Co-infection with *Mycoplasma pneumoniae* and cytomegalovirus resulting in an acute demyelinating polyneuropathy in a pediatric patient

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A co-infection with Mycoplasma pneumoniae and cytomegalovirus (CMV) resulting in an acute demyelinating polyneuropathy is reported in an immunocompetent girl. Two months following a respiratory infection, the patient showed a symptomatology consisting of weakness in lower limbs, followed by facial asymmetry and arm weakness. Serum *M. pneumoniae* antibodies were elevated and active CMV infection was diagnosed by polymerase chain reaction (PCR) performed on cerebrospinal fluid. Treatment with oral clarithromycin, intravenous immunoglobulins and ganciclovir was associated with rapid improvement and complete recovery.

It is very probable that clinical findings were secondary to the reactivation of CMV caused by persistent *M. pneumoniae* infection in the respiratory tract.

This may be the first report in the pediatric literature of a co-infection of *M. pneumoniae* and CMV resulting in peripheral nervous system involvement.

Key words: co-infection, demyelinating polyneuropathy, Guillain-Barré syndrome, Mycoplasma pneumoniae, cytomegalovirus, children.

Neurological complications of acquired cytomegalovirus (CMV) infection are very rare in immunocompetent pediatric patients and include encephalitis, meningitis, myelitis, and Guillain-Barré syndrome (GBS)[1]. CMV can sometimes be correlated to a co-infection with other pathogens, like *Mycoplasma pneumoniae* (*M. pneumoniae*). The authors report a 13-year-old immunocompetent female who two months after a *M. pneumoniae* infection developed peripheral nervous system involvement consisting of an acute demyelinating polyneuropathy due to a reactivation of CMV, detected by nested polymerase chain reaction (PCR) performed on cerebrospinal fluid (CSF). It is likely that the persistence of mycoplasma in the respiratory tract, causing elevated antibody levels, can represent non-specific immune reactivation of CMV with direct localization to the peripheral nervous system.

Case Report

The patient was a 13-year-old female, the first-born to non-consanguineous parents. She was born at 39 weeks of gestation by normal delivery after an uncomplicated pregnancy. Birthweight was 3,380 g; the perinatal period was uneventful and her psychomotor development was normal.

Two months before admission, the patient developed fever, cough, tachypnea and wheezing treated with an oral cephalosporin. These symptoms progressed for 7-10 days and a chest radiograph revealed interstitial infiltration in both lungs.

Two months later she presented with leg weakness with difficulty in climbing stairs and running; three days later she developed facial asymmetry and mild arm weakness. After 10 days, she was admitted to the Department of

Pediatrics of the University of Catania; her weight was 41 kg (25th percentile), height 156 cm (50th percentile) and head circumference 55 cm (75th percentile). On examination she was alert and afebrile; cardiovascular and respiratory inspection was normal. Abdomen was normotensive and tractable; liver and spleen were non-palpable.

Neurological examination revealed a left-sided peripheral type of facial palsy. The examination of all other cranial nerves was normal, as well as ocular funduscopy. There were no signs of meningeal irritation; muscle trophism and cerebellar tests were normal. Distal weakness was present, more evident in the legs. The muscular strength of the lower limbs, evaluated by Medical Research Council[2], revealed a score of 3. Sensation to pain, touch, and temperature and joint positions were normal. Deep tendon reflexes were symmetric with patellar hyporeflexia.

On laboratory investigations, peripheral white blood cell count was leukocytes 13,850/mm^3, lymphocytes 7,800/mm^3, monocytes 1,100/mm^3, SGOT 55 UI/L and SGPT 70 UI/L.

The following clinical and instrumental investigations were all within normal range: brain and spine magnetic resonance imaging (MRI), chest radiography, urinalysis, erythrocyte sedimentation rate, C-reactive protein, hemoglobin, red blood cell count, platelet count, glucose, serum urea, serum electrolytes, bleeding time, fibrinogen, immunoglobulins, IgA and IgG antigliadin antibodies, IgA antiendomysium antibodies, anti-transglutaminase antibodies, anti-GQ1b antibodies, anti-GM1 and GM2 antibodies, antibodies to Campylobacter jejuni, Epstein-Barr virus, Toxoplasma gondii, human immunodeficiency virus (HIV), Borrelia burgdorferi and Chlamydia pneumoniae.

Serum anti-M. pneumoniae antibodies, tested by a microparticle agglutination assay, were 1,320, and the serum immunoblot assay revealed positive IgA, IgM and IgG responses against *M. pneumoniae*. Serum anti-CMV IgG antibody titers were 32.0 UI/ml and anti-CMV IgM antibody titers were 4.79 IR,(0-0.9), suggesting the possibility of an acute CMV infection. Blood CMV antigen research by pp65 antigenemia assay was positive.

