The first presentation of X-linked agammaglobulinemia (Bruton) with vaccine-associated paralytic poliomyelitis: Case Report

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Abstract

Vaccine-associated paralytic poliomyelitis (VAPP) is a rare adverse event of Oral Polio Vaccine (OPV) due to mutation or reversion of the vaccine virus to a more neurotropic form. Herewith, we present the case of an Albanian child with X-linked agammaglobulinemia who appears for the first time with paralytic complication due to OPV. The patient is a 4-month old boy. The patient underwent a routine national vaccination schedule in Albania, receiving two doses of OVP administered at two and four months of age. Fifteen days after the second dose of OPV, he exhibited a prodromal picture with fever and irritability, followed by a generalized weakness. The first clinical examination showed a poor appearance, fever, hypotonia and abdominal breathing. His first faecal specimen was positive for Sabin type 3 strains. Laboratory evaluation revealed low levels of IgM, IgA and $CD19^{+}B$ and $CD20^{+}B$ cells of less than 1% of the lymphocyte population. The BTK gene analysis of the patient's DNA revealed the presence of the mutation c.[1922G>A] p.[R641H], according to the published data on this disease.

The patient presented suggests that a negative history for recurrent infections does not exclude the presence of a primary defect in the immune system. Vaccine-associated paralytic poliomyelitis (VAPP) may be the first presentation of some primary immunodeficient patients. Introduction of neonatal screening programs for immunodeficiencies such as SCID and XLA could help prevent inadvertent exposure of patients to OPV.

Keywords: OPV, vaccine-associated paralytic poliomyelitis, X-linked agammaglobulinemia.

Introduction

X-linked agammaglobulinemia (XLA) is a primary immunodeficiency caused by mutations in the gene for Bruton tyrosine kinase (BTK) that results in the deficient development of B lymphocytes (1,2). Affected individuals have hypogammaglobulinemia, markedly reduced levels of serum antibodies and markedly reduced levels of B cells (2-4). As a result, they have an increased susceptibility to a variety of infections caused by encapsulated bacteria and enteroviruses, microorganisms against which the antibodies play an especially critical role in host defense. X-linked agammaglobulinemia (XLA) is characterized by recurrent bacterial infections in affected males in the first two years of life. Vaccine-associated paralytic poliomyelitis (VAPP) may be a first presentation of X-linked agammaglobulinemia (3-7). The risk of VAPP ranges from 1 per 750,000 in the normal population to 7,000 times higher for people with certain types of immunodeficiencies, particulary B-lymphocyte disorder (e.g. agammaglobulinemia and hypogammaglobulinemia) (5,6,8-10).

Case presentation

The patient is a 5-month old male, with a normal perinatal period. His parents were healthy, and there was no condition indicating an immunodeficiency state in the relatives. The patient underwent a routine national vaccination schedule, receiving two doses of OVP administered at two and four months of age. Bacillus Calmette-Guerin (BCG) and Hepatitis-B vaccines were also applied during the first week after birth. Tetanus, diphtheria, pertussis (DTP) vaccine was administered at the ages of two and four months. The patient had been quite healthy until the age of five months, when he developed an acute paralysis. Upon admission to the hospital, the patient had a prodromal picture of fever and irritability for the previous 9-10 days, followed by generalized weakness. The first clinical examination showed a poor appearance, fever, hypotonic, tachypnea and abdominal breathing. Neurological examination revealed a normal mental status, normal cranial nerves and a flaccid paresis of the right leg and left arm, with impaired tendon reflexes and plantar response. The left lower extremity and right upper limb were normal. The sensory examination results were also normal.

The initial cerebrospinal fluid (CSF) examination showed pleocytosis (196mm^3); lymphocytosis 95% and neutrophils 5%. The electro-diagnostic (ENG) examination of the right leg indicated remote distal axonal neuropathy of the deep peroneal nerve. No abnormalities were observed in the brain and spinal MRI. Fecal specimens were sent to the Institute of Public Health in Tirana, Albania, and later to the Istituto Superiore di Sanità in Rome, Italy. The first fecal specimen was positive for Sabin 3 strain. The fecal cultures showed no Cox-B and Echovirus.

