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Evolving spectrum of LRBA deficiency-associated chronic arthritis: is there a causative role in juvenile idiopathic arthritis?

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ABSTRACT

Lipopolysaccharide-responsive, beige-like anchor protein (LRBA) deficiency causes common variable immunodeficiency (CVID) disorders and autoimmunity. LRBA deficiency has become a clinically variable syndrome with a wide spectrum of clinical manifestations. We report a patient with LRBA deficiency associated chronic non-erosive arthritis. This report highlights the spectrum of arthritis in such patients and the potential causative role of LRBA gene in juvenile arthritis.

Introduction

Common variable immunodeficiency (CVID) disorders are a heterogeneous group with variable clinical and genetic findings (1, 2). Lipopolysaccharide-responsive, beige-like anchor protein (LRBA) is a member of the BEACH-WD40 protein family and is expressed in several tissues (3). Recently, LRBA deficiency has represented a novel primary immunodeficiency disease with expanding clinical dmanifestations (4-6). LRBA deficiency was first characterised by early-onset hypogammaglobulinaemia, autoimmune manifestations including hypothyroidism and autoimmune enteropathy, and recurrent infections (4, 5). Subsequently several reports identified LRBA deficient patients with susceptibility to inflammatory bowel disease (IBD) and variable autoimmune disorders such as autoimmune haemolytic anaemia, autoimmune thrombocytopenia and type 1 diabetes mellitus, and juvenile arthritis (5, 6-8). Arthritis is among the autoimmune features that is seen in LRBA deficient patients. However, at present, the available information about the nature and outcome of arthritis in such patients is far from clear. Yet, a recent report described a case of LRBA deficiency with early onset chronic erosive polyarthritis (9).

The exact role of LRBA in immunity is not well defined. However, mutations of the LRBA gene possibly through interaction with environmental factors trigger the autoimmunity phenomena, which indicate the fundamental role of LRBA protein in the normal immune system (4, 8, 10).

We report a patient with LRBA deficiency presented with chronic enteropathy and other autoimmune manifestations in addition to chronic non-erosive arthritis. This report highlights the spectrum of arthritis in such patients and the potential causative role of the LRBA gene in juvenile arthritis.

Case report

An 18-year-old Saudi male from consanguineous parents, presented at age of one year with chronic non-bloody diarrhea and poor weight gain. His celiac profile including tissue transglutaminase antibodies was negative. However, his serum immunoglobulin levels confirmed low IgA level (<0.05; normal range 0.7–4.0 g/L). Moreover, human leukocyte antigen (HLA) typing showed DRB1* 03:01- DQB1*02:01. Small intestinal histopathology revealed total villous atrophy, crypt hyperplasia and intraepithelial lymphocyte infiltrates. Accordingly, he was started on a gluten-free diet with minimal response. He found to have diffuse lymphadenopathy without splenomegaly; there was no evidence of autoimmune thrombocytopenia or anaemia. During the follow-up, he developed vitiligo and hypothyroidism, which was treated with thyroxin. At that time autoimmune enteropathy was considered and he was treated empirically with courses of corticosteroids but with partial improvement; azathioprine (2 mg/ kg/ dose orally) was added and then switched to cyclosporine (5 mg/ kg/ dose orally) with minimal response.

At the age of 7, he presented with bilateral knee chronic synovitis in the form of pain, swelling and limited range of motion. Antinuclear antibody and rheumatoid factor were negative. He underwent an intraarticular steroid injection but with minimal response. An eye examination revealed bilateral anterior chronic uveitis. Cyclosporine was replaced with methotrexate (10mg weekly orally) and intravenous infliximab infusion was added (5 mg/ kg/ dose) at 0, 2 and 6 weeks then every 8 weeks. Initially, the patient showed good response. However, his disease flared so infliximab was switched to subcutaneous adalimumab injection (20 mg) every other week. Unfortu-

nately, few months later he developed psoriasis.

