Summary

- It is becoming clear that multiple genes with complex interactions underlie autism spectrum disorders (ASD). A small subset of people with ASD, however, actually suffer from rare single-gene disorders –
- Important to diagnose because this affects recurrence risk predictions for the family and prognosis for the patient.
- Most importantly, some of these conditions are metabolic disorders with specific therapies that, when started early, can prevent irreversible brain damage.
- This talk will focus on how to rule out the treatable metabolic causes of ASD.

Definitions

- Autistic Disorder
- Listed as one of the Pervasive Developmental Disorders (PDD)
  - Diagnostic and Statistical Manual of Mental Disorders (DSM IV – TR)
  - International Classification of Diseases (ICD-10)
- Autism Spectrum Disorders = Autism
  - Autistic Disorder + Asperger + PDD-not otherwise specified
  - Rett syndrome + childhood disintegrative disorder

Syndromic versus Etiologic

- Syndromic – categorization based on collection of observed symptoms / behaviours
  - “markedly abnormal or impaired development in social interaction and communication and a markedly restricted repertoire of activity and interests”
  - Repetitive / stereotypic behaviour
- Etiologic – categorization based on underlying biological cause
  - Phenylketonuria (PKU) – deficiency of phenylalanine hydroxylase leading to blood phenylalanine levels greater than 600 uM

Why does it matter?

- Autism recurrence risk 2-6%
  - Effect of treatment on prognosis...
- Metabolic disease recurrence risk 25%
  - For some diseases large effect of treatment on prognosis
  - Usually prenatal diagnosis is available
Genetic syndromes

- Fragile X: 2-5% of autism
- Tuberous sclerosis: 3-4%
- 15q (Angelman/PWS): 1-2%
- 16p11 deletion: 1%
- 22q deletion: 1%

Metabolic disorders

- Aminoacid disorders
- Creatine deficiency disorders
- Neurotransmitter disorders
- Organic acid disorders
- Purine / pyrimidine disorders
- Lysosomal storage disorders
- Cholesterol biosynthesis disorders
- Mitochondrial disorders

Inborn Errors of Metabolism

A defect reducing protein function (enzyme activity) that causes a block in a metabolic pathway, leading to:

1. deficiency of product
2. accumulation of substrate(s)
3. formation of unusual metabolites

Phenylketonuria

- PKU
- Phenylketones in the urine
- Amino acid disorder
- Deficiency of enzyme phenylalanine hydroxylase
- Hyperphenylalaninemia
- Smell, decreased pigmentation, mental retardation (IQ 35), seizures, autism

PKU Pathophysiology

- Autosomal recessive, 1/10K-20K, PAH deficiency
- Dietary intake Phe necessary
- Phenylalanine hydroxylase deficiency
- Melanin production inhibited
PKU Treatment
- Treated early, very good outcome
- Treated later...
- Dietary phenylalanine control
- Tