Ataxia-telangiectasia (A-T) is a rare multisystem, neurodegenerative genetic disorder. We present a case of a 6-year-old girl who had a history of frequent respiratory infections and also had ocular and immunological features of this syndrome. The absence of neurological symptoms, which is very unusual for a patient of this age, raised many difficulties in the diagnosis of the disease. It is concluded that a normal neurological assessment must not exclude the diagnosis of A-T and delay the proper interventional measures.

Case History

A 6-year-old girl was referred to our department for further evaluation because she had been suffering from bronchitis since one month, which did not improve, despite therapy with bronchodilators and antibiotics. Her maternal grandmother and aunt had died from breast cancer, while her paternal grandfather had died from pancreatic cancer. The patient had no perinatal problems and her developmental milestones were normal. She had recurrent nasal infections and two episodes of bronchitis, which were treated with antibiotics. She showed improvement, but there was no resolution. She was coughing occasionally when drinking liquids.

On physical examination, the girl had no peripheral cyanosis or clubbing (SATO2: 97%). She was normocephalic, weight and height were between the third and fifth percentile. There were obvious telangiectasias on the bulbar conjunctiva bilaterally. She had purulent nasal discharge and some rales bilaterally without wheezing. Neurological assessment was normal. She had normal eye movements, normal cranial nerve examination, normal strength, muscle tone and tests of cerebellar function.

The girl was hospitalised and treated with intravenous antibiotics and bronchodilators for almost two months, with a very slow resolution of symptoms. A variety of diagnostic studies were performed. The patient had lymphopenia: WBC was normal (6500/mm³) but she had only 13% lymphocytes (absolute count 850/mm³). She also had low serum levels of IgA (<7 mg/dl), IgE (<2 IU/ml), IgG2 and IgG4, with normal IgG (551 mg/dl) and elevated IgM (319 mg/dl). Serum AFP was elevated (94 ng/ml, normal range 0-20 ng/ml) and absolute CD4 count was low. Serum complements, alpha1-antitrypsin and sweat chloride test were normal. RAST assays and virologic studies were negative. Subsequent laboratory tests documented persistent IgA deficiency, lymphopenia and elevated AFP serum level. Lymphoblasts were cultured and irradiated with 6 Gy in the G2 phase of the cell cycle. Chromosome fragility analysis showed an increased percentage of breaks (5 breaks/cell, normal <1.5). Moreover, after two successive mitoses no repair of these breaks was observed. A possible diagnosis of the A-Ô syndrome was suspected and a genetic laboratory test defined a homoygous specific mutation in the ATM gene. Protein truncation test was done, and the cDNA amplification products of unexpected size were sequenced, together with the relevant exons from genomic DNA. One pathological allele showed an abnormally spliced cDNA fragment: the skipping of exon 63 appeared to be caused by a transversion of the last nucleotide of the same exon (8850G>T). The patient was started on prophylactic infusions of IVIG 400 mg/kg every three weeks, cefaclor 20 mg/kg and fluticasone 50 mcg once daily. A cine-esophagopharyngogram showed oropharyngeal dysfunction in swallowing.

Discussion

The diagnosis of A-T syndrome is established in patients over one year of age who show ataxia or significant motor incoordination with a serum level of AFP more than twice the upper limit of normal. Patients are also required to fulfil three of the following four criteria: (1) incoordination of the head and eyes in lateral gaze deflection; (2) ocular or cutaneous telangiectasias before the age of five years; (3) gait ataxia; and (4) lymphopenia, especially of CD4, and immunoglobulin deficiency.
cies, mainly of IgA and/or IgG subclasses. Patients with less than three of these criteria should have the diagnosis confirmed by the finding of radiation-induced chromosomal breaks in lymphocytes and low ability of repairing them. The molecular study of the ATM gene that has been cloned to the long arm of Chromosome 11 (11q22-23) confirms the diagnosis. Very few patients with A-T have been described with late onset disease and/or survival into the 4th decade. Other immunodeficiency disorders or multisystemic diseases (e.g. cystic fibrosis) must be differentiated in the absence of neurological symptoms. Patients homozygous for a single truncating mutation or a missense mutation. However, the splice site alteration 8850G>T of the ATM gene that has been detected in our patient, was found also in an Italian boy who had the typical clinical picture of the disease.

Our patient had fulfilled two of the A-T criteria, but the absence of involvement of the neurological system was responsible for the delay of the A-T syndrome diagnosis. The A-T syndrome usually affects cerebellar function progressively from the second year of age. Speech becomes dysarthric, movements are awkward and slow. Patients with the A-T syndrome lose the ability of maintaining balance, ability to read and write due to progressive neurodegeneration. On the contrary, our patient at age 6 had normal motor activities, normal speech development and she had learnt to write a few words. An unusual persistent episode of bronchitis, which did not improve, despite therapy with bronchodilators and antibiotics, was the cause of the referral to a tertiary centre, where the diagnosis was established after extensive laboratory studies.

Prompt diagnosis of the A-T syndrome was important because, apart from early administration of prophylactic treatment, it helped in the detection of oropharyngeal dysfunction. The defect in DNA repair puts our patient at risk of chromosomal damage and therefore lymphoreticular malignancy from exposure to X-rays. Heterozygotes of the A-O gene also have the same defect, that’s why many members of the patient’s family suffered from cancer. Oropharyngeal dysphagia predisposes to microaspirations. Our patient should be encouraged to eat frequently, small amounts of food with high caloric density and nutritional value that do not require a great deal of chewing.

The prognosis in our report is likely to be unfavourable, although the neurological course of the disease remains mild until now. Respiratory insufficiency due to bronchiectasias from recurrent infections is the leading cause of death. The frequency of neoplasms is very high. The patients usually survive only into the late teens or twenties, although some affected individuals have reportedly survived into the sixth decade. There is no cure or medical treatment for this disease.

In summary, A-T syndrome is a multisystem disorder that affects mainly the brain and the immune system, with no cure, and with unfavourable prognosis. There is accumulating evidence to assume that some mutations conferring residual ATM activity are associated with an attenuated clinical phenotype. Subsequently, a normal neurological assessment must not exclude the diagnosis of A-T and delay the proper interventional measures.

References