Abstract
Recurrent meningitis is an uncommon life-threatening condition. Here, the case of a 6-year-old boy is reported who had two episodes of meningitis with an IgG3 subclass deficiency. The boy had aseptic meningitis at the age of 3 years, followed by bacterial meningitis at the age of 4 years. Primary immunoglobulin deficiencies are a group of disorders associated with an increased incidence and/or severity of infection. Recurrent infections, sinusitis, bronchitis, and pneumonia are the most frequently observed illnesses in patients with IgG subclass deficiencies, of which an IgG3 subclass deficiency is the most common, especially in adults. Although cases of recurrent viral or bacterial meningitis have been reported, herein a patient is presented with recurrence of aseptic and bacterial meningitis 1 year after the initial episode. Some researchers recommend that all children with episodes of recurrent meningitis should be screened for primary immunoglobulin or complement deficiencies.

Keywords: Recurrent meningitis, IgG3 subclass deficiency, Children.

Introduction
Meningitis is a severe life-threatening infection associated with a high rate of morbidity and significant disability among survivors. Recurrent meningitis is defined as at least two episodes of meningitis caused by different organisms or a recurrent episode caused by the same organism more than 3 weeks after the completion of therapy for the first episode. Potential long-term neurological sequelae include cranial nerve palsies, hemiparesis, hydrocephalus, and seizures, as well as visual and hearing impairments. Iatrogenic recurrent meningitis following a neurosurgical operation, otorhinolaryngological intervention or other cranial-maxillofacial surgical procedures resulting in cerebrospinal fluid (CSF) leakage are more common presentations. Recurrent meningitis in children should always prompt an investigation of the underlying cause, as it is usually associated with a predisposing factor, such as an immune deficiency or craniospinal defect.

Case Report
A 6-year-old boy presented with recurrent meningitis and an IgG3 subclass deficiency. The first episode of aseptic meningitis occurred at the age of 3 years; this was followed by bacterial meningitis at the age of 4 years. In March of 2010, during the patient’s first attack of meningitis, he was admitted to Bezmialem Vakif University Faculty of Medicine Hospital with a headache, fever, abdominal pain, nausea, and vomiting. Preauricular swelling had been observed by the boy’s family 2 days earlier. A neurological examination indicated neck stiffness. The results of a funduscopic eye examination and cranial computed tomography (CT) scans were normal. Blood tests revealed a normal white blood cell (WBC) count (9,200 mm^{-3}) and C-reactive protein level (0.5 mg L^{-1}). An examination of the boy’s CSF revealed a clear, colourless fluid with a WBC count of 86 mm^{-3} (86% lymphocytes), protein level of 0.55 g L^{-1}, and glucose level of 60 mg dL^{-1} (blood glucose: 89 mg dL^{-1}). Gram staining of the patient’s CSF was negative. Microbial agents were not detected in blood cultures or in the patient’s CSF; however, his blood amylase level was high and his serum test was positive for anti-mumps IgM antibodies. A diagnosis of aseptic meningitis was made secondary to mumps.

One year later, the boy again presented with a headache, vomiting, and neck stiffness. He was admitted to the hospital with a diagnosis of bacterial meningitis in June 2011. His peripheral WBC count was 28,700 mm^{-3} with a differential of 91% neutrophils. Serum level of C-reactive protein was 20.8 mg dL^{-1}. CSF examination revealed a WBC count of 1,450 mm^{-3} (86% multinucleated cells), elevated protein (2.4 g L^{-1}; normal: <45 mg dL^{-1}), and a low level of glucose (5 mg dL^{-1}; normal: >45 mg dL^{-1}). A diagnosis of bacterial meningitis was made. Streptococcus pneumoniae was identified in the patient’s CSF. The patient was given intravenous vancomycin and ceftriaxone. From his history, it was learnt that the patient had not suffered from recurrent or severe infections until
he was 3 years old. His childhood immunizations were up to date (including the MMR and pneumococcal vaccines), and he had no history of trauma, intracranial surgery, or other childhood medical illnesses.

Comprehensive immunological screening showed a low IgG3 level. The patient’s IgG3 level was 5.6 mg dL⁻¹ (normal range: 17-97 mg dL⁻¹); all other IgG subclasses were in the normal range, and his total IgG level was 650 mg dL⁻¹ (normal range for his age: 633-1280 mg dL⁻¹). Serological studies, including HIV, were negative. The patient’s IgA, IgM, and IgE levels and the results of a lymphocyte subset analysis were normal (CD19, CD4 count, CD8 count, and CD4/CD8 ratio). Immunologic studies revealed normal results as follows: C3, 117 mg/dL (86-166 mg/dL⁻¹) and C4, 26 mg dL⁻¹ (13-32 mg dL⁻¹). A complete blood count, renal and liver function tests, blood biochemical analysis, autoantibody studies, complement studies, chest X-ray, and paranasal sinus X-ray were normal. Testing for anti-mumps IgG was positive. A CT scan of the patient’s brain was normal.

