Abnormal haematology results in children

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Summary

Care must be taken when interpreting haematology results in children. They have different physiology from adults so the normal ranges for results differ. The results also vary according to the age of the child. To ensure children are not misdiagnosed or incorrectly investigated, it is important to know if the reporting laboratory has established age-specific reference ranges for children.

Key words: haemoglobin, blood coagulation factors, partial thromboplastin time, prothrombin time.

Introduction

Pathology tests are an integral part of current medical practice. The accurate and appropriate interpretation of these tests is essential when they are being used for diagnosis or disease monitoring. The critical issues include:

- the choice of the correct test for the clinical situation

- an understanding of the 'normal' or expected results of the test

- an understanding of all of the potential causes of an abnormal result, including spurious causes

- the relative 'weight' that should be given to an abnormal result given the full clinical context.

Children add an additional layer of complexity to each of these issues. For example, issues related to sample collection and the use of capillary blood are particularly relevant causes of spurious results. Perhaps the most misunderstood issue is the concept of 'normal' in different age groups. Countless children are misdiagnosed or over-investigated because of a lack of understanding that they are not just 'little adults', but are physiologically different in many respects. This lack of understanding often extends to the laboratory reporting the results. The clinician may be led astray by reports that would be correct for adult patients, but are non-contributory or wrong in children. Nowhere is this more obvious than within haematology. Developmental or age-related changes in haemopoiesis and haemostasis have significant effects on the interpretation of some common pathology tests.

Full blood examination

In the full blood examination the greatest numerical difference between children and adults is seen in the white cell count and differential. The white cell count is significantly higher in children of all ages, until mid-adolescence where it approximates adult counts.

Neutrophils

A high neutrophil count is commonly seen, particularly in neonates. The neutrophil count may be up to 14×10^9/L in a normal neonate.[1] These 'normal' differences must be considered, for example in the diagnosis of bacterial infection. Other considerations are the potential response of the child to sepsis (very sick children may have neutropenia) and the effects of concomitant therapies such as steroids in croup or asthma. Features such as neutrophil vacuolation, toxic granulation or left shift with increased band forms are important determinants in the interpretation of neutrophil counts in children.

Lymphocytes

Compared to adults, a relative lymphocytosis is common in normal children. Lymphocyte counts up to 11×10^9/L are normal in children under twelve months and elevated counts persist until mid-adolescence.[1] Results that may suggest lymphoproliferative disorders in adult patients, are usually either normal, or reflect common clinical and subclinical viral infections in children. Less commonly understood is the fact that morphologically normal lymphocytes in young infants often appear atypical, or even blast-like. Experience with paediatric blood films is required to avoid the unnecessary suggestion of leukaemia in many children, or the overdiagnosis of specific viral infections associated with atypical lymphocytes.

Erythrocytes and haemoglobin

Red cell parameters vary significantly between the various age ranges. Relative polycythaemia is normal in the early days of life in both the term and premature newborn. The normal haemoglobin concentration ranges from 13.5 g/dL to 22.0 g/dL in the first weeks of life. This occurs in response to high fetal erythropoietin levels stimulated by the relative hypoxia experienced *in utero*.

The haemoglobin concentration in normal infants declines after birth to reach the physiological nadir at approximately

eight weeks of age (normal range 9.0–14.0 g/dL). Adverse neonatal events, prematurity and haemolysis (due, for example, to maternal-fetal ABO incompatibility) may impact significantly on the rate and extent of this decline. The causes of the decline include accelerated red cell loss around the time of delivery, reduced survival of neonatal red cells (approximately 90 days v. 120 days) and erythropoietin deficiency as a result of negative feedback from increased oxygenation after the normal neonatal circulation is established. The fall in haemoglobin reactivates erythropoietin production, and the normal feedback mechanism that persists for the remainder of life is established.[2]

Red cell size follows a similar pattern to the haemoglobin concentration. Fetal red blood cells are macrocytic relative to adults, with the normal range of mean cell volume (MCV) at birth 100–120 fl. This reduces to 85–110 fl by one month and 70–90 fl by six months, before increasing again from early adolescence to reach normal adult values (80–97 fl) by late adolescence.[2] The initial reduction in MCV occurs as the macrocytic fetal red cells are replaced during the first months of life.

Deviations in red cell size may indicate significant disease in children. Macrocytosis is commonly due to hepatic dysfunction, anticonvulsant therapy, hypothyroidism or B_{12}/folate deficiency, and is an early marker of significant bone marrow disorders such as aplastic anaemia. A reduced MCV suggests conditions such as iron deficiency or a thalassaemia syndrome. While iron studies and haemoglobinopathy screening are warranted in adults with an MCV in the high 70s fl, this result is normal for the majority of children through the years of mid-childhood. In the absence of prematurity or substantial blood loss, microcytosis in the first six months of life almost always indicates an α-thalassaemia carrier. Normal fetal iron stores are sufficient during this time, irrespective of diet, and β-thalassaemia carriers do not develop microcytosis until after haemoglobin chain switching (from fetal to adult haemoglobin) occurs at around six months.

