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A Role for Nucleotide-Binding Oligomerization Domain (NOD)-Like Receptor Protein 12 (NLRP12) in Paediatric Inflammatory Bowel Disease (IBD): A Case Report and Literature Review

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1. Abstract

Paediatric inflammatory bowel disease (IBD) is a chronic disease with a multifactorial etiology. The role of nucleotide-binding oligomerization domain (NOD)-like receptor protein 12 (*NLRP12*) in IBD pathogenesis and the clinical relevance of variants of *NLRP12* in IBD disease course have not yet been clarified. We report a child with IBD and a wide range of extra-intestinal symptoms in whom many years after IBD onset a novel variant-of-unknown clinical significance (VUS) in the *NLRP12*-gene was found. Targeted adjustment of therapy improved the clinical course of the extra-intestinal manifestations, suggesting a causative relation with this VUS. We provide an overview of the available literature on the role of *NLRP12* in the pathogenesis of IBD. Clinicians should be aware of underlying gene mutations in young children with IBD, particularly when disease course is complicated by multiple unexplained extra-intestinal symptoms and deteriorating growth retardation without catch-up growth despite clinical and biochemical remission of IBD.

2. Introduction

The pathophysiological mechanisms of (paediatric) inflammatory bowel disease (IBD) involve complex interactions between inflammatory, genetic, metagenomic and microbial factors. Inflammasomes, multiprotein oligomers, play a major role in activation of the inflammatory response. Pattern recognition receptors (PRRs) are proteins that can form inflammasomes and subsequently recognise pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), molecules released by damaged cells. After activation, PRRs contribute to IBD pathogenesis (in)directly by modulating inflammatory signalling cascades. The nucleotide-binding oligomerization domain (NOD)-like receptor protein (NLRP) is a family of cytoplasmic PRRs [1,2]. *NLRP12* is a NLRP family member that has been shown to negatively regulate immune signalling pathways and thus attenuate exaggerated inflammation [3]. However, persistent and/or chronic dysregulated PRR stimulation can result in collateral tissue damage, chronic inflammation and autoimmunity in the gut [1,4]. Several studies in mice consistently showed that *NLRP12* plays an important role in protecting the host from IBD pathogenesis. In humans, variants of *NLRP12* have been associated with *NLRP12* autoinflammatory disease (*NLRP12*-AD), also known as familial cold autoinflammatory syndrome 2 (FCAS2). *NLRP12*-AD is characterized by recurrent fever, fatigue and musculoskeletal symptoms after cold ex-

posure, and skin manifestations such as urticaria [5]. Only around thirty children with autoinflammatory disease related to *NLRP12* variants have been reported in literature so far. [5-10] *NLRP12*-AD concomitant with IBD has not been reported previously. Here, we describe a patient diagnosed with a novel variant of unknown clinical significance (VUS) of *NLRP12* and IBD. Written informed consent was obtained. We reviewed the literature to search for variants in *NLRP12* in paediatric IBD patients.

3. Clinical Case

A nine-year-old boy of North African ethnicity presented with episodes of recurrent abdominal pain and bloody diarrhoea since several months. His medical history revealed growth retardation (-2.5 SD) since the age of two years. Physical examination at presentation revealed a height of 108.4 cm (-4.2 SD) and a weight of 18.1 kg (-3.5 SD). Laboratory investigations showed an elevated erythrocyte sedimentation rate (ESR) of 31 mm/h and a faecal calprotectin (FCP) level of 595 µg/g (normal value <50 µg/g). Microbial cultures of the faeces were negative. Colonoscopy was performed under suspicion of IBD which showed a pancolitis with ulcers and erosions. Colonic biopsies and histopathological investigations showed diffuse chronic moderately active inflammation, classified as ulcerative colitis (UC) type IBD.

The patient was initially treated with oral steroids and 5-aminosalicylic acid (ASA) and *Helicobacter pylori* was successfully eradicated. A few months later he suffered from ASA-related pancreatitis. 5- ASA was discontinued, and infliximab was started together with methotrexate (MTX). Due to severe nausea and vomiting (unresponsive to anti-emetics) MTX was discontinued, and infliximab monotherapy was continued once every 8 weeks.

A year later, he developed perianal abscesses and a trans-sphincteric fistula, treated by surgical incision, drainage and fistulectomy. Based on these findings the original diagnosis of UC was switched to Crohn's disease (CD). Two years after starting infliximab, his symptoms of diarrhoea, malaise and weight loss returned. Laboratory results showed positive antibodies (25 AE/ml) against and low serum levels (0,04 µg/ml) of infliximab. Following dose intensification, he experienced a severe infusion reaction from infliximab. Colonoscopy at that time showed no active inflammation and FCP was low (95 µg/g). Therapy was adjusted to adalimumab monotherapy 40 mg once every two weeks. On this regimen, sustained clinical and biochemical remission of the colitis was achieved.

Since early age patient suffered from multiple concomitant extra-intestinal symptoms, including episodes of occipital headache (normal MRI cerebrum) and severe, deteriorating growth retardation without catch-up growth despite clinical and biochemical remission of his IBD. Evaluation of skeletal maturity showed delayed bone age of 5 years and 9 months at the age of eight. For that reason, genetic and endocrinologic analysis was performed. Pathogenic variants in the short stature homeobox-containing gene (SHOX) and fibroblast growth factor receptor 3 (FGFR3) were excluded. The growth hormone stimulation test showed no abnormalities and normal insulin-like growth factor 1 (IGF-1) values were measured.

