Guidelines for the diagnosis of inherited metabolic disease in children with dysmorphic features

Dysmorphic features include abnormalities of the face and other organs. They may be apparent at birth or develop progressively with age. They can be an important diagnostic clue to a number of inborn errors of metabolism especially if associated with one or more other features including neurological problems, skeletal abnormalities, liver disease, failure to thrive, renal dysfunction, cardiomyopathy or ocular abnormalities.

1. The Dysmorphic Neonate

In the neonate mild dysmorphic features are difficult to detect and easy to imagine. However, obvious severe dysmorphism indicates an intrauterine insult or an inherited disorder. In the vast majority of cases there is a chromosome abnormality or intrauterine infection. However, in some cases it may be due to an inborn error of metabolism. It is important to perform a full clinical examination for other features e.g. neurological problems, skeletal abnormalities, liver disease, renal abnormalities, and cardiac anomalies as well as to collect an appropriate specimen for chromosome analysis.

2. The Dysmorphic Child and Infant

Dysmorphic features may not be present at birth but may develop with age at varying rates. Sometimes other clinical symptoms may pre-date the detection of dysmorphic features whilst in other cases dysmorphism may be the reason for referral and other symptoms may not develop for some time. It is important to distinguish between coarse features and other dysmorphic features. As stated earlier it is important to look for other clinical features particularly those affecting the skeletal system and the eyes.

Biochemical Investigations

The pattern of clinical symptoms may suggest a particular disorder. However in general to investigate for inborn errors of metabolism in the above patients the following specimens should be considered as first line investigations.
Please contact your local MetBioNet laboratory (http://www.metbio.net/metbioLaboratories.asp) for sample requirements as they may vary from centre to centre.

1) Urine for organic acids, glycosaminoglycans (MPS), oligosaccharides and amino acids.

2) Blood for lactate, acylcarnitines, phytanic acid, cholesterol, 7-dehydrocholesterol, very long-chain fatty acids, I-cell screen, chitotriosidase and analysis of transferrin isoforms. (N.B. This latter test may give false negative results in premature babies and neonates).

Other investigations that would be considered as second line (or first line if the clinical symptoms indicate) would include plasma sterols and specific enzyme assays in leucocytes or fibroblasts for lysosomal storage diseases or other disorders.

The following table lists inborn errors of metabolism that can present at various ages with marked dysmorphic features as a main feature together with other clinical features that may give a clue to diagnosis and the first line tests that are usually done to diagnose these disorders. The terms Congenital and Later onset refer to the ages when the first clinical symptoms may occur.

Disease	Onset of Dysmorphism	Other Features	First Line Test	Diagnostic Test
C=Congenital L = Later Onset Co = Coarse Facies				
LYSOSOMAL STORAGE DISEASES [1]				
I-cell Disease (Mucolipidosis III)	C (Co)	Heart disease, skeletal abnormalities	Plasma I-cell screen (grossly elevated plasma lysosomal enzymes)	Mutation Analysis
Pseudo-Hurler Polydystrophy (Mucolipidosis III)	L (Mild)	Skeletal abnormalities which may be mild in younger patients	Plasma I-cell screen (grossly elevated plasma lysosomal enzymes)	Mutation Analysis
GM1-Gangliosidosis	C or L (Co)	Skeletal abnormalities, hypertonia	Urine oligosaccharides and enzyme assay	β-galactosidase

Multiple sulphatase deficiency	C or L (Co)	Variable - may present like an MPS disorder, ichthyosis	Urine MPS (may show variable patterns and can be normal)	Leucocyte and plasma sulphatases
Disease	**Onset of Dysmorphism**	**Other Features**	**First Line Test**	**Diagnostic Test**
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MUCOPOLYSACCHARIDOSES				
Hurler syndrome (MPS I)	L (Co)	Mental retardation, skeletal abnormalities, corneal clouding	Urine MPS	α-iduronidase
Hunter syndrome (MPS II)	L (Co)	Mental retardation, skeletal abnormalities	Urine MPS	α-iduronate sulphatase
Sanfilippo syndrome (MPS III)	L (Mild)	Mental retardation, hyperactivity, sleep disturbance	Urine MPS	One of four enzymes of heparan sulphate degradation
Morquio syndrome (MPS IV)	L (Co)	Skeletal abnormalities	Urine MPS (Two dimensional cellulose acetate electrophoresis)	galactose-6-sulphatase
Maroteaux-Lamy syndrome (MPS VI)	L (Co)	Skeletal abnormalities	Urine MPS	arylsulphatase B
Sly syndrome (MPS VII)	C or L (Co)	Variable presentation, skeletal abnormalities, mental retardation, hydrops.	Urine MPS (enzyme assay may be necessary)	β-glucuronidase