Coagulation studies

Developmental haemostasis can produce significant discrepancies between normal ranges of coagulation studies, such as the prothrombin time and activated partial thromboplastin time (APTT), depending on age and prematurity.[3] Table 1 shows the normal ranges for APTT in our laboratory compared to the age-related reference ranges published in the literature. The impact of different reagent and analyser systems is obvious.

Most laboratories do not have the resources required to establish age-appropriate reference ranges, however, until such systems are put in place, over-investigation of normal children whose coagulation results are labelled abnormal will continue. The clinical dilemma is that significant conditions such as Von Willebrand's disease may exist in children with a mildly prolonged APTT.

Often the clinical rationale for coagulation testing in children relates to 'abnormal' bruising that may raise questions of non-accidental injury. The interpretation of results then becomes a matter for legal debate as well as clinical management. Simple calculations show that in our laboratory, if we used the adult reference range, approximately 30% of all 1–10 year-olds would be labelled as abnormal and further investigations would ensue. The direct costs of these further investigations (such as repeat APTT, intrinsic factor assays, and Von Willebrand's screening) amounts to hundreds of dollars per child.[4] This does not consider the indirect costs such as cancelled surgery, referral for specialist review, and missed work (parents) and school to attend hospital appointments.

There is therefore a considerable imperative for all laboratories performing coagulation studies in children to report the results accurately based on age-related reference ranges that are specific to their analyser and reagent systems. The clinician must also be circumspect in the interpretation of all coagulation studies in children.

Abnormalities of coagulation testing have different interpretations in children and adults. For example, a prolonged APTT that fails to correct on mixing studies (mixing studies usually involve a one-to-one mix of patient plasma with normal plasma before APTT testing) is commonly due to a so-called lupus anticoagulant. These non-specific antiphospholipid antibodies can be associated with autoimmune disease in

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Table 1

Normal ranges for activated partial thromboplastin time according to age

APTT (in seconds)	Age (years)				
	< 1	1–5	6–10	11–16	Adults
* Laboratory data[5]					
mean (range)	38 (26–50)	37 (30–45)	37 (29–46)	37 (31–44)	33 (28–38)
Published data[3,6,7]					
mean (range)	35.5 (28.1–42.9)	30 (24–36)	31 (26–36)	32 (26–37)	33 (27–40)

* As performed by the Royal Children's Hospital Laboratory on the STA-compact analyser with STAGO reagent systems (Diagnostica STAGO, France)

APTT   activated partial thromboplastin time

adults, and in particular thrombotic manifestations. While the same is true in children, they are far more frequently a transient phenomenon seen after viral illness and in these circumstances are rarely associated with significant pathology.

Conclusion

Misinterpretation of haematology tests in children is common. Specific issues need to be considered to ensure appropriate interpretation of results. In particular, an understanding of 'normal' for different age groups is critical to both full blood examination and coagulation studies. Many laboratories within Australia do not report these parameters appropriately, and the clinician must be aware of this to guide subsequent management and investigation.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 79)

3. Children bruise easily because they have a shorter partial thromboplastin time than adults do.
4. Microcytosis in a neonate is usually a sign of iron deficiency.

Book review

Statistics with common sense. David Kault. Westport (CT): Greenwood Publishing; 2003. 272 pages. Price $65 approx.*

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This is a refreshing change from the standard textbook on statistics. Rather than presenting statistics as a dry mathematical endeavour with the objective authority of an oracle, the author casts it as a useful decision aid in the context of making subjective and complex judgements in medicine.

The particular strength of the book is the explanation of the conceptual framework surrounding the 'frequentist' school of statistics and hypothesis testing, given in chapters 1 and 6. For anyone who has ever wondered what a p-value or a 95% confidence interval **really** mean, this is the section to read. There is also a good introduction to Bayesian statistics.

The author takes an unorthodox approach to explaining the principles behind various statistical tests that, by and large, works well. In chapters 3, 4, 5, 8 and 9 the author communicates an intuitive understanding of the principles behind t-tests, chi-square, ANOVA, regression, and various non-parametric tests. This is challenging and demanding; although those who are math-phobic will not find this easy, the educated practitioner who is not afraid to tackle the text and follow the logic will be rewarded. In some cases though, the unorthodox approach does not quite succeed; I found myself confused by the order in which the various tests are presented, and the relation between them, for example regression and correlation are presented together in chapter 8. Chapter 7 presents an absolutely first-rate discussion of causality, one that every clinician reading papers should know.

The book is very readable; the author uses accessible examples that do not require a medical background and builds his explanation like a narrative. This is both a strength and a weakness, in that it makes it a little more difficult to use the book as a reference (although there is a good index). The author also provides a free statistics software program on his web site which is useful.

In summary, this book has much to recommend it, and although it is neither a quick nor simple read, it lives up to its title as an excellent synthesis of statistics and common sense, a rare book that will give the persistent reader a better understanding of the uses (and misuses!) of statistics.

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