Laboratory results showed lymphopenia and anemia. The levels of immunoglobulin subclasses (IgA, IgM) were low and the $CD19^+$ and $CD20^+$B-lymphocytes count was diminished. The level of immunoglobulin G (IgG) was normal. HIV serology testing was negative.

Table 1. Imunophenotypic analysis

Markers	Results	Reference interval
CD3	90%	56.0-84.0%
CD4	64%	35.0-55.0%
CD19	0.0%	4.0-19.0%
CD20	0.0%	4.0-19.0%

Table 2. Immunoglobulin electrophoresis

Immunoglobulins	Results	Reference interval	Units
IgG	1060	470-1230	mg/dL
IgA	<6.67	21.0-145	mg/dL
IgM	5.7	47.0-175	mg/dL

The immunological data (the absent $CD19^+$ and $CD20^+$B lymphocytes in a male with hypogammaglobulinemia) favored a diagnosis of X-linked agammaglobulinemia. The patient was treated with intravenous Immunoglobulin and physical therapy. The fecal samples became virus-negative. Immunodeficiency of the patient was set under control, notwithstanding residual paralysis and atrophy of the right leg.

A decreased BTK protein function was recorded (with Flow Cytometry), with a substantially reduced number of B-Lymphocytes in the circulation and a reduction of the bone marrow populations of myeloid line (monocytes, granulocytes). This picture correlates well with the genetic change of the position of BTK. The analysis of BTK gene on the patient's DNA revealed the presence of the c.[1922G>A] p.[R641H] mutation, in accordance with the published data on this condition. Mother's fluorocytometric assays of myeloid cell line showed that she was not a carrier of genetic alterations of the BKT locus.

Discussion

X-linked agammaglobulinemia (XLA), or "Bruton agammaglobulinemia", is an inherited immunodeficiency disease, caused by mutations in the gene coding for Bruton tyrosine kinase (BTK) (8,9,11). BTK is necessary for the proliferation and the differentiation of B-lymphocytes (12-15). In the absence of functional BTK, mature B cells that express surface immunoglobulines and CD19-markers are few to absent. In the absence of mature B cells, patients lack lymphoid tissue and fail to develop plasma cells, which are the antibody-manufacturing cells. As a result, they have an increased susceptibility to a variety of encapsulated bacteria and enteroviruses. More than 90% of affected males present with unusually severe or recurrent sino-pulmonary infections and conjunctivitis. Meningitis, sepsis, osteomyelitis and gastrointestinal tract infections are less common initial manifestations of XLA (13,14). Infants typically develop recurrent otitis media, pneumonia, and sinusitis before the age of one year, but always after the first three months of life. The infectious agents involved are usually *S. Pneumoniae* or *H. Influenzae, type b*. Both are extracellular encapsulated bacteria (9,10,15-17).

Several authors have shown that the neurological signs compatible with vaccine-associated paralytic poliomyelitis (VAPP) may be the first presentation of agammaglobulinemia and hypogammaglobulinemia in children less than one year of age (16,17).

Oral Polio Vaccine (OPV) has been efficiently used for over 40 years and is associated with few adverse effects (15). Its most commonly recognized adverse event, vaccine-associated paralytic poliomyelitis (VAPP), is estimated by the World Health Organization to cause one per one million births and by minor (3,4) to cause about one case per 6.2 million doses of OPV distributed (15,16). This is because OPV contains live-attenuated viruses that sometimes become neurovirulent again – that is, it causes paralysis (9,14,17). Children with immunodeficiency have a risk of VAPP almost 7,000 times higher, particularly those with B-lymphocyte disorders (12,17,18).

Almost all immune-compromised infants are vaccinated with OPV at two, four and six months, when their immunodeficiency state is not identified. There is a potential risk for these patients to both develop paralysis and excrete the vaccine strains for long periods of time (11,19).