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GLYCOPROTEINOSES				
α-Mannosidosis	L (Co)	Deafness, skeletal abnormalities, mental retardation, corneal opacities	Urine oligosaccharides (enzyme assay may be necessary)	α-mannosidase
β-Mannosidosis	L (Co)	Skeletal abnormalities, mental retardation, variable presentation	Urine oligosaccharides (enzyme assay may be necessary)	β-mannosidase
Fucosidosis	C & L (Co)	Hypotonia, mental retardation, dementia, ataxia, skeletal abnormalities	Urine oligosaccharides (enzyme assay may be necessary)	α-fucosidase
Galactosialidosis	C or L (Co)	Skeletal abnormalities, mental retardation, hepatosplenomegaly, hydrops, cherry red spot.	Urine oligosaccharides (enzyme assay may be necessary)	β-galactosidase and fibroblast α-neuraminidase
Mucolipidosis I (Sialidosis type 2)	C or L (Co)	Skeletal abnormalities, mental retardation, hepatosplenomegaly, hydrops, cherry red spot.	Urine oligosaccharides (enzyme assay may be necessary)	Fibroblast α-neuraminidase and β-galactosidase
Sialic Aciduria (Salla Disease)	C or L (Co)	Mental retardation, dystonia, cardiomegaly, hydrops, hepatosplenomegaly	Urine oligosaccharides (sialic acid)	Quantitation of sialic acid in urine or fibroblasts
Aspartyglucosaminuria	L (Co)	Hepatosplenomegaly, developmental delay, skeletal abnormalities	Urine oligosaccharides (enzyme assay may be necessary)	Aspartylglucosaminidase
Pycnodysostosis	L	Short stature, osteosclerosis, bone dysplasia, fractures, dental abnormalities	Mutation Screening of Cathepsin K Gene	Mutation Screening of Cathepsin K Gene

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PEROXISOMAL DISORDERS [2]				
Zellweger syndrome and isolated disorders of peroxisomal fatty acid oxidation	C or L	Seizures, hypotonia, characteristic dysmorphic features, failure to thrive, dev delay	Plasma VLCFA	Fibroblast DHAP-AT, red cell plasmalogens, plasma phytanate/pristanate and bile acids. Fibroblast beta oxidation and mutations of beta oxidation deficiencies.
Rhizomelic Chondrodysplasia Punctata	C	Proximal limb shortening (rhizomelia), punctuate calcifications, corneal clouding,	Red cell plasmalogens plasma phytanic acid (diet related)	DHAP-AT enzyme assay

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DISORDERS OF CHOLESTEROL BIOSYNTHESIS [3]				
Smith-Lemli-Opitz Syndrome	C	Microcephaly, mental retardation, syndactyly, congenital heart defects, cystic dysplasia of kidneys, aganglionic colon, genital malformation	Plasma 7-dehydrocholesterol	Mutation analysis of the 7-dehydrocholesterol reductase gene
Desmosterolosis	C	Ambiguous genitalia, macrocephaly, anomalous pulmonary venous drainage, renal hypoplasia	Plasma sterols (Desmosterol)	3β-hydroxysterol Δ^{24}-reductase gene (*DHCR24*) mutation
Conradi-Hünermann Syndrome	C, L	Ichthyosis, chondrodysplasia punctata, asymmetric limb shortening, cataracts, short stature	Plasma sterols (8-dehydrocholesterol and cholesten-8(9)-OL but this can be normal).	Mutation analysis of the sterol Δ^{8}-Δ^{7}isomerase gene (CDPX2)
CHILD syndrome (Congenital Hemidysplasia with Ichthyosiform skin lesions)	C	Unilateral dysmorphology, ichthyosis, ipsilateral limb shortening, calcific stippling	No reliable test (4-Dimethylcholesterol may be increased).	*NSDHL* mutation testing
Lathosterolosis	C.L	Mental retardation, polydactyly, vertebral anomalies, liver disease	Plasma sterols (Lathosterol)	Mutation analysis of the 3β-hydroxysterol Δ^{5}-desaturase gene
HEM/Greenberg Skeletal Dysplasia	C,L	Macrocephaly, foetal hydrops, limb shortening, abnormal calcification, Pelguer-Huet anomaly in granulocytes	Plasma sterols (Cholesta-8,14-dienol)	Mutation analysis of the 3β-hydroxysterol Δ^{14}-reductase gene

