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Case Report Open Access

Ileocecal Appendix Involvement in Fabry Disease Mimicking an Acute Abdomen

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Abstract

Anderson-Fabry disease (AFD) is a rare, X-linked, lysosomal storage disorder due to a deficiency of alpha-galactosidase A. The direct consequence is a lipid storage with the accumulation of glycosphingolipids throughout the body.

The clinical picture is highly variable and depends on cellular storage deposition ranging from neurological, cutaneous and renal symptoms to cardiac and gastrointestinal ones.

We are reporting about the case of a young female carrier of alpha-galactosidase A (agalA) gene mutation who was treated at our out-clinic practice for minimal neurological involvement (achroparaestesia). She was subsequently admitted in order to undergo appendectomy because of an acute severe abdominal pain. The histological examination of her appendix revealed only a deposition of globotriaosylceramide (Gb3) without any sign of acute inflammation.

This case confirms the extreme clinical variability of Fabry disease and how the gastrointestinal involvement diagnosis can be missed.

Keywords: Anderson-Fabry disease; Gastrointestinal involvement; Ileocecal appendix involvement; Alpha-galactosidase A

Introduction

The Anderson-Fabry disease (AFD) is a rare, X-linked, lysosomal storage disorder due to a deficiency of alpha-galactosidase A. This causes a derangement of the degradation of many glycosphingolipids with the intra-lysosomal accumulation, mainly globotriaosylceramide (Gb3) [1].

The disease usually occurs in childhood; males and females can be affected although the disease is usually milder in females and has a later onset [2]. Affected hemizygous males, with no residual α-galactosidase A activity, may display all the characteristics of the clinical picture while heterozygous females can have symptoms which range from very mild to severe [1,3].

The clinical symptoms are proteiform depending on many factors such as the amount of cellular storage deposition, organ involvement, genetics and others [4].

Characteristic symptoms are neurological (pain in the extremities, or acroparaesthesia), cutaneous (angiokeratoma), renal (proteinuria, renal failure), cardiovascular (cardiomyopathy, arrhythmia), cochlea-vestibular and cerebrovascular (transient ischemic attacks, strokes), and gastrointestinal (pain, diarrhoea, constipation) [5]. Gastrointestinal symptoms are due to the accumulation of Gb3 within enlarged ganglion cells of the myenteric plexus. However, all the cells and systems that contribute to intestinal structure and function may be affected: epithelial cells, smooth muscle, myofibroblasts, vascular endothelial cells and immune cells [6].

We are describing a case of a young female with acroparaesthesia who underwent a surgical procedure due to clinical suspicion of acute appendicitis.

Case Report

The case of a 24 year old young female carrier of a mutation of the α-galactosidase A (GLA) gene (IVS6 1G>A) with normal enzymatic activity in leucocytes 370.42 ± 58.20 nm/mg/h (normal value 2589.43 ± 3360.63 nm/mg/h) is reported. Her father died five years ago and had been affected by a severe Fabry cardiac and renal involvement.

She was following clinical and laboratory follow-ups every six months at our outpatient practice. The only AFD symptom present was the acroparaesthesia of the upper fingers when she played volleyball. All other investigations included in the Fabry observational studies for the heart, kidney and central nervous system were negative.

In October 2013, the patient suffered acute abdominal pain and was referred to the hospital emergency department. A physical examination and all laboratory tests were negative. An ultrasound investigation of abdominal organs did not display any alteration. However, due to the persistent, intense abdominal pain, acute appendicitis was suspected and an appendectomy was carried out on the patient. After the procedure, the pain disappeared and the patient

was fine and consequently she was discharged from the hospital a few days after the operation.

The pathology report describe an ileocecal appendix of 7 cm in length, 0,7 cm in width, formalin fixed.

Paraffin embedded sections of 2-3 μm were set up and stained with hematoxylin and eosin (EE).

A microscopic examination showed only follicular hyperplasia (Figure 1) without any evidence of acute inflammation. The pathological diagnosis was an appendix with follicular lymphoid hyperplasia. Nothing was reported about an AFD involvement.

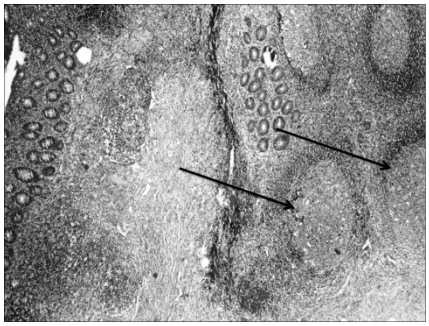

Figure 1: Chronic appendicitis: arrows display intramucosal follicular hyperplasia (EE 2,5X).