Cerebrospinal fluid protein was mildly elevated (60 mg/dl with a reference value < 0.40 mg/dl) with normal cell count; CSF/serum albumin was increased with a value of 9.6 (normal range 2.0-7.4). PCR for *M. pneumoniae* was negative and no antibodies to mycoplasma, enterovirus, herpes simplex virus, varicella-zoster virus, and echovirus were found in the CSF; search for viral DNA for CMV performed with nested PCR in the serum, saliva and CSF was positive.

Nerve conduction studies and needle electromyography showed decrease in motor conduction velocities and reduction of nerve action potential amplitude, with prolongation of distal latencies. These findings were consistent with an acute motor demyelinating polyneuropathy.

Therefore, specific therapy with oral clarithromycin for 10 days, intravenous immunoglobulins (IVIg) 1 g/kg/day for two days and ganciclovir 10 mg/kg/day for 21 days was started, with progressive clinical improvement and complete recovery one month from the onset of symptoms.

Discussion

The patient reported here showed a clinically and instrumentally well-documented acute demyelinating polyneuropathy. Just two months before the onset of neurologic symptoms, she presented with a lower respiratory tract infection due to *M. pneumoniae*, as documented by the presence and persistence of elevated serum antibodies. Active CMV infection was diagnosed by serum titers, antigenemia assay and by PCR performed on CSF.

The main pathological findings correlated to acquired CMV infection in childhood include encephalitis, meningitis, cranial nerve palsies, retinitis, myelitis, polymyeloradiculitis and GBS; these usually are more common in immunocompromised patients, above all in acquired immunodeficiency syndrome and in bone marrow transplantation[1]. Generally, the methods to detect human CMV infection are viral culture, serologic assay such as enzyme-linked immunoabsorbent assay (ELISA), antigenemia assay and conventional PCR; the latter has been very useful not only in aiding in the diagnosis but also in determining the severity and predicting infection[3]. Moreover, antigenemia and PCR are both very useful in the early detection of CMV reactivation, particularly after allogenic stem cell transplantation.

Guillain-Barré syndrome, or acute inflammatory demyelinating polyradiculoneuropathy (AIDP), is characterized by limb weakness and areflexia and is considered the prototype of postinfectious autoimmune disease; molecular mimicry in response to an antecedent infection is a possible mechanism[4].

The CMV infection is considered the most common viral antecedent and is identified in 10-15% of patients with GBS by the presence of CMV-specific IgM antibodies. Many reports assume the hypothesis that in acute CMV infection, anti-GM2 IgM antibodies are induced by molecular mimicry between GM2 and CMV antigens. The detection of CMV during neurological illness would support a close association between CMV infection and GBS[5]. Patients with CMV-related GBS have a different clinical pattern; in particular, they can show cranial nerve involvement and severe sensory loss[6].

In our patient, neurologic illness was preceded by bronchitis due to a *M. pneumoniae* infection. There is sometimes evidence of a co-infection of *M. pneumoniae* and other pathogens, such as the herpes virus group, especially in encephalitis cases[7]. One possible explanation of this phenomenon is that *M. pneumoniae* can induce a non-specific polyclonal antibody response and an activation of human lymphocyte subpopulations[8,9].

The present case showed some interesting aspects not previously reported in the literature. In fact, this is, to our knowledge, the first example of a co-infection of M. pneumoniae and CMV in an immunocompetent pediatric patient resulting in peripheral nervous system involvement.

The presence of positive antigenemia and CMV DNA in the CSF probably explains a reactivation of a CMV infection caused by persistence of a pneumotropic infective agent like *M. pneumoniae* in the bronchopulmonary tract (10), even if immune system activation against CMV would usually not result in PCR positivity because it should reduce it if the immune system is competent.

Another important aspect is represented by the course of the illness, with facial nerve involvement and exclusive motor compromise, not frequently reported in classical GBS. The lack of serum anti-ganglioside antibodies (anti-GM1, GM2 and GQ1b) furthermore seems to exclude, at the moment, a molecular mimicry between virus surface epitopes and cranial and peripheral nerves gangliosides.

With respect to the pathogenetic mechanism, it is assumable according to Tsiodras et al.[11] that the persistence of elevated anti-mycoplasma antibody levels could represent a non-specific immune activation of the CMV, even though the molecular and immunological mechanisms of the neurologic involvement are still unknown.

Further studies are necessary to analyze the relationships between *M. pneumoniae*, viral infections, immunological assessment and the central and peripheral nervous system.

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