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Title

Novel Adenosine Deaminase 2 (ADA2) Mutations Associated With Hematological Manifestations

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Introduction

Deficiency of adenosine deaminase 2 (DADA2) is an autoin- flammatory disorder characterized by various forms of vas- culitis and is rarely manifesting as pure red cell aplasia (PRCA) or neutropenia. Very few reports in the literature document these associations. We, therefore, report two dif- ferent novel mutations in the ADA2 (also known as cat eye syndrome chromosome region 1 gene) in two different patients that result in DADA2 and presented with pure red cell aplasia in the first reported patient and persistent neu- tropenia in the second one. PRCA is normocytic normochro- mic anemia with severe reticulocytopenia and markedly reduced erythroid precursors in the bone marrow. It can be inherited as in Diamond-Blackfan anemia (DBA) or acquired.1 The latter can be further classified into parvovi- rus-associated PRCA, drug-induced, primary idiopathic which is frequently antibody-mediated autoimmune disor- der, or secondary PRCA that can be due to collagen vascu- lar disorders, autoimmune diseases, lymphoproliferative disorders, or malignancies. On the other hand, persistent neutropenia can result from different disorders such as malignancy, hematologic disorders, metabolic disorders, or infectious causes. Determining the cause of neutropenia is critical in defining a successful plan for treatment.

Methodolgy

1.Type of study
Retrospective review of 2 cases with ADA2 deficiency who presented with hematological manifestations, in addition to a literature review.
2. Place of study
Two cases were reported in King Salman Armed Forces Hospital (KSAFH) which is located in Tabuk/KSA and serves as a tertiary hospital and referral center for the northwestern region of Saudi Arabia.
3. Data collection
Records of two pediatric patients with ADA2 deficiency and hematological manifestation were retrieved from the outer database in KSAFH. Medical data and laboratory values were reviewed. Clinical and demographic data were retrieved from the patient medical files.
4. Literature review and search strategy
We searched for studies using the words "adenosine deaminase type 2 deficiency, "ADA2 deficiency," and "DADA2" in PubMed. Between 2014 and 2020, we conducted a comprehensive review of DADA2 case series and case reports published in the literature and only those with hematological associations were reviewed and reported. Research focuses on English language studies. In addition, we use Saudi Digital Library (SDL) to enable open access of some articles, that was established with the aim of providing advanced information services. The library provides one umbrella for all Saudi universities, through which it negotiates with publishers.
5. Whole exome sequencing
Whole exome sequencing (WES) has become a valuable tool for diagnosing genetic disorders and better understanding genotype-phenotype relationships (Schepp et al., 2016). WES was performed in our 2 pediatric cases after collect blood and send it to international reference laboratory. Blueprint Genetics Whole Exome Plus Test (version 2, Feb 9, 2018) focuses mainly on well-known disease genes that have previously been linked to genetic disorders. Exome variant data is also examined for variants that are not found within known clinically associated genes but have characteristics that suggest they could be disease-causing. If more patients with the same phenotype and variants in the same gene are discovered over time, the variant may be reclassified as a probable cause of the disorder. The test targets all protein-coding exons, exon-intron borders, and selected non-c coding, deep intronic variants. There are over 3750 genes that have been linked to clinical outcomes (and the number is constantly updated). Single nucleotide variants and small insertions and deletions (INDELs) up to 220 bps, as well as copy number variations characterized as single exon or larger deletions and duplications, should be detected with this test. The procedure in the laboratory was by a bead-based technique was used to extract total genomic DNA from the biological sample. Electrophoretic techniques were used to determine the quality and quantity of DNA. By ligating sequencing adapters to both ends of DNA fragments, a sequencing library was created. To ensure optimum template size, sequencing libraries were size-selected using a bead-based method and amplified using polymerase chain reaction (PCR). The hybridization-based target capture technique was used to target regions of interest (exons and intronic targets). This method was showed the actual evidence base for using WES and WGS in clinical practice is very limited in terms of health economics. To support their translation into clinical practice, studies that carefully assess the costs, efficacy, and cost-effectiveness of these tests are urgently required.

Results

The whole-exome plus identified the following mutations in our two reported cases. In the first case, a homozygous frameshift variant CECR1 c.714_738dup, p. (Ala247Glnfs*16) and a heterozygous missense variant G6PD c.563C>T, p. (Ser188Phe) were identified, to the best of our knowledge this the first mutation to be recorded. The second patient was homozygous for ADA2 c.1447_1451del, p. (Ser483Profs*5), and this mutation has been reported only once before, by Fahad et al (Alabbas et al., 2019). Hematological manifestations have been illustrated in association with DADA2 in several reports. We reviewed a total of 153 patients who were included in 28 published reports for patients with DADA2 in which hematologic manifestations were part of their presentations. One hundred and two patients, (66.6%, Female n=52), presented with hematologic manifestations. The median age at disease onset was 5 years, range (1 month to 52 years). It was noticed that different types of anemia including (AIHA, Evans syndrome, PRCA, anemia, and DBA like features) were the most frequent presentation occurring in 53% of patients, in which PRCA constitutes 12.7%, AIHA 3.9%, Evans syndrome 1.96%, anemia 14.7%, and DBA was 18.6%. This was followed by lymphopenia and organomegaly (splenomegaly +/- hepatomegaly), 32% each. Of particular concern, our first patient has PRCA which was the main manifestation in 12 patients without typical features of DBA nor vasculitis. Our second patient presented with neutropenia and relapsed HL knowing that HL has been reported in 2 cases only from the total of 102 patients. Four patients were successful on hematopoietic stem cell transplant (HSCT), 2 on anti-tumor necrosis factor (TNF), 2 failed on steroids and 2 failed on anti-TNF, while the others are either maintained on blood transfusion, steroids, or monthly intravenous immunoglobulins.

Conclusion

We report two different DADA2 variants in two children; the first presented with PRCA and the second presented with persistent neutropenia. DADA2 is extending phenotypically beyond its known manifestations to include various hemato- logic presentations. We emphasize the utilization of genetic testing that can lead to a better understanding of different hematologic disorders with improved detection and diagno- sis, which will ultimately offer different therapeutic options and prevent unnecessary interventions.

Recommendation

Future researches are needed to fully elaborate on the exact pathogenesis of ADA2 and its correlation with hematological disorders.

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