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EDITORIAL COMMENTARY

Autoimmune Hemolytic Anemia, Inborn Errors of Immunity and Genetics: An Evolving Arena

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Autoimmune hemolytic anemia (AIHA) in children is a rare and often perplexing disease. The journal's current issue contains a single-center ambispective analysis of childhood AIHA from a center in Puducherry, India [1]. The authors have done an impressive and detailed assessment while describing a cohort of 46 children with AIHA over 8 y, including 2 y of prospective enrolment. The demonstrated epidemiology of childhood AIHA stands out in the current study, with a predominance of mixed-AIHA (m-AIHA) in the cohort. The data of large studies from the West has warm antibody AIHA (w-AIHA) as the commonest subtype, accounting for 60–70% of cases, followed by cold agglutinin syndrome and paroxysmal cold hemoglobinuria (PCH). The m-AIHA is reported to be the rarest subtype, accounting for <5% of all AIHA [2, 3]. Multiple single-center analyses from India have shown a variable distribution of the AIHA subtypes [4–6]. In the current study, the majority (59%) had m-AIHA, while w-AIHA, the next most common subtype, was observed in merely one-fourth of the cohort. Another interesting finding was the absence of PCH; none of the cases had a demonstrable Donath-Landsteiner antibody. Detecting Donath-Landsteiner antibodies involves a laborious investigation and is not readily available; hence, PCH in children often goes undetected.

Current guidelines for AIHA recommend a detailed assessment of secondary AIHA at the outset, before the initiation of steroids and intravenous immunoglobulin. Progressively, more patients are being identified with secondary etiology for AIHA, including inborn errors of immunity (IEI). The screening investigations to assess for IEI include an immunoglobulin profile, a lymphocyte subset analysis, and an assessment for autoimmune lymphoproliferative syndrome (ALPS) for all patients with w- or m-AIHA, along with screening for systemic lupus erythematosus (SLE) as well as assessment for various infections [2, 7]. Further detailed genetic evaluation, typically by whole exome analysis, is indicated in children with warning signs of immunodeficiency, which includes refractoriness to more than one line of treatment, a positive family history, chronic viral infections, or abnormalities noted in the first-line evaluation [8].

While the current article does not mention the details of the evaluation, underlying secondary causes were identified in 63% of the cohort, with SLE being the most common. IEI was noted in 10% [1]. National data from France and Italy found secondary causes in 60% and 40% of patients, respectively [2, 9]. Primary immunodeficiency disorders formed 16% of the secondary AIHA subgroup in the study from France, affecting 23 children among a cohort of 141 patients with secondary AIHA [9]. IEI is increasingly being recognized in association with AIHA, particularly among those developing Evans syndrome. In a large study of childhood Evans syndrome, 65% of patients had an underlying genetic diagnosis [9].

The assessment for secondary AIHA also identifies a subset of patients who are likely to have an adverse outcome with poor response to conventional treatment. Specific therapy may be required depending on the cause of AIHA, with options including sirolimus for ALPS or abatacept for LRBA and CTLA-4 deficiency. Rarely, a patient may progress to require hematopoietic stem cell transplantation [7]. Pertinently, in this paper, children <5 y with m-AIHA had a worse prognosis with a higher relapse. It may likely be due to an as-yet-undiscovered secondary cause, plausibly IEI. While it is unclear how many patients required more than one/multiple lines of treatment, the most common second-line agent used in the current study was mycophenolate mofetil in one-third of the cohort.

Information on the overall treatment duration and percentage of patients attaining complete responses at specific

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intervals would have been helpful. Resistant or steroid-dependent disease has not been separately detailed in the study. A flowchart on the choice of second-line agents according to the type of AIHA, response to first-line therapy, or the underlying etiology would have added more value [1]. In a nationwide study from France, >1/4th of children remained dependent on immunosuppressive agents at 3 y of diagnosis [9]. The antibody profile of the direct Coombs test did not affect the outcome in this study [1]. However, in the national data from Italy, patients with isolated C3d positivity had a superior outcome than those with IgG positivity with or without C3d [2]. The relatively high mortality of 15% may indicate a referral bias to a tertiary-care institute. The international mortality rates in childhood AIHA have now reduced to between 4–10% [9, 10].

The paper reflects the importance of reference laboratories and centers that can identify the secondary causes of AIHA and have the facility for long-term follow-up of this rare disorder to generate data from our population. Increasingly, targeted assessment with next-generation sequencing or whole exome analysis would help identify patients with previously overlooked secondary causes of AIHA, which may require the early addition of second-line agents.

Declarations

Conflict of Interest None.

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