National Metabolic Biochemistry Network

Best Practice Guidelines for the Biochemical Investigation of Patients with Foetal and Neonatal Hydrops

INTRODUCTION

Hydrops is defined as the presence of skin oedema plus effusions in at least one body cavity. In some cases foetal or congenital ascites may be the main presenting feature. Both these aspects must be present. A recent meta-analysis (Bellini et al 2009) suggests inborn errors of metabolism are a relatively rare cause of non-immune hydrops however this may be an underestimate due to lack of awareness and a failure to collect suitable samples. However, when the more common causes have been excluded and particularly when there have been repeated cases in the family, it is important to exclude certain groups of disorders, which have been reported to be associated with this presentation.

Therefore, before investigating for an inherited metabolic disease, the following non-metabolic causes should be considered: -

1. Cardiac structural abnormalities
2. Other cardiac disorders e.g. infection, tumours, conduction disorders
3. Chromosome abnormalities e.g. 45X, Trisomy 21, Trisomy 18
4. Intrathoracic abnormalities e.g. chylothorax, congenital cystic adenomatous malformation of lung.
5. Twin-twin Transfusion
6. Haematological disorders (Foetal Anaemia)
7. Infections e.g. CMV, Toxoplasmosis, Parvovirus
8. Musculo-skeletal disorders e.g. certain lethal skeletodysplasias
9. Tumours eg sacrococcygeal teratoma
10. Vascular abnormalities e.g. foetal angiomas
11. Urogenital abnormalities

12. Gastrointestinal disorders

13. Liver disease - infection can be a cause foetal liver disease

14. Maternal disorders

15. Foetal akinesia e.g. lethal multiple pterygneal syndrome' arthrogryposis multiplex congenita.

GUIDELINES FOR INVESTIGATION FOR INHERITED METABOLIC DISEASES

A list of diseases in which there have been reports of foetal or neonatal hydrops is provided in the attached table. If there is no obvious cause for the hydrops and an inherited metabolic disease is suspected, then collection of the following specimens should be considered.

Skin biopsies are preferred to blood samples for enzyme analysis, as in neonates it is difficult to obtain sufficient blood for the wide range of tests required.

We have deliberately not included details of sample volumes, anticoagulants, transport requirements etc as these can vary between laboratories. These should be confirmed with your local specialist IMD laboratory (see http://www.metbio.net) before collection.

SPECIMEN COLLECTION

The specimens that can be collected depend upon whether hydrops is detected in utero and whether a hydropic baby is born dead or alive.

Specimens Which May Be Collected For The Investigation Of A Hydropic Foetus In Utero

An amniotic fluid sample for culture and for one and two dimensional mucopolysaccharide (glycosaminoglycan) electrophoresis of the supernatant.

Specimens Which May Be Collected For The Investigation Of The Dead Foetus

The potential importance of a perinatal autopsy should be discussed in such cases. The following specimens are suggested:-

1. Foetal skin for culture for chromosome analysis and biochemical tests (enzyme analysis).

2. Foetal blood for investigation of haemoglobinopathies.

3. Placental tissue for histological analysis.
Culture of this tissue is also possible; however, such cell lines often show early senescence.

4. Foetal urine (if available).

5. Liver and muscle for histology/histochemistry.
Histological examination for possible lysosomal or cytosolic storage material is important

6. A tissue sample (unfixed) e.g. liver or spleen for possible DNA analysis.

Specimens Which May Be Collected For The Investigation Of The Live Neonate

1. Urine for mucopolysaccharide, oligosaccharide and organic acid analysis.

2. Blood for plasma acylcarnitines, I-cell screen 7-dehydrocholesterol, chitotriosidase, very long chain fatty acids and transferrin electrophoresis.

Note:- In Congenital Disorders of Glycosylation the pattern of transferrin isoforms may be normal in neonates.

3. Blood lactate.

4. Blood in EDTA for DNA extraction and storage

5. Blood ferritin.

6. Blood for assay of erythrocyte enzymes (if there is a haemolytic anaemia).

7. Blood for leucocyte or plasma lysosomal enzymes (after discussion with the local Metabolic Disease Laboratory). If the blood volume required is too large or a reliable test is not available in leucocytes then a skin biopsy for fibroblast culture may be required.

8. Consider a bone marrow biopsy/aspirate to look for foam cells and electron microscopy for inclusions.

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DISCLAIMER

These are laboratory guidelines reflecting current best practice in specialist metabolic laboratories the UK. They are not evidence based but reflect expert opinion. The network cannot accept any responsibility for any errors/omissions and users must take responsibility for use.