The patient’s functional immunoglobulin response was assessed prior to and 2 weeks post immunization with a pneumococcal vaccine. The patient’s specific anti-pneumococcal antibody titer increased to an adequate level. Abdominal ultrasonography showed a normal spleen, and there was no evidence of Howell-Jolly bodies in his peripheral blood. The patient did not have any complications of meningitis. He had been well until the age of 6 years when he started to attend school. Then, he suffered from recurrent upper respiratory tract infections with mild symptoms of asthma. At his 9-month follow-up appointment, the patient had pneumonia. Consolidation of the right and left lower lobes was noted on chest X-ray. Nitro blue tetrazolium (NBT) staining was performed to rule out chronic granulomatous disease. The result was normal (NBT: 100%). A thoracic CT scan was suggestive of a pulmonary fungal infection but further detailed investigation revealed pneumococcal pneumonia. This case was followed for 2 years after the attack of bacterial meningitis. Intravenous immunoglobulin (IVIG) was initiated after the attack of pneumonia. The patient’s response was good, based on a decrease in both the frequency of infections and use of antibiotics.

Discussion

Several conditions have been reported to be associated with increased risk of meningitis, including immunodeficiencies, splenic dysfunction/absence, complement deficiencies, HIV infection, alcoholism, congenital basal skull defects and head injuries. Tebruegge et al.³ found 363 cases of recurrent bacterial meningitis in 2008 by retrospectively reviewing 144 publications for the last 20 years. Of these cases, 59% were related to anatomical problems, 36% were related to immune deficiencies and 5% were related to parameningeal infections. An anatomical abnormality was located in the cranial or cervical region in 93% of the cases and in the lumbosacral region in 7% of the cases.

An IgG3 deficiency can be detected based on recurrent respiratory infections and obstructive lung disease and it can be observed in association with an IgG1 deficiency. IgG3 is most frequently produced in response to protein antigens. IgG3 accounts for 4-8% of the total IgG; it is the heaviest subclass, with a molecular weight of 165,000 kDa. It has a short half-life of 9 days compared with 23 days for other IgG subclasses. IgG3 deficiency occurs less frequently in children than do other IgG deficiencies. Meyts et al.⁴ reported that six patients with an isolated IgG3 deficiency suffered from recurrent invasive sinopulmonary infections. De Baets et al.⁵ reported an equally high prevalence of IgG3 and IgG2 subclass deficiencies in a paediatric population with recurrent bronchitis. Snowden et al.⁶ reported the case of a young adult female who had suffered three episodes of lymphocytic meningitis of enteroviral etiology over a 5-year period due to an IgG3 deficiency.

Asymptomatic individuals with ≥1 subclass deficiencies, defined as levels >2 standard deviations below the age-dependent mean, do not require treatment; they represent 2.5% of the normal population.⁷ Patients with severe recurrent respiratory tract infections, meningitis, an IgG subclass deficiency and a selective antibody deficiency are candidates for treatment. Prophylactic antibiotics are the first-line treatment. If infections are frequent and severe, combination treatment with prophylactic antibiotics and immunoglobulins may be warranted. Thrice weekly IVIG treatment or weekly subcutaneous immunoglobulin treatment may be beneficial. An IVIG dose of 400-600 mg kg⁻¹ every 3-4 weeks or 100 mg kg⁻¹ subcutaneously can be used. The IVIG preparation used in this case did not contain enough IgG3, which has a short half-life. The peak levels of IgG3 following IVIG administration are normal but decrease rapidly.⁸ The presented patient had a single episode of pneumonia and two episodes of meningitis and was subsequently given IVIG, to which he responded well (a decrease in both the frequency of infections and use of antibiotics). At the time this report was prepared, the patient had been receiving monthly...
IVIG therapy for 6 months.

**Conclusion**

It should be kept in mind that IgG subclass deficiencies in children may be transient. The levels of IgG, IgM, and IgA should be measured in children who have a history of recurrent infections, including meningitis, sepsis, or recurrent respiratory tract infections.

**Acknowledgement**

Written informed consent was obtained from the patient’s parents for publication of this case report.

**References**


