Fifteen-minute consultation: Red flags for metabolic disease in routine bloods

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CLINICAL CASE

A 5-year-old boy attends your paediatric clinic with a history of seizures, global developmental delay and autistic spectrum disorder. He has been extensively investigated previously but has no unifying diagnosis. Results from genetic tests are pending. After an outpatient clinic appointment, you notice that his blood results are flagged up as being abnormal. On review of these the only number outside the reference range is creatinine, which is low at 15 µmol/L. From his previous test results, you notice that he has had a persistently low creatinine level. You wonder whether he is unable to produce creatinine and if this is significant to his presentation. After a literature review you refer to the metabolic clinic.

INTRODUCTION

In paediatrics the concept of 'routine bloods' is a misleading term as blood tests are invasive and investigations should only be requested if they will influence practice. Recent debate has highlighted a need for culture change to prevent overinvestigation.[1] However, it is reasonable to suggest that in most paediatric units, there is a standard set of baseline bloods and that many children will have a range of blood tests taken as part of a standard work-up when their diagnosis is unclear. These may be taken with little expectation of abnormalities, and subtle variants from the normal range, especially those below the reference range, could be potentially overlooked, felt to be insignificant or serially checked with no clear conclusion. In contrast, a 'metabolic screen' involving a wide range of investigations is considered in specific patients to seek out inborn errors of metabolism (IEM) and increased weight may be placed on more specialised tests. Here we discuss markers of IEM that may be hidden in the routine test results pile.

ROUTINE TESTS

It is worth noting that the most common tests in each unit will vary slightly and the components measured in each may differ, along with the normal ranges based on local population or reference standards. We will therefore discuss specific findings from tests without reference ranges and will cover the more common tests observed in the authors' experience.

Full blood count

Within the full blood count there is the potential to detect a range of abnormalities of relevance to paediatric metabolic disorders.

Macrocytic anaemia

Perhaps the most obvious cause of this is a potential disturbance in folate or cobalamin (vitamin B_{12}) metabolism.[2–5] This may also be seen in other disorders such as some mitochondrial conditions. In disorders of cobalamin or folate metabolism, there may be additional features such as neurological symptoms, depending on the part of the relevant pathway which is affected.[6]

Haemolytic anaemia

This may also have a metabolic cause as in galactosaemia, Wilson disease and erythropoietic porphyrias, among other conditions.[3] Again, these conditions will have other presenting features that assist in directing further investigation.

It is worth considering that anaemia may also be present in patients with an IEM as a consequence of a combination of

factors including disease complications or as a reflection of nutritional status and chronic illness.

Blood film findings

Some laboratories my automatically provide a blood film or comment on the presence of specific cell abnormalities. This may suggest a diagnosis or prompt further investigation, although a blood film is not always sufficient to establish a diagnosis. Sideroblastic anaemia may be a particular feature in some mitochondrial disorders in which there is bone marrow involvement.[7] Acanthocytes, spur cells, may be seen in a number of conditions where the red cell membrane lipid structure is altered. Relevant metabolic diseases include abetalipoproteinaemia and Wolman disease, which have a neonatal onset with diarrhoea and failure to thrive being prominent symptoms. These cells may also occur in vitamin E deficiency, advanced uraemia, postsplenectomy, hypothyroidism, severe liver cell damage or anorexia nervosa, so their presence does not immediately diagnose an IEM.[2] The presence of vacuolated lymphocytes is suggestive of lysosomal storage disorders such as Pompe disease and ceroid lipofuscinosis (Batten disease),[2 3 5] although their absence on a routine blood film does not exclude such disorders and further specific blood film analysis may be required.

Furthermore, thrombocytopaenia, leucopenia and pancytopaenia may feature in IEMs to differing degrees. Relevant disorders include organic acidurias, lysinuric protein intolerance and Gaucher disease (and other disorders with splenomegaly) to name a few.[3]

Electrolytes

These may be checked on blood gas analysis or on serum samples. Sodium, potassium, chloride, calcium, phosphate and magnesium are the most likely to be considered in decreasing order of frequency. The potential for disturbance of these in relation to metabolic disease is extensive and multiple factors may influence levels so these will not be discussed at length. For example, hypocalcaemia is a particular feature of organic acidurias in a sick neonate.[4] Derangement of several electrolytes could be a feature of renal tubulopathy related to an IEM, such as mitochondrial disorders, tyrosinaemia type 1 or cystinosis.[3]

Renal function

Dependent on local laboratory test request formats, 'renal function' tests may include some electrolytes as listed above, but the urea and creatinine are also of importance in metabolic disorders.

