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LOUIS BAR SYNDROME: TWO FAMILY CASES AND REVIEW OF THE LITERATURE

KAHINA OUAHBI
Department of Pediatrics, El Biar Hospital (Birtraria), Algiers, Faculty of Medicine, Benyoucef Benkhedda University Algiers 1, Algeria.

OURIDA GACEM
Department of Pediatrics, El Biar Hospital (Birtraria), Algiers, Faculty of Medicine, Benyoucef Benkhedda University Algiers 1, Algeria.

NACERA HAMADOUCHE
Department of Pediatrics, El Biar Hospital (Birtraria), Algiers, Faculty of Medicine, Benyoucef Benkhedda University Algiers 1, Algeria.

NAZIHA MEHABA
Department of Pediatrics, El Biar Hospital (Birtraria), Algiers, Faculty of Medicine, Benyoucef Benkhedda University Algiers 1, Algeria.

MOHAMED SAMIR LADJ
Department of Pediatrics, El Biar Hospital (Birtraria), Algiers, Faculty of Medicine, Benyoucef Benkhedda University Algiers 1, Algeria.

Abstract

Ataxia-telangiectasia (AT), also known as Louis-Bar syndrome, is a rare genetic disorder, which is one of the DNA-breaking diseases. It is the second most common cause of autosomal recessive cerebellar ataxia, secondary to a mutation in the Ataxia-telangiectasia mutated (ATM) gene. It combines progressive cerebellar ataxia, ocular and cutaneous telangiectasias, a severe mixed immune deficiency mainly affecting humoral immunity and a strong predisposition to malignant tumors, mainly lymphomas. We report the case of two brothers suffering from ataxia telangiectasia, aged 2 and 4 years respectively, from young 3rd degree consanguineous parents. The first patient was diagnosed during a serious infection and the second during a family inquiry.

Index Terms: Ataxia Telangiectasia, Ataxia-Telangiectasia Mutated, Immune Deficiency, Recurrent Infections.

I. INTRODUCTION

Ataxia-telangiectasia mutated belongs to a family of large phosphoprotein kinases present in diverse organisms and expressed ubiquitously. Functional inactivation of the ATM gene product represents a complex disorder with a highly complex phenotype called ataxia telangiectasia (AT) [1], with an estimated prevalence of 1:40,000 to 1:100,000 [2]. Ataxia telangiectasia is a multi-systemic neurodegenerative and immunosuppressive disease. The severity of clinical involvement varies greatly from one individual to another. We report the case of two brothers with ataxia telangiectasia, aged 2 and 4 respectively, from young third-degree consanguineous parents. The first was diagnosed in the presence of a serious infection and the second during the family investigation. The aim

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of these two observations is to suggest ataxia telangiectasia in the presence of characteristic clinical manifestations and a primary immune deficiency.

II. DESCRIPTION OF THE CASE

A 2-year-old male infant with a horseshoe kidney and grade II vesicoureteral reflux on the right side, with a history of recurrent ENT and pulmonary infections and repeated episodes of fever of unknown origin since the first months of life, was admitted to our hospital with measles complicated by macrophagic activation syndrome. He received immunoglobulins combined with antibiotic therapy. The development has been favorable. Clinical examination revealed growth retardation in height and weight, prominent blood vessels on the bulbar conjunctiva and several café-au-lait spots on different parts of the body (Figure 1, 2).

Figure 1: café-au-lait spots

Figure 2: prominent blood vessels on the bulbar conjunctiva

Immunological tests were carried out because of the patient's history of repeated infections. It revealed a combined immunodeficiency associating a quasi-absence of IgA, hyper IgM, frank T and B lymphopenia and a strong expansion of memory LB and B CD21 (low). A family investigation was subsequently carried out. Examination of the 4-year-old older brother revealed static and kinetic cerebellar ataxia, ocular telangiectasia and café-

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au-lait spots on the body (Figure 2). An immunological test was carried out on him and found the same disorders as his brother.

Taking into account the history of the two brothers' disease, the association of cerebellar ataxia in one and combined immune deficiency with telangiectasia and café au lait spots in both; ataxia telangiectasia or Louis Bar syndrome is strongly suggested, confirmed by the significant increase in alpha-fetoprotein (AFP) in both brothers.

Substitution cures of multivalent immunoglobulins combined with prophylactic antibiotic therapy have enabled our patients to significantly reduce serious infectious episodes. It should be noted that during follow-up, one of the patients presented with thrombocytopenia requiring a myelogram revealing dysmyelopoiesis requiring regular monitoring.