Despite the intensive treatment, he continued to have diarrhoea and bilateral knee swelling and contracture. Radiograph of the knees showed joint effusion with smooth articular margins (Fig. 1). Furthermore, multiplanar multisequential magnetic resonance imaging of both knees demonstrated thickening and synovial proliferation with enhancement post contrast infusion, but in the subchondral cortical bone no erosive changes were seen and the overlying hyaline articular cartilage was intact (Fig. 2).

Immunological assessment revealed normal serum immunoglobulin levels apart from low IgA. Furthermore, lymphocyte markers were within accepted range.

Because of the constellation of enteropathy, endocrinopathy and autoimmunity the possibility of immune dysregulation, polyendocrinopathy, enteropathy, and X-lined (IPEX) syndrome was raised. However, genetic testing for mutation in the *FOXP3* gene was negative. Subsequently, use of a targeted next generation primary immunodeficiency (PID) panel that encompasses 162 PID genes revealed a mutation in *LRBA* (NM_001199282.2:c.3985_3986del:p. D1329Yfs*18). Details of the T-NGS PID panel have been previously published (11). The mutation was confirmed through bidirectional Sanger sequencing (Fig. 3), and results in a homozygous 2 basepair frameshift deletion in exon 24 which predicts a premature stop codon 18 residues later at codon 1346, thereby causing truncation of >50% of the protein which at full length is 2851 residues. This mutation has not been reported in any other patients.

Based on genetic diagnosis he was started on abatacept (500 mg) infusion every 4 weeks with partial response.

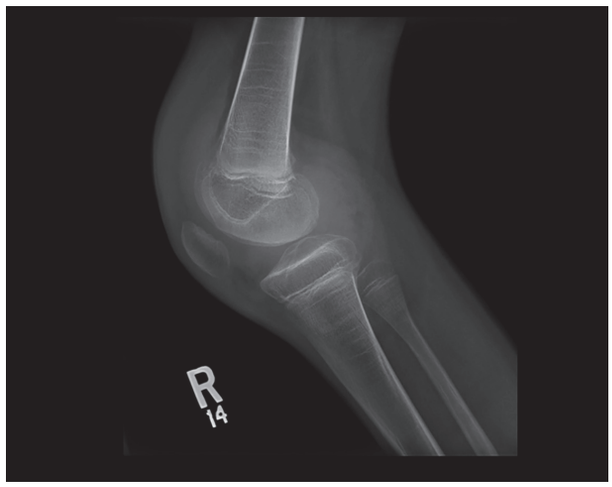

Fig. 1. Right knee radiograph showed moderate joint effusion with smooth articular surfaces.

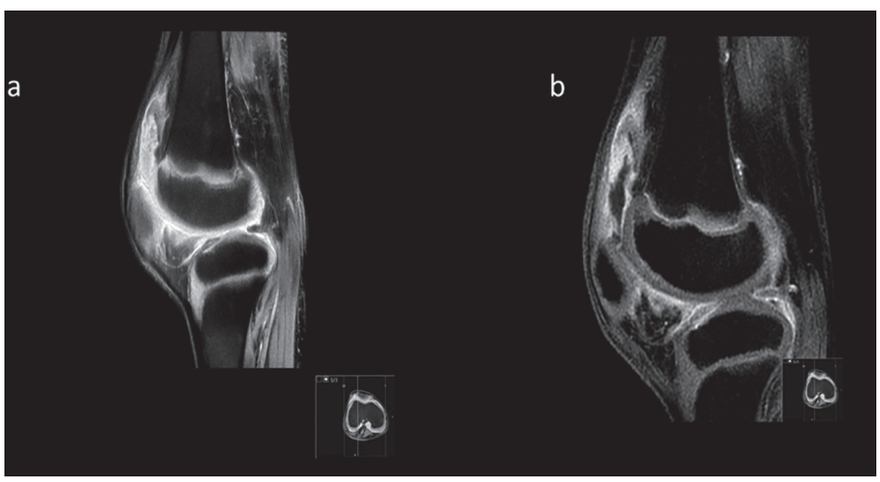

Fig. 2. Sagittal proton density fat sat (a) Sagittal T1Fat sat post gadolinium enhancement (b) of right knee demonstrated synovial thickening and proliferation with moderate enhancement. No erosive changes or articular cartilage morphological abnormality