Creatinine

A low creatinine is a feature of disorders of creatine biosynthesis.[3 5] These disorders lead to cerebral creatine deficiency, and therefore epilepsy, intellectual disability and speech impairment.[2]

Urea

An elevated urea level can be a feature in malonyl-coA decarboxylase deficiency, hyperoxaluria, cystinosis[4] and of course renal impairment of any aetiology. A low urea level can be seen in urea cycle disorders and lysinuric protein deficiency[4] due to disruption of the urea cycle. Specialised tests are indicated to support these diagnoses, and care is required in interpretation as urea levels are dependent on protein intake, lean body mass and hydration among various other factors.[8] In the absence of an obvious cause of elevated or reduced urea levels, further investigation should be undertaken.

Bicarbonate

Renal function tests may also include a measure of bicarbonate, and this should be noted so as not to disregard evidence of underlying metabolic acidosis or, less commonly, alkalosis which has not otherwise been suspected. In particular it is worth calculating the anion gap when metabolic acidosis is present.

Anion gap = $[Na^+] - [Cl^- + HCO_3^-]$, normal range 7–16 mmol/L.

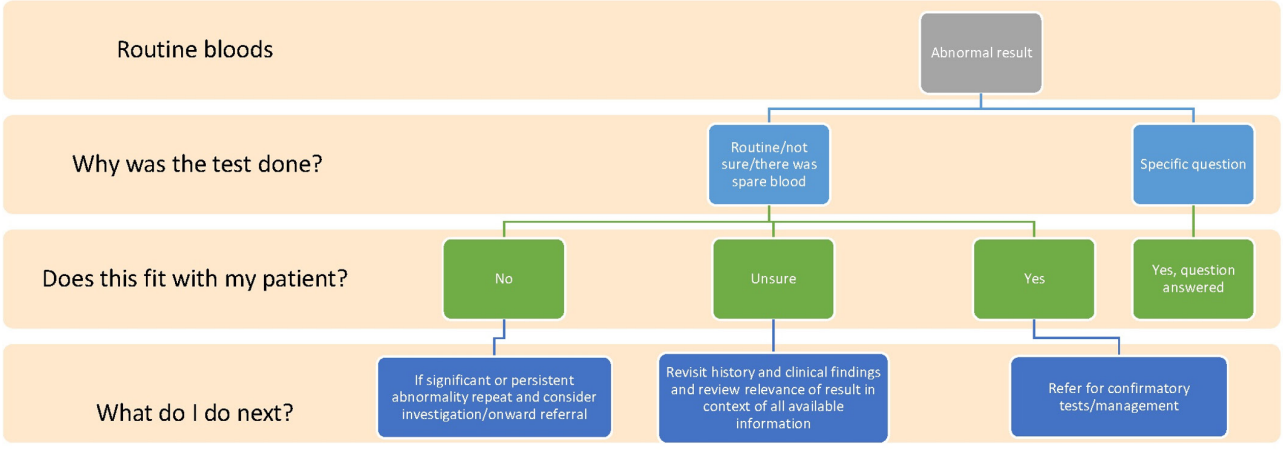

Figure 1 Decision tool to guide management of abnormal 'routine' blood tests.

A metabolic acidosis with a normal anion gap may be due to a variety of diseases causing renal or gastrointestinal bicarbonate loss. However, a raised anion gap metabolic acidosis signifies the presence of organic anions. These may be acquired or reflect an underlying metabolic disorder depending on the clinical context.[2] For example, an elevated lactate could be secondary to tissue hypoxia in a child with severe shock or present in a relatively well patient with a respiratory chain disorder; both patients would have a raised anion gap metabolic acidosis. Accumulation of other compounds such as propionic acid in propionic acidaemia will also generate a raised anion gap. Urine organic acid analysis is an appropriate next investigation.