A few days after the histological diagnosis, the nephrologist referred her clinical history to the pathologist and a review of the specimen was immediately carried out. PAS-diastase (PAS-D) staining (Carlo Erba Periodic Acid-Schiff reactive) was carried out in order to highlight the possible accumulation of glycolipids.

An accumulation of glycolipids in enlarged ganglion cells of the myenteric plexus and in endothelial cells was demonstrated (Figure 2 and 3).

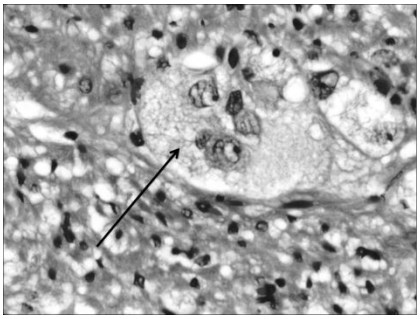

Figure 2: Enlarged ganglion cell (see arrow): detail (EE 40X).

Discussion

AFD is a rare, progressive, X-linked inherited disorder of the glycosphingolipid metabolism due to a deficiency or absence of the α-galactosidase A enzyme. AFD is pan-ethnic, and the reported annual incidence is variable from 1:17,000 to 1:117,000 and its true prevalence may be underestimated [1,7].

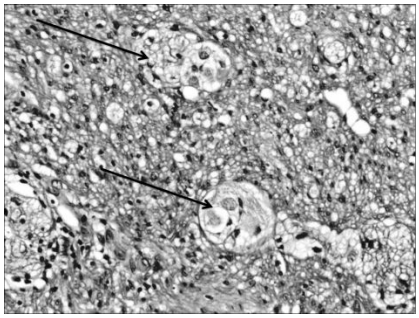

Figure 3: Enlarged ganglion cells of the myenteric plexus: note the "foamy" cell deposits (arrows) of a light pink color within cytoplasm (PAS-D 20X).

Classically affected hemizygous males with no residual α-galactosidase A activity may display all the characteristic neurological (pain), cutaneous (angiokeratoma), renal (proteinuria, reduction of the glomerular filtration rate), cardiovascular (cardiomyopathy, arrhythmia), cochlea-vestibular and cerebrovascular (transient ischemic attacks, strokes) signs of the disease. The heterozygous females have a clinical picture with a wide range, from very mild to severe symptoms, which has a later onset and slower progression [2,8]. In this report, the only AFD sign was the acroparaesthesia of the upper fingers while playing volleyball.

Gastrointestinal involvement is frequent in Fabry patients and the incidence is higher in females than in males [4]. Hoffmann [9] described gastrointestinal symptoms in 342 patients with AFD and demonstrated that the overall prevalence of gastrointestinal complaints was 52.0%. Interestingly, female patients reported gastrointestinal symptoms more often than male patients (54.2% vs. 48.9%).

The most prevalent gastrointestinal symptom was a cramping abdominal pain which was present in 32.5% of the patients tested. It is remarkable that no difference was in the prevalence between male and female patients and the median age at onset of abdominal pain was 14.0 years.

The most frequently observed combination of gastrointestinal symptoms in patients with Fabry disease was abdominal pain and diarrhoea (14.3%), followed by abdominal pain and nausea (9.4%), and abdominal pain and constipation (7.3%). Episodes of abdominal pain resembling acute abdomen are reported in the literature [1,5,10]. In our patient pain disappeared after the surgical procedure and that is likely due to a spontaneous remission or it might as well be associated with medications (analgesics and anaesthetics) employed during the surgical procedure.

The abdominal pain associated with AFD is most likely due to Gb 3 deposition in the neuronal and vascular tissue of the bowel submucosa [5,11]. In addition, it is possible that some aspects of gastrointestinal symptomatology in Fabry disease may relate to as yet unidentified and subtle immunological alterations relating to lymphocytes and Gram-negative bacteria [12-14].

From this clinical and histological evidence we can reasonably affirm that the abdominal pain in our patient was a sign of AFD rather than acute appendicitis. As a matter of fact, while the accumulation of

glycolipid within enlarged ganglion cells of the myenteric plexus and endothelial cells was proven, there were no signs of the appendix being inflamed. Moreover, this report demonstrates how a diagnosis of AFD can be easily missed, not only in everyday clinical practice, but even in histological specimens without a clinical suspicion. On the other hand, this case confirms the ubiquity presence of foamy cell deposits in the gastrointestinal tract and the importance of data collection in understanding this important aspect of AFD.

Last but not least, the issue arising in this case is the patient's treatment with enzyme replacement therapy (ERT). The timing in starting ERT in Fabry females is an unresolved question [8] and is not dealt with in this report. At present, the patient in question is undergoing a complete re-evaluation of her disease. We are consulting with neurologists on the central nervous system: the presence of even a minimal lesion [15] could be a signal to start ERT.

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