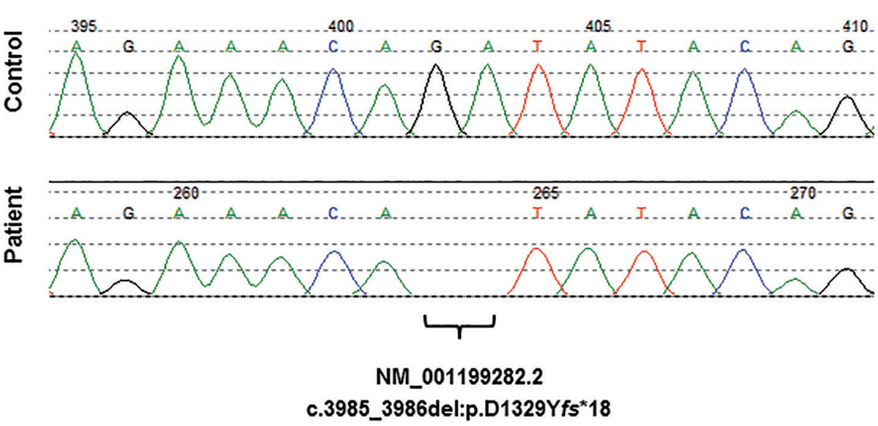

Fig. 3. Sequence chromatogram of a control individual along with the patient for the relevant region in *LRBA*, with the site of mutation denoted by curly brackets.

Discussion

Juvenile idiopathic arthritis (JIA) is not uncommon in CVID. Several studies showed that environmental and genetic factors could influence the onset of arthritis in such patients, yet the exact causative relationship is not fully elucidated (1, 10). Recently, identified forms of arthritis are associated with LRBA deficiency; it can broadly be septic arthritis and inflammatory arthritis (6, 7). It is not uncommon to consider IBD associated arthritis in such patients, particularly, patients with LRBA deficiency presented with IBD or IBD like manifestations (5). So far, one published report has described a LRBA deficient patient from a consanguineous

family developed early erosive polyarthritis and associated uveitis in addition to type I diabetes mellitus (9).

Here, we identified a patient with LRBA deficiency who presented with chronic enteropathy and autoimmune thyroiditis; then the disease course complicated with progressive chronic non-erosive arthritis with partial response to different biological agents including abatacept. Work up including histopathology failed to classify them as IBD or reactive arthritis to enteric infection. Though, he carried the HLA risk alleles for celiac profile, the autoimmune panel for celiac was negative. Our patient and the patient from the previous report (9) might be classified as JIA, which is the most common chronic inflammatory arthritis in children.

The International League of Association for Rheumatology (ILAR) criteria for classification of juvenile arthritis is widely accepted. However, it is unable to classify all children with idiopathic arthritis (12). Though, the specific etiopathogenesis of JIA is not well understood, it has become increasingly clear that JIA is as multifactorial disorder and via the interaction of environmental factors and genes in polygenic models influences the disease predisposition, expression and complication.

Moreover, identification of a likely candidate gene in rare Mendelian forms of JIA showed certain strong gene mutations are involved in susceptibility to inflammatory arthritis (13, 14). Cytotoxic T lymphocyte antigen-4 (CTLA4) regulates CD28-mediated T cell co-stimulation and has been implicated in predisposition to several autoimmune disorders including JIA. However, the available data is a bit inconsistent (15, 16).

Lo *et al*. found that patients with LRBA deficiency showed sustained improvement to abatacept which is a CTLA4-immunoglobulin fusion agent and they hypothesised that LRBA regulates CTLA4 (17).

Noticeably, the spectrum of LRBA deficiency associated arthritis is evolving and expanding with overlapping manifestations to JIA. Furthermore, chronic arthritis associated with autoimmunity in CVID possibly needs to be considered in future classification and nomenclature of JIA particularly, if the affected individuals have genetic findings related to the immunopathogenesis of JIA.

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