectively, and the percentage and the absolute number of CD8-positive T-cells was 58.9% and 5,751/μL, respectively, and the CD4/CD8 ratio was 0.31. Compared to the normal range for the absolute counts at this age (medians, 5–95% CI of CD4 T-cells and CD8 T-cells

Table 1 Immunological investigation

		DOL 0	DOL 8	DOL 34	DOL 41	DOL 148
White blood cell	/μL	21,700	15,500	11,600		10,000
Lymphocyte	%	29.7	63.0	71.5		70.0
Neutrophil	%	65.4	13.0	18.5		22.0
Basophil	%	1.1	0	1.0		1.0
Eosinophil	%	0.2	2.0	2.0		1.0
Monocyte	%	3.6	12.0	6.5		6.0
Hemoglobin	g/dL	18.3	15.2	14.1		15.4
Platelet	/μL	14.0×10^4	14.0×10^4	15.9×10^4		23.3×10^4
Lymphocyte	/μL	6,445	9,765	8,294		7,000
CD3+	%		75.6	62.3		54.0
CD19+	%		8.6	17.7		32.9
CD3+CD4+	%		18.1	18.4		21.6
CD3+CD8+	%		58.9	46.4		32.5
CD4/CD8	%		0.31	0.40		0.67
CD3-CD56+	%		9.6	10.8		
IgA	mg/dL	70	35	11		15
IgG	mg/dL	1,547	1,323	1,052		449
IgM	mg/dL	274	200	84		23
Con A	cpm				40,400	
PHA	cpm				34,500	
TRECs	copies/μL				17.5	
KRECs	copies/μL				201	
RNase P	copies/μL				6,540	

DOL: day of life
IgA: immunoglobulin A
IgG: immunoglobulin G
IgM: immunoglobulin M
Con A: concanavalin A
PHA: phytohemagglutinin
TRECs: T-cell receptor excision circles
KRECs: K-deleting recombination excision circles
RNase P: ribonuclease P

are 1345, 612–2701, and 667, 312–1389, respectively), the absolute number of CD8 T cells was at a very high level in this patient.[5]

Gradually, the CD8-positive T-cell level began to decrease from the 34th day of life, whereas the CD4/CD8 ratio began to increase from the 34th day of life (Table 1). T-cell receptor excision circles (TRECs) are a reliable indicator of new T-cells emigrating from the thymus and have advantages as markers of thymic function. In a review of TREC-based newborn screening for

severe combined immunodeficiency disease,[6] the cutoff TREC level was 20–252 TRECs/μL. The level of TRECs was 17.5 copies/μL in our patient, indicating that our patient's T-cell generation was impaired. We evaluated his central nervous system. Hearing loss, abnormal neuroimaging in computed tomography and magnetic resonance imaging, seizures in electroencephalography, and chorioretinitis in ophthalmoscopy were not detected.

Thrombocytopenia, neutropenia, and skin petechiae were detected after birth. However, the conditions improved spontaneously within 5–6 weeks after birth. Moreover, as he had no viremia of cCMV, we did not provide treatment for cCMV. He was discharged on the 41st day of life with home oxygen therapy and antimicrobial prophylaxis. After discharge, the ratio of CD4/CD8 increased to 0.66 on the 148th day of life (Table 1). The patient died suddenly on the 158th day of life. The cause of death was unknown. An autopsy was not performed because we could not obtain consent from his parents. Our investigation was approved by our institution's Research Ethics Committee (approval ID 2701). Written informed consent was obtained from the parents for publication of the case.

DISCUSSION

The most common chromosomal microdeletion disorder is 22q11.2 deletion syndrome. The prevalence of this disorder is approximately 1 in 3,000 to 1 in 6,000 live births.[7] The prevalence of cCMV infection has increased by up to 0.2–6.1% worldwide.[4] According to this calculation, around one or two newborn infants who have both 22q11 deletion syndrome and cCMV infection will be born each year in Japan. Infants with 22q11.2 deletion syndrome usually have major congenital malformations, including congenital heart diseases, chronic infection, hypocalcemia, feeding difficulties, and developmental and language delays. As with the other phenotypic features, there is a broad range of immunologic defects in patients with chromosome 22q11.2 deletion syndrome, which affects up to 75% of pediatric patients with 22q11.2 deletion syndrome because of thymic hypoplasia and impaired T-cell production. However, the degree of immunodeficiency varies.[8,9]

