TRANSIENT HYPOGAMMAGLOBULINAEMIA OF INFANCY

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INTRODUCTION

Transient hypogammaglobulinaemia of infancy (THI), which affects infants and young children, is a relatively frequent primary immunodeficiency and an asymptomatic finding in most cases. It occurs more commonly in families of patients who suffer from other antibody deficiencies. THI was first described as a clinical entity by Gitlin and Janeway. Normal newborn infants rely on passively transferred maternal immunoglobulins (Igs) in the first three to six months of life, when they reach a nadir of immunoglobulin G (IgG), until sufficient production of their own antibodies. Serum immunoglobulin A (IgA) may be variably low, immunoglobulin M (IgM) levels are very rarely reduced and B cell numbers (CD19) are normal (Figure 1). Antibody responses to protein immunisations are either normal or near normal.

THI is one of the most common primary humoral immunodeficiencies. It is characterised by a delay in the child’s own IgG production, while normal IgG levels are usually reached by the age of four years. The diagnosis of THI needs to be established by the exclusion of other primary or secondary causes and it is confirmed retrospectively. Although the prognosis is good for the majority of children, a minority may develop other primary immunodeficiencies and hence a follow up of THI is indicated.

DEFINITION

The strict definition of THI is applied according to the European Society of Immunodeficiency Diseases (ESID) Registry. ‘Working definitions for clinical diagnosis of PID’ of 31 August 2016, clearly state the terms and age ranges of diagnosis for this condition (see Figure 2):

For PID registry classifications these patients will initially be registered as unclassified hypogammaglobulinaemia and then changed to THI, if there is spontaneous resolution before the age of four years. Hence, the confirmed diagnosis of THI can be made only retrospectively. Hypogammaglobulinaemia due to prematurity is excluded.

AETIOLOGY

The aetiology of THI remains unknown. THI has been observed more commonly in male infants, estimated to be as frequent as 0.061–1.1 cases per 1 000 life births and is thought by most to represent an exaggeration of the physiological process of immune maturation. Some authors, however, regard THI as reflecting a diverse group of errors of the immune system which include documentation of reduced CD19 expression with decreased memory B cell numbers and transient elevation of circulating regulatory T cells. THI must be differentiated from true hypogammaglobulinaemia where IgG levels are two or more standard deviations below the normal mean levels for age and where B cell numbers
may be low. B cell proportion is similar to that in adults at birth, the B cell absolute number is, however, significantly higher in infancy than in adulthood. Despite this, the normal neonate has immature antigen-specific immune responses and relies on actively transferred, third-trimester maternal transplacental IgG for protection from infection in the first part of life. Hence, the expected nadir of IgG at 3–6 months of life can be much lower in a premature infant, especially if born before 32 weeks of age. IgA, IgM and IgE serum levels are normally low even in term infants because these Igs cannot cross the placenta. IgA and IgM production takes place in the foetus to neoantigens, and IgM can be stimulated significantly by in utero infections. Switching of Ig isotypes is also delayed when challenged in infancy. This manifests with earlier ability to respond to T cell-dependent and only later T cell-independent response maturation of antibody formation.

**CLINICAL PICTURE AND INVESTIGATIONS**

The investigation for recurrent infections, which commonly occur during the physiological IgG nadir of even normal infancy, or the routine screening for other causes may alert to the diagnosis. Infections, if they occur, are usually respiratory and limited mainly to the upper respiratory tract, they become less frequent with age and pneumonia is uncommon. Although 2.5 per cent of infants may fall below the 95 per cent confidence range for normal serum IgG levels, this is rarely diagnosed – the true incidence therefore being unknown. THI also does not impair the ability to produce specific antibodies to T-dependent antigens (e.g. tetanus or diphtheria toxoid); however, the response to polysaccharide antigens may be transiently impaired or not sustained and require repeat vaccinations (e.g. pneumococcal vaccine). The majority of THI infants develop normal Ig levels by 24 months of age, but this may be delayed until around 48 months. Infants who fail to achieve any normalisation of Ig levels after 24 months continue to have infections or develop autoimmune manifestations and show reduced IgM production and reduced switched memory B cells are diagnosed as having true hypogammaglobulinaemia and may be presenting as emerging common variable immunodeficiency (CVID). Therefore diagnosis of THI cannot be made with confidence until full resolution of the clinical and laboratory findings.⁵

**TREATMENT AND FOLLOW UP**

With a working diagnosis of THI, parents need to be reassured of the transient nature of the problem, but a plan of follow up should be structured with limited investigations to document maturation of the immune system and ultimate diagnosis of THI. Serial Ig measurements and, if available, vaccine antibody responses are indicated to document eventual resolution of the hypogammaglobulinaemia and a functional humoral immune response. For infants with persistent or recurrent infections, general measures such as reducing exposure to infections (e.g. a smaller daycare centre, restriction of exposure to other children) and prompt, appropriate treatment of respiratory infections is indicated. Inactivated (killed) vaccines (diphtheria, tetanus, pertussis, haemophilus influenzae and pneumococcal vaccines, killed influenza and polio vaccines, inactivated hepatitis A and B vaccines) should be given as scheduled. Live viral vaccines (measles, mumps, rubella, varicella, rotavirus) should be postponed. Some patients may need prophylactic antibiotics. Atopic manifestations including asthma which appear to be more common in THI should be treated appropriately. Ig replacement is only very rarely required and is not indicated if the infant is otherwise healthy. Monitoring Ig levels and vaccine antibody levels should be done at four to six month intervals. Despite good prognosis and overall mild clinical course, it is recommended that infants with THI should be followed up long term.

**KEY MESSAGES**

1. The diagnosis of THI is provisional until age four years and must be followed up at least until serum Ig levels normalise.
2. In THI the B cell must be greater than 2 per cent of peripheral blood lymphocytes in order to differentiate the condition from agammaglobulinaemia.
3. Where available, it is useful to document antibody vaccine responses to protein antigens which should be protective in THI

**DECLARATION OF CONFLICT OF INTEREST**

The authors declare no conflict of interest.

This article has been peer reviewed.

**REFERENCES**


**Further reading:**