III. DISCUSSION

Ataxia-telangiectasia is an autosomal recessive multi-systemic neurodegenerative and immunosuppressive disease causing severe handicap. It is caused by mutation of the ATM (ataxia telangiectasia mutated) gene (11q22.3) [3], [4] which is ubiquitously expressed and codes for a protein kinase that plays a key role in maintaining genome stability, particularly in Purkinje cells of the cerebellum and in cerebral, cutaneous and conjunctival endothelial cells. AT is a rare disease with an estimated birth prevalence of 1 in 40,000 to 100,000 live births. Its incidence is higher in populations with higher rates of consanguinity [5], [6].

The severity of clinical damage varies greatly from one person to another and depends on residual ATM activity. Three phenotypes are generally recognised:

Generally classical Ataxia-telangiectasia presents either at birth, with partial combined immunodeficiency, or in early childhood, where young children develop progressive cerebellar ataxia with balance disorders, dysarthria and oculomotor apraxia, which are progressively aggravated by extrapyramidal involvement and sensitivomotor neuropathy. Mucocutaneous telangiectasias appear between the ages of 3 and 6, and even in adolescence, but are not constant and are sometimes associated with other lesions such as café-au-lait spots. Biologically, elevated serum alpha-fetoprotein (AFP), T-cell lymphopenia and immunoglobulin deficiencies are characteristic. Progressive lung diseases and haematological malignancies are major causes of morbidity and mortality.

Ataxia-telangiectasia variant presents a little later, around the age of ten in most cases, with milder cerebellar dysfunction and extrapyramidal movement disorders. Malignant tumors tend to appear later in life and may include a higher proportion of solid malignancies. heterozygous forms show none of the classic clinical manifestations of AT, but they have a higher incidence of coronary heart disease and adult malignancies (breast cancer, pancreatic cancer and other solid tumors) at a later age younger than the general population.

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Immune deficiency, which affects both cellular and humoral immunity, occurs in around 70% of patients with TA, and is partial cellular and humoral, leading to recurrent infections, particularly of the lungs, often preceding the onset of neurological signs. There is a decrease in IgA and IgG2 subclasses, and IgM is normal or sometimes elevated, with a partial circulating CD4 deficiency [7]. The risk of neoplasia is high (100 times / the normal population) due to radiosensitivity and chromosomal instability. Radiological investigations should be kept to a minimum [8]. Regarding the presence of renal malformations in our patient, Nijmegen syndrome was suggested. This is a condition similar to AT with the same cytogenetic abnormalities, characterised by an immune deficiency and a poly malformative syndrome with a horseshoe-shaped kidney but no neurological signs or telangiectasias, and normal serum AFP levels allowing it to be eliminated.

The diagnosis of AT is established by the identification of pathogenic variants on the two alleles of the ATM gene. The old clinical and laboratory criteria have largely been replaced by genetic testing [9]. Criteria for possible and probable AT in the absence of genetic testing were based on ocular or facial telangiectasia, serum IgA deficiency, elevated AFP, café au lait staining and increased spontaneous and radiation-induced chromosomal fragility in cultured cells. Note that telangiectasia usually appears after the age of five and that not all patients with TA have elevated AFP levels.

Management is symptomatic, with polyvalent immunoglobulin substitution and prophylactic antibiotic therapy, which improves the infectious prognosis but not the progressive neurological deterioration requiring physiotherapy.

The risk of recurrent sinopulmonary infections is high, and management includes antibiotics in the event of acute infection. Diagnostic tests involving exposure to radiation should be avoided wherever possible. Ataxia-telangiectasia presents a considerably increased risk of haematological malignancy during childhood, requiring vigilance for variations in the blood count, easy bruising, persistent adenopathy, weight loss or unexplained fevers; as a result, our patient's dysmyelopoiesis requires rigorous monitoring, given the risk of progression to leukaemia.

The management of haematology and other malignancies in patients with ataxia-telangiectasia is difficult because of the increased risk of radiotoxicity and cytotoxicity from chemotherapy. Therapeutic radiotherapy should be used only in rare circumstances and only with reduced Classical TA is difficult to treat and has a poor prognosis due to its multisystem implication. Many patients succumb to progressive lung disease or cancer, and the average lifespan is around 25 years [10].

IV. CONCLUSION

Ataxia-telangiectasia is a chronic, disabling disease that presents with partial combined immunodeficiency early in life or, in young children, with progressive cerebellar ataxia, telangiectasia and café-au-lait spots. Recognizing ataxia in children may be challenging.

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It may be overlooked mainly in very young children and erroneously related to a delay of coordination. Physical examination and correct maneuvers are useful for highlighting its clinical sign. The prognosis is severe, particularly in view of the neurodegenerative syndrome and the risk of infection and malignant degeneration. Doses and close monitoring.

Declaration of Competing Interest

The authors of this manuscript declared that there is no conflict of interest

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