To our knowledge, there have been no previous reports of 22q11.2 deletion syndrome complicated with cCMV. Some case reports in infants with 22q11.2 deletion syndrome and acquired CMV after birth have been described.[10,11,12] Lingman et al reported a retrospective analysis of TREC-based newborn screening results and phenotypes in infants with 22q11.2 deletion syndrome.[12] In this review, a patient with abnormal TRECs copies was diagnosed with severe CMV infection at 3.5 months of age. The patients with almost complete thymic absence died at 5 months of age following thymic transplantation. The prognosis of CMV infection is thought to be related to the size of the thymus in 22q11.2 deletion syndrome.

There are three discussion points about the immunological situation raised regarding this patient. The first point is the extremely high level of CD8+ T-cells at birth in the patient. In our patient, the absolute number of CD4+ T-cells was relatively low, but that of CD8+ T-cell level was very high (5,751/μL; median 667, range 312–1389 in reference). A review paper has shown that CD8+ T cells were normal or slightly decreased in 22q11.2 deletion syndrome patients.[13] On the other hand, Marchant et al reported that human CMV infection in fetal life induces the oligoclonal expansion of differentiated CD8+ T lymphocytes.[14] It might be plausible that the patient had tried to eradicate CMV in utero. He had no CMV viremia and seemed to successfully fight against CMV at birth. However, we still do not understand whether the extremely high level of CD8+ T-cells is a particular finding in 22q11.2 deletion syndrome or not.

The second point is the extremely high levels of immunoglobulins in the patient's cord blood.

He showed high levels of not only IgM but IgG and IgA in his cord blood, even though he was a preterm patient. Usually, a fetus is not able to effectively produce IgG in utero, and IgG in cord blood is transferred from his mother through the placenta. However, the patient showed not only high levels of IgG but also IgA, which cannot pass through the placenta. Therefore, it should be plausible that the patient produced high levels of IgG and IgA himself. Bluestone et al reported in 1973 that the ranges of IgG, IgA, and IgM in patients with asymptomatic cCMV infection were 470–2050 mg/dL, <32–275 mg/dL, and 36–140 mg/dL, respectively.[15] However, we could not find any paper which showed high levels of immunoglobulins in the cord blood of preterm patients with cCMV. It might be possible that the relatively low function in CD4+ T-cells, including regulatory T-cells, was related to the high-level production of immunoglobulins in the patient with 22q.11.2 deletion syndrome. More information about this finding in such patients should be accumulated.

The third point is TREC, Kappa-deleting recombination excision circles, and change of immunological situation after birth in patients with 22q11.2 deletion syndrome. The level of TREC was relatively low in this patient, suggesting insufficient immune status. TRECs are a reliable indicator of new T-cells emigrating from the thymus and have advantages as markers of thymic function. In a review of TREC-based newborn screening for severe combined immunodeficiency disease,[6] the cut-off TREC level was 20–252 TRECs/μL. As abnormal TREC assays are associated with a high false-positive rate in premature infants,[16] the TREC assay was performed at corrected 39 weeks of gestation in our patient.

Our patient had immunological abnormalities from birth, but he had a hypoplastic thymus, and the levels of TRECs were relatively high compared to that of patients with SCID. Therefore, the immunological abnormalities were not so severe, and the symptoms of CMV infection may have been mild. In the patient, CD4 and CD8+ T cells and immunoglobulin levels were gradually improved after birth. His level of Kappa-deleting recombination excision circles was also maintained within the normal range. As a review mentioned, immunological functions in patients with partial DiGeorge syndrome with hypoplastic thymus may be improved after birth. From these points of view, we do not necessarily think that the patient had a severe acute infection at the time of his death.

According to the calculation, one or two newborn infants who have both 22q11.2 deletion syndrome and cCMV infection will be born yearly in Japan. Newborn screening using TREC may be important in 22q11.2 deletion syndrome patients in the future. Healthcare providers should give more attention to this medical situation, and we should accumulate more information about immunological function and prognosis in such patients.

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FINANCIAL DISCLOSURE

The authors have no financial relationships relevant to this article to disclose.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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