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CASE REPORT

Cytomegalovirus infection – the need for detailed differential diagnostics

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Abstract

Background: Cytomegalovirus infection represents the most common congenital and acquired infection. The symptomatology is very broad and usually non-specific, ranging from asymptomatic forms to status with organ damage or even to severe systemic infection. This makes CMV infection mimic other disorders and diseases.
Case description: Here we report two cases of CMV infection diagnosed after the second month of life in children who were referred to the infectious disease ward for extended diagnosis. Despite the late identification of infection, the clinical manifestation (psychomotor retardation, hearing loss, lenticulostriate vasculopathy) suggested a diagnosis of congenital infection was highly probable.
Discussion and evaluation: The further diagnostic process led to the correct diagnoses of congenital heart defect and cystic fibrosis, and administration of adequate specialist treatment.
Conclusions: CMV infections are common and it is worthy to remember that the diagnosis of CMV infection can be not the only one in multisymptomatic infants so the thorough differential diagnostics is necessary.
Keywords: cystic fibrosis, congenital infection, psychomotor retardation, cytomegalovirus infection, heart defect

Introduction

Even though cytomegalovirus infection is common in the population, diagnostic and therapeutic challenges are still encountered in clinical practice; this is particularly true in the case of congenital CMV infection. The symptoms of CMV infection may also be the same for other diseases, and since it is common in infants, its identification should not prompt one to abandon the process of full differential diagnosis. The cases reported below concern confirmed CMV infections that had probably been acquired and

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had an asymptomatic course, whereby the observed signs and symptoms, although coincidentally similar to those appearing in congenital infections, resulted from other serious conditions.

Case 1

A 6-month-old girl, diagnosed with psychomotor retardation, was referred to our department following a diagnosis of CMV infection. The child was a full term-neonate, of the second pregnancy and second birth, with a birth weight of 3520 g and 10 points on the Apgar scale. The first (screening) hearing test was normal. Psychomotor retardation was observed from the second month of life. Physical examination revealed dysmorphic features (flat occiput, wide-set eyes, low-set ears, short neck). Moreover, generalized hypotonia was observed. A consultation with a neurologist took place, and intensive rehabilitation was initiated. An outpatient transfontanelle US scan revealed lenticulostriate vasculopathy. The diagnosis was extended to include serology tests which showed positive IgM and IgG anti-CMV antibodies. The girl was referred to the hospital (at the age of six months) with a suspicion of congenital cytomegalovirus infection. In our department additional test results were as follows: urine CMV PCR – positive; blood CMV PCR 1000 copies/ml; CSF CMV PCR – negative. It was not possible to perform a CMV PCR test on the dried blood spot collected from the newborn screening test. The ABR test showed profound hearing impairment. Because of the child's age at the diagnosis, it was impossible to determine whether the infection was congenital or acquired, but the signs (lenticulostriate vasculopathy, hearing loss and psychomotor retardation) and confirmed positive CMV PCR tests made a diagnosis of congenital infection highly probable. On admission to our department both high-frequency, loud, grade IV/VI systolic murmur along the left sternal border and tachycardia were found. The circulatory insufficiency was diagnosed and the treatment started. Cardiac ECHO demonstrated a transitional atrioventricular septal defect. Soon some improvement was seen in the child's psychomotor development. At 13 months, the congenital heart defect was repaired, and within 3 months after the cardiac surgery, the child's psychomotor development improved significantly. The girl started to walk at the age of 21 months, and a follow-up ABR examination revealed normal hearing. Due to subtle dysmorphic features, the child was referred to the Genetics Clinic; the test results returned normal.