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Inherited Metabolic Disorders that may present with Hydrops

In this table we do not distinguish between first and second line tests. The tests performed will be influenced by the samples that can be obtained and the volumes available.

Disorder	Diagnostic Test	Specimen Requirements
Congenital Disorders of Glycosylation	Plasma transferrin electrophoresis or isoelectric focusing	Plasma or serum (NB Affected neonates may have a normal pattern)
Carnitine deficiency	Plasma carnitine/acylcarnitines	Blood sample
Cytochrome oxidase deficiency (or other disorder of the respiratory chain	Blood & CSF lactate Muscle biopsy Fibroblast cytochrome oxidase	Muscle and skin biopsies
Enzymopaenic anaemias e.g. Pyruvate kinase deficiency, hexokinase deficiency, G6PDH deficiency, glucose phosphate isomerase deficiency	Erythrocyte enzymes	Blood sample
Farber disease	Leucocyte or fibroblast acid ceramidase	Blood sample or a skin biopsy
Fumarase deficiency	Urine organic acids Fibroblast fumarase assay	Urine Skin Biopsy
Gaucher Disease	Plasma chitotriosidase Leucocyte or Fibroblast β-glucosidase	Plasma or serum Blood sample or a skin biopsy
Glycogen Storage Disease IIb (Danon Disease)	Immunohistological Assay of LAMP2 Sequencing of LAMP2 gene	Blood sample
Glycogen Storage Disease Type IV (Brancher Defect)	Leucocyte or Fibroblast Brancher Enzyme	Blood sample or a skin biopsy
GM1 Gangliosidosis, Galactosialidosis	Urine oligosaccharides Leucocyte or fibroblast β-galactosidase and α- neuraminidase	Urine, Blood sample or a skin biopsy
Hurler disease (MPS I)	Urine mucopolysaccharides Leucocyte or fibroblast α-iduronidase	Urine Blood sample or a skin biopsy

Hydrops-ectopic calcification-moth-eaten skeletal dysplasia (Greenberg Dysplasia)	Plasma Sterols	Blood sample
I-cell Disease	Plasma I-cell screen (grossly elevated lysosomal enzymes)	Plasma or serum
Mevalonic Aciduria	Urine organic acids (these may only be abnormal in acute episodes) Mevalonate Kinase Assay and/or mutation analysis	Urine Blood sample or skin biopsy
Morquio disease type A (MPS IVA)	Urine mucopolysaccharides (2D-electrophoresis) Fibroblast or leucocyte galactose-6-sulphatase	Urine Blood sample or a skin biopsy
Mucolipidosis type I (Sialidosis)	Urine oligosaccharides Leucocyte or fibroblast α-neuraminidase	Urine Blood sample or a skin biopsy
Multiple Sulphatase Deficiency	Urine mucopolysaccharides Leucocyte or fibroblast sulphatases	Urine Blood sample or a skin biopsy
Neonatal haemochromatosis	Plasma iron, ferritin & TIBC Liver iron	Blood sample or a liver biopsy
Niemann-Pick disease type A	Plasma chitotriosidase Leucocyte or fibroblast sphingomyelinase	Plasma or serum Blood sample or a skin biopsy
Niemann-Pick disease type C	Plasma chitotriosidase Bone marrow biopsy Skin biopsy for cholesterol uptake studies and cholesterol staining DNA analysis for common mutations and full mutation screening	Plasma or serum Skin biopsy for culture Blood sample
S-Adenosylhomocysteine hydrolase deficiency	Plasma amino acids and S-adenosylhomocysteine quantitation	Plasma sample.
Sialic acid storage disease	Urine oligosaccharides Fibroblast sialic acid	Urine or a skin biopsy
Sly's disease (MPS VII)	Urine mucopolysaccharides Plasma, Leucocyte or Fibroblast β-glucuronidase	Urine Plasma or Serum Blood sample or a skin biopsy
Smith-Lemli-Opitz Syndrome	Plasma 7-dehydrocholesterol	Plasma or serum
Transaldolase Deficiency	Urine Polyols	Urine
Wolman Disease	Leucocyte or fibroblast acid esterase	Blood sample or a skin biopsy
Zellweger Syndrome	Plasma VLCFA	Plasma or serum

Please contact your local Metabolic Laboratory for details of specimen requirements (www.metbio.net).