Disease	Onset of Dysmorphic Features	Other Features	First Line Test	Diagnostic Test
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AMINO ACID DISORDERS				
Maternal PKU [4]	L	Microcephaly, heart defects, IUGR	Maternal plasma phenylalanine quantitation	
ORGANIC ACID DISORDERS				
Glutaric Aciduria type 2 [5]	C	Hypoglycaemia, hypotonia, heart disease, abnormal odour	Urine organic acids & plasma acylcarnitines	Fibroblast fatty acid oxidation studies, or ETF or ETF reductase assay
Carnitine Palmitoyl Transferase 2 [6] Deficiency	C	Hypoglycaemia, hypotonia, heart disease,	Urine organic acids & plasma acylcarnitines	Fibroblast fatty acid oxidation studies or specific enzyme assay.
Cobalamin F Disease [7]	C	Trigonocephaly, micrognathia, asymmetric eras, congenital heart defect	Urine organic acids & plasma acylcarnitines	Fibroblast incorporation and complementation analysis & mutation analysis of the LMBRD1 gene
D-2-Hydroxyglutaric Aciduria [8]	C	Epilepsy, hypotonia, visual failure, developmental delay	Urine organic acids & plasma acylcarnitines	Fibroblast D-2-hydroxyglutrate dehydrogenase assay.
3 Hydroxyisobutyric Aciduria [9]	C	Failure to thrive, seizures, multiple abnormalities	Urine organic acids& plasma acylcarnitines	3-hydroxyisobutyryl-CoA deacylase assay
Fumarase Deficiency [10]	C	Seizures, microcephaly hydrocephalus, enecephalopathy	Urine organic acids	Fibroblast fumarase assay
Glycerol kinase deficiency [11] (Contiguous gene syndrome)	C	Abnormal genitalia, muscle weakness, short stature, mental retardation	Urine organic acids, plasma CK	Glycerol kinase assay, X-chromosome FISH analysis
Mevalonic Aciduria [12]	L (Malformations)	Mental retardation, myopathy, hepatosplenomegaly, cataracts, failure to thrive	Urine organic acids(these may only be abnormal in acute episodes)	Mevalonate kinase assay or mutation analysis.

SULPHATION DISORDERS				
X-linked Chondrodysplasia Punctata [13]	C or L	Short stature, distal phalangial hypoplasia, punctate calcification	Fibroblast arylsulphatase E assay or mutation analysis	
Diastrophic Dysplasia [14] Atelosteogenesis type II Achondrogenesis type IB	C or L	Neonatal forms are lethal. Later onset forms can survive to adulthood. Short limbs, short stature, deformities of joints and limbs	Sulphate transport in fibroblasts or mutation analysis	

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OTHERS				
Pyruvate dehydrogenase deficiency [15]	C	Hypotonia, metabolic acidosis. Severe forms may have frontal bossing, a depressed nasal bridge, anteverted nasal tip and a large and unusually shaped ear. Agenesis of the corpus callosum	Plasma/CSF lactate (these may be normal in the first 24 hours after birth)	Fibroblast pyruvate dehydrogenase
Congenital disorders of glycosylation (CDG syndrome) [16] (Complex set of N- and O-linked glycosylation defects, CDG type I is the most common)	C & L	Developmental delay, liver disease, cardiomyopathy, ataxia, cerebellar hypoplasia, hypogonadism, mental retardation, inverted nipples, abnormal fat pads on buttocks, multiple forms of eye abnormalities.	Serum transferrin electrophoresis/isoelectric focusing	Phosphomannomutase or isomerase assays (CDG I) and lipid-linked oligosaccharide analysis in fibroblasts
Lowe Syndrome [17]	C	Corneal clouding, glaucoma, Fanconi syndrome, hypotonia	Urine amino acids. (generalised amino aciduria)	Phosphatidylbisphosphatase assay, mutation analysis of OCR1 gene

Molybdenum Cofactor Deficiency and Isolated Sulphite Oxidase deficiency [18]	C	Tonic/Clonic seizures, lens dislocation, psychomotor retardation	Plasma/urine S-sulphocysteine	Fibroblast sulphite oxidase assay. Mutation screening of molybdenum cofactor synthesis genes or sulphite oxidase genes.
Transaldolase deficiency [19]	C	Bleeding tendency, thrombocytopaenia, hepatosplenomegaly, haemolytic anaemia, antimongoloid slant, low set ears, cutis laxa	Urine polyols	Fibroblast, lymphoblast or liver transaldolase assay

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Disclaimer

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