Furthermore, he experienced periodic unexplained joint pain, without swelling or redness, sometimes accompanied by fever but with normal C-reactive protein levels and white blood cell count. He also suffered from multiple infections, among others a severe *Staphylococcus aureus* sepsis at the age of 11 years, for which antibiotics were administered for six weeks. At the age of 14 years old he developed episodes of severe swelling, redness, and itchiness of his face (lips, cheeks and nose) and general malaise, not responding to antihistamines and topical steroids and without a specific trigger. His gastrointestinal complaints were stable at that time. Skin biopsy of affected skin lesions showed granulomatous dermatitis, interpreted as an extra-intestinal skin manifestation of CD. He was again referred to the clinical geneticist because of multiple symptoms in different organ systems without common denominator. Molecular testing based on gene panel next-generation sequencing was performed using Illumina HiSeq 2500. A gene panel targeting 54 genes involved in autoimmunity, hemophagocytic lymphohistiocytosis and immune dysregulation and a panel for short stature including 354 genes, were analysed. A heterozygous frameshift variant was identified in the *NLRP12*-gene: NM_144687.4; c.3184_3185dup p.(*1062Cysext*10) (Chr19(GRCh37): g.54297304_54297305dup). This insertion in the stop codon is predicted to result in an elongated protein. The variant is not present in the Leiden Open Variation Database (LOVD) database [11], ClinVar [12] and has not been identified in controls in gnomAD (v2.1.1) [13]. The variant was inherited from his (healthy) mother and classified as a variant of unknown clinical significance. No pathogenic variants were identified in the other genes of both gene panels. Both his healthy brother and father showed to have a heterozygous genotype of this VUS of *NLRP12*, none of his other siblings showed to be carrier of this VUS. Our patient finally achieved clinical remission of his CD on TNF-α blockers. Furthermore, treatment with interleukin-1 receptor antagonist Anakinra was started 1,5 years ago and shows promising results with decrease of skin lesions and general malaise (Figure 1).

Figure 1. Before (left) and after (right) treatment with Anakinra.

4. Discussion

Paediatric IBD is a complex chronic disease with multifaceted etiology and the role of *NLRP12* as a negative immune regulator in IBD is becoming increasingly clear [1,14-16]. Here, we present a child diagnosed with IBD, a wide range of extra-intestinal symptoms and a novel VUS in *NLRP12*. A possible association between IBD and NLRP12 has been described previously. *NLRP12* showed to be protective against the development of chemically induced colitis [16] and plays an anti-inflammatory role in experimental colitis [17,18]. Furthermore, *NLRP12*-deficiency in mice resulted in increased colonic basal inflammation and lead to a less-diverse microbiome. Interestingly, a similar microbiome profile has been reported in IBD patients [14]. Others showed that *NLRP12* activity was significantly downregulated in active UC patients compared to their healthy twins or inactive UC cohorts [14]. In literature, only three children with IBD and a VUS in the *NLRP12*-gene have been described, of which details were reported previously [19]. However, according to the LOVD and based on allele frequencies in gnomAD these variants are likely benign and are found in respectively 0.9% and 9.4% of healthy controls [11,13]. Furthermore, in ClinVar or Decipher, both online databases that aggregate information about genomic variation and its relationship to human health, no concomitant and IBD-diagnosis was reported in patients with *NLRP12* sequence variants or with copy number variants including the *NLRP12*-gene [12,20]. Also in patients reported in the LOVD database, IBD was not mentioned as phenotype (however, phenotypic data are sparse).

Around 41-48% of *NLRP12*-AD patients have gastrointestinal symptoms, showing an overlap of symptoms between *NLRP12*-AD and IBD [9,21]. Approximately 50 genetic disorders are found to be associated with IBD-like immunopathology, but *NLRP12* has not been described in relation to IBD before [22,23]. In humans, other NLRS do contribute to development of colitis, such as mutations in NOD protein 1 (NOD1), NOD2 and NLRP3 [18].

Regarding IBD concomitant with the VUS of *NLRP12* in our patient, several explanations exist. Our patient might suffer from two non-related illnesses at the same time. Alternatively, both his IBD and FCAS2 could be caused by abnormal function of *NLRP12*. His poor response to conventional immunosuppressive IBD therapy, similar to children with IBD with underlying genetic disorders, could be an argument for this explanation [24]. A third possibility is that the VUS of *NLRP12* is not causing dysfunction of *NLRP12* and is not of clinical relevance. The presence of this VUS in his healthy mother supports this explanation. However, his many extra-intestinal complaints and good response to Anakinra, prescribed in patients with auto-inflammatory fever syndromes such as Cryopyrin-Associated Periodic Syndromes (CAPS) and Familial Mediterranean fever (FMF), are not in line with this explanation [25]. In conclusion, this is the first case reporting a child with IBD and a novel VUS of *NLRP12*, of which the interaction between these two is not yet completely understood. Paediatric IBD may be accompanied by concomitant gene mutations when multiple unexplained extra-intestinal symptoms and deteriorating growth retardation without catch-up growth despite clinical and biochemical remission of IBD are present. Future research should focus on targeted therapies and shine light on the relation of *NLRP12* in paediatric IBD.

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6. Conflicts of Interest

All authors declare that they have no conflicts of interest.

7. Data Availability Statement

Due to privacy and ethical concerns, neither the data nor the source of the data can be made available.

8. Author Contributions

N.S.G and T.G.J.M. contributed to the literature search, study design and data-collection. All authors contributed to data interpretation and writing.

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