Case 2

A 2.5-month-old boy was admitted to our so that diagnosis of a cytomegalovirus infection could be continued and treatment begun. The child was born at 39 weeks of gestation (para 1, gravida 1, natural delivery) with a birth weight of 3300 g and Apgar score of 10. The maternal obstetric interview disclosed controlled gestational diabetes (dietary management), Hashimoto's thyroiditis (euthyroid), a normal TORCH screen and tests for other infectious agents; the mother was not tested for a CMV infection. The results of neonatal screening and hearing tests were normal. Due to poor weight gain (about 300 g per month; the boy was fed with expressed breast milk) and persisting diarrhoeal stools (watery, celadon in colour), an outpatient CBC was ordered which revealed significant anaemia (Hb 8.5 g/dl). The child was initially referred to the district hospital where packed red blood cells were transfused, and then the boy was transferred to a university hospital. Upon admission to the clinical ward, the physical examination revealed pale skin with numerous, fine papular lesions with signs of superinfection and a haemorrhagic component at the elbow flexor surfaces, inner thighs, chin and neck, and pitting oedema, mainly of the lower legs. The laboratory findings were as follows: evident improvement of red blood cell parameters (Hb 10.9 g/dl, Hct 32.2%), thrombocytopenia (118 000/µl), hypoproteinaemia (24.5 g/l), hypoalbuminaemia (11.5 g/l), elevated transaminases ALT 71 U/l, AST 107 U/l (RR ALT 0–55 U/l, AST 5–34 U/l) signs of cholestasis GGT 152 U/l (RR 12–64 U/l), coagulation disorders (prolonged PT, hypofibrinogenaemia), and signs of subclinical hypothyroidism. Stool analysis revealed occult blood, while serology was positive for IgM and IgG antibodies against CMV and Parvovirus B19. CMV DNA was found in the urine (by PCR). It was not possible to test for CMV PCR on the dried blood spot from the screening sample taken at birth. An abdominal US scan revealed a thickened, hypoechoic gallbladder wall. An elemental formula was administered for feeding with a good result. The child was transferred to our department for extended diagnosis and possible treatment of the CMV infection. In our department, vertical and active infections with Toxoplasma gondii, HCV, HSV and HIV was excluded. In an ophthalmologic examination no irregularities were found. The alpha-1 antitrypsin and ceruloplasmin concentrations were normal. The patient was still fed with an amino acid formula, and vitamin supplementation was begun with good tolerance and with weight gain. The entire clinical picture indicated a cytomegalovirus infection with concomitant enteritis. Furthermore, a sweat test was performed as part of the diagnostic workup and revealed a high sweat chloride level 110 mmol/L (RR 20–40 mmol/L). The boy was immediately referred to

a cystic fibrosis clinic. Finally, genetic tests confirmed a classic (typical) form of cystic fibrosis.

Discussion

Cytomegalovirus is a species-specific virus and is one of the eight human herpesviruses (HHV5); taxonomically, it belongs to the family *Herpesviridae* and the subfamily *Betaherpesvirinae*. It is characterized by a long incubation period (4–8 weeks), long replication (24–72 hours) and may also be a significant factor in the reactivation of other herpesviruses. The worldwide prevalence of CMV infection is estimated at 40–100% of the population and is highest in countries of a low socioeconomic status. Furthermore, CMV causes the most common congenital infection in developed countries (0.2–2.5% of live births) [3,4,7,10,11,12]. The pathogenicity of CMV depends on the immune status of the infected person. The most common signs and symptoms in immunocompetent individuals include fever, pharyngitis and tonsilitis, lymphadenopathy, hepato- and splenomegaly (not as pronounced as in EBV infection), rash multiforme, headache and weakness. Rare manifestations of CMV infection in immunocompetent individuals include pneumonia, colitis, meningitis, Guillain-Barré syndrome, myocarditis and pericarditis. Laboratory tests typically reveal lymphocytosis with atypical lymphocytes (10–35%), elevated transaminases, hyperbilirubinaemia, haemolytic anaemia and thrombocytopenia. Congenital infection can occur both during pregnancy (transplacental infection) and during birth (infection by contact with cervicovaginal fluid or blood). The risk of transmission exists both in primary maternal infection and in viral reactivation or infection with a different strain. Primary infection is associated with the great risk of vertical transmission (average 30–40%), which increases in consecutive months of pregnancy. The clinical presentation is most severe when infection occurs in the first half of pregnancy (this results from the direct pathogenic impact of CMV on the foetus and from placental damage that decreases transplacental blood flow and causes secondary hypoxia). The symptoms of the disease are only manifested after birth in 10–15% of infected children, whereas 85–90% remain asymptomatic. The symptoms can appear several months or years later. The clinical presentation depends on the timepoint during pregnancy at which foetal infection occurred. Infection in the first or second trimester of pregnancy usually results in severe organ injury and in extreme cases may lead to miscarriage or intrauterine foetal death. It is acute, generalized and the most serious form of congenital CMV infection. The findings in the physical examination include hypotrophy, microcephaly, hepatosplenomegaly, petechiae, a “blueberry muffin”

rash, and muscle tone disorders or seizures. Infection in the second/third trimester of pregnancy mainly results in the "organ-related" clinical course of the disease and manifests as pneumonia, hepatitis, enteritis, chorioretinitis, myocarditis, aseptic meningitis or bone marrow involvement. Neonates infected in the third trimester of pregnancy tend to be asymptomatic after birth (asymptomatic congenital CMV infection) or present with a mild form of lymphadenopathy, hepatosplenomegaly, hepatitis or pneumonia. Severe long-term consequences, mainly progressive hearing loss (sensorineural in nature), vision disorders (abnormalities of the posterior eye segment, strabismus) and impaired development of mental and motor functions, occur in 5–15% of patients. The most common laboratory findings are anaemia, neutropenia, lymphocytosis or lymphopenia, thrombocytopenia, elevated aminotransferases (typically not higher than 200–300 IU/L; may persist for many weeks or months) as well as elevated alkaline phosphatase and γglutamyltransferase. Approximately 30% of neonates with hepatitis also have jaundice (increased concentrations of total and direct bilirubin). CSF findings usually show an elevated white blood cell count with a predominance of lymphocytes. In mild forms, each of these irregularities can be present as an isolated sign. Imaging abnormalities include CNS findings (lenticulostriate vasculopathy, calcification, ventriculomegaly, subependymal cysts, white matter lesions and brain developmental defects, and intracranial haemorrhage), hepato- and splenomegaly, ascites, echogenic bowel and generalized oedema. Perinatal infection may also occur while breast-feeding. It is estimated that the risk of this transmission is 58–69%. These infections are mostly asymptomatic or have a mild course [2,6,9,10,12,13]. The main diagnostic methods in CMV infection (congenital/acquired) include serology and molecular testing. The detection of the virus in urine or saliva using PCR in the first 21 days of the child's life is a "gold standard" in the diagnosis of congenital CMV infection. If the number of the virus copies in the urine exceeds 500 (0.5 × 103 copies/ml), it is indicated to extend the diagnostic process and test body fluids as well. Blood testing using this method should be treated as a supplementary examination since it is significantly less sensitive. The detection of CMV DNA in the CSF carries a poor prognosis. In immunocompetent individuals, infection usually resolves spontaneously. In the case of mononucleosis-like syndrome, the management is symptomatic [1,5,8,12,14]. None of the antiviral drugs currently used for adults in immunosuppression has been approved for the treatment of congenital cytomegalovirus infection in neonates. That is why treatment indications are determined individually. Candidates for therapy are neonates with a confirmed, symptomatic congenital CMV infection. Treatment should begin

as soon as possible after birth (within the first 28–30 days of life), and its duration depends on disease severity. The drug of choice is currently oral valganciclovir at a dose of 16 mg/kg every 12 hours (intravenous ganciclovir is used in patients who do not tolerate an oral form of the drug or with impaired intestinal absorption). According to international recommendations, it should last at least six weeks under the control of a serum drug concentration [1,8,12]. In the first case, a six-month-old child was referred to our department for an extended diagnosis following the detection of serology markers of CMV infection (IgM and IgG antibodies) and psychomotor retardation. Because of the child's age, the laboratory tests (blood PCR for CMV 1000 copies/ml, urine – a positive result) did not allow an unequivocal diagnosis of either a congenital or acquired infection, but the clinical presentation (lenticulostriate vasculopathy, psychomotor retardation and profound hearing loss) made a congenital infection highly probable. During hospitalisation, the girl was diagnosed with a transitional atrioventricular septal defect. The presence of this heart defect, which is associated with circulatory failure, was responsible for the signs and symptoms observed (lenticulostriate vasculopathy and psychomotor retardation), which is confirmed by the fact that these symptoms regressed after surgical correction of the cardiac defect [15,16]. The CMV infection was only a coincidence. Follow-up examinations revealed normal hearing parameters. In the second case, the 2.5-month-old boy was referred to hospital due to poor weight gain and significant anaemia. The entire clinical picture (diarrhoeal stools, fine papular skin lesions with signs of superinfection and a haemorrhagic component) and laboratory findings (positive anti-CMV IgM and IgG antibodies, positive urine PCR CMV test, anaemia, thrombocytopenia, elevated transaminases, signs of cholestasis, faecal occult blood) indeed indicated a symptomatic CMV infection, with the differentiation between a congenital or acquired infection being impossible. The meticulous diagnostic process led to the final diagnosis of classic cystic fibrosis. In this case the CMV infection was also a coincidence.

To sum up, CMV infection is a common infection. An extended diagnostic panel with CMV detection markers should be considered only in patients with immunodeficiency and in atypical, difficult situations. In a congenital CMV infection, laboratory irregularities and clinical signs and symptoms are similar to those seen in other TORCH infections, metabolic disorders, cardiac diseases, genetic conditions and sepsis. This has consequences in the form of the high probability of an overlap syndrome. In most cases, the detection of serological and molecular markers of infection at an age later than three weeks precludes the differentiation as to whether the infection is congenital or acquired. In each such case, one

should be very vigilant when conducting the diagnostic process and the test panel should be extended to include all diseases with a similar spectrum of clinical signs and symptoms.

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