Liver function tests

Many IEMs involve the liver and result in derangement in liver function tests.

Bilirubin

A cholestatic jaundice, elevated conjugated bilirubin, is a feature of metabolic disorders such as galactosaemia, tyrosinaemia type 1, arginase deficiency and long-chain 3-hydroxyacy-CoA dehydrogenase deficiency to name a few.[3]

Liver enzymes

Of course, liver function tests need to be considered in the clinical context, and some IEMs will result in a liver impairment during acute illness. General derangement of the liver enzymes is seen in the conditions listed above, but also some congenital disorders of glycosylation, fatty acid oxidation disorders, and certain mitochondrial and lysosomal storage disorders.[3] The age of the patient and the presence or absence of associated symptoms determine how to proceed with further investigations. More specifically, a raised alkaline phosphatase is a feature of bile acid synthesis defects and hypoparathyroidism.[2 5] A low alkaline phosphatase is found in hypophosphatasia.[2]

Uric acid

Uric acid is a test which may be requested in cases of diagnostic uncertainty and abnormal levels can reflect significant abnormalities. In particular, low levels may indicate disorders of purine metabolism and molybdenum cofactor deficiency. Levels above the reference range may also be present in some purine disorders, but also glycogen storage disorders, mitochondrial disease, fatty acid oxidation disorders and fructose intolerance.[2] Again, any abnormal result needs to be considered within the clinical context as demonstrated in the decision tool in figure 1.

CONCLUSION

The list of 'routine' investigations we have covered is by no means comprehensive, and there are undoubtedly more conditions involving metabolic pathways that influence these test results. However, this brief review of the more commonly performed blood tests in paediatrics shows that these are relevant to the investigation for IEMs. We have demonstrated that it is possible to find markers of complex and at times difficult-to-diagnose disease in the 'basic' tests if an open mind is kept.

Key messages

- All investigation results need to be carefully considered and evaluated in the clinical context.
- Abnormal results outside the reference range, either high or low, may indicate a disease process.
- Inborn errors of metabolism are a diverse group of conditions and require consideration of all available information to assist diagnosis.
- Sometimes it is possible to detect a rare diagnosis with a simple, everyday test, if vigilant.

Test your knowledge

1. Vacuolated lymphocytes are a feature in:
   A. Pompe disease.
   B. Respiratory chain disorders.
   C. Batten disease.
   D. Congenital disorders of glycosylation.
   E. Menkes disease.
2. Acanthocytes may be seen in:
   A. Vitamin C deficiency.
   B. Abetalipoproteinaemia.
   C. Wolman disease.
   D. Hyperthyroidism.
   E. Uraemia.
3. An elevated urea level is seen in:
   A. Urea cycle disorders.
   B. Propionic aciduria.
   C. Cystinosis.
   D. Lysinuric protein deficiency.
   E. Hyperoxaluria.
4. The following associations are true:
   A. Folate metabolism defect–macrocytic anaemia.
   B. Organic acidurias–hypomagnesaemia.
   C. Bile acid synthesis disorder–low alkaline phosphatase.
   D. Fatty acid oxidation disorders–deranged liver enzymes.
   E. Mitochondrial disorders–low urea.
5. Inborn errors of metabolism associated with cholestatic jaundice include:
   A. Hypothyroidism.
   B. Tyrosinaemia.
   C. Porphyria.
   D. Galactosaemia.
   E. Phenylketonuria.

Answers to the quiz are at the end of the references.

CASE STUDY OUTCOME

The patient is seen at a metabolic clinic and the diagnosis of guanidinoacetate methyltransferase (GAMT) deficiency, a form of cerebral creatine deficiency, is suspected. Genetic tests confirm compound heterozygous mutations in the *GAMT* gene and biochemical tests support this. Treatment with creatine and then ornithine supplements is commenced. When you next review the patient, his parents are happy to report that they have noted some developmental progress.

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Answers to the multiple choice questions

1. A, C.
2. B, C, E.
3. C, E.
4. A, D.
5. B, D.