Our patient had been quite healthy until five months of age before the acute paralysis occurred. He had

received the first OPV dose at the age of two months. However, the paresis occurred one month after administration of the second dose. In some studies (17,19), the median interval between administration of the last OPV dose and iVAPP onset was reported as 3.1 months. Khesturiani et al. (20,21) found a median interval of 2.3 months. In addition, the median interval between the last OPV and onset of VAPP in the 23 iVAPV excretors reported during 1962-2004 was 0.6 years. According to some authors, iVAPP happened 7-14 days after they received the orally administered polio vaccine (OPV) (18,19).

All patients with Bruton agammaglobulinemia are males. Males with XLA have a total or almost total absence of B-lymphocytes and plasma cells. XLA is an inherited disease that occurs in approximately one out of 250,000 males. Female carriers show no clinical manifestations. The infection begins once the transferred maternal immunoglobulin G (IgG) antibodies have been catabolized, typically at the age of about six months. After the second month of life, the level of circulating maternal antibodies is very low or absent, facilitating an increased dissemination of the vaccinal virus (8,12).

The virulent strain isolated from our patient was a Sabin-derived type 3 virus. Same authors state that Sabin type 3 virus is associated with the highest rate of VAPP in immune competent patients, whereas type 2 has been the most prominent type of iVDPV (6,20). The World Health Organization (WHO) recommends that the laboratory diagnosis of poliomyelitis should be confirmed by isolation and identification of poliovirus in the stool, with specific identification of wild-type and vaccine-type strain (19,21,22). In suspected cases of acute flaccid paralysis, two stool specimens should be collected 24-48 hours apart, as soon as the diagnosis of poliomyelitis is suspected. Poliovirus concentrations in the stool are high in the first week after the onset of paralysis, which seems to be the optimal time for collection of stool specimen. As vaccinal enterovirus strains may still be eliminated through the feces for up to months after contact, they can be found even in samples collected 15-40 days after the onset of the symptoms. Some authors state that the shed viruses by the vaccinated people have undergone mutations and their neurovirulence is modified (17,20).

Ferraz-Filho et al. observed that MRI could be used in differentiating between vaccine-associated poliomyelitis and other conditions, and in assessing the extent of lesions (23). Other authors that studied poliomyelitis in India have concluded that MRI reveals signal changes in both substantia nigra and anterior horns of the spinal cord that could be of diagnostic significance in a child with poliomyelitis (24,25).

The final diagnosis of X-linked agammaglobulinemia (Bruton) with vaccine-associated paralytic poliomyelitis is based on the presence in a male child with asymmetric paralysis of marked reduction of serum immunoglobulin subclasses and low or absent $CD19^{+}$B cells and $CD20^{+}$B cells, and on the isolation and identification of the poliovirus in at least two stool specimens.

The analysis of BTK gene on the patient's DNA revealed the presence of the c.[1922G>A] p.[R641H] mutation, in accordance with the published data on this condition.

More than 600 different mutations in the BTK gene have been found to cause X-linked agammaglobulinemia (XLA). Most of these mutations result in the absence of the BTK protein. Other mutations change a single protein building block (amino acid), which probably leads to the production of an abnormal BTK protein that is quickly broken down in the cell. The absence of functional BTK protein blocks B-cell development and leads to a lack of antibodies, causing an increased susceptibility to infections in people with XLA (26).

The prognosis for children with XLA has improved in the last 30 years as a result of earlier diagnosis, development of preparations of Immune Gamma Globulin that allow normal concentration of serum IgG to be achieved and more liberal use of antibiotics. Treatment with pooled Gamma Globulin cannot restore a functional population of B cells, but it is

sufficient to reduce the severity and the number of infections due to the passive immunity offered by the exogenous antibodies.

Conclusion

The medical history of this patient suggests that a negative history for recurrent infections does not exclude the presence of a primary defect in the immune system. VAPP may be the first presentation of some primary immunodeficient patients. Introduction of neonatal screening programs for some immune deficiency states, such as SCID and XLA, could help in preventing an inadvertent exposure of affected patients to OPV.

Conflicts of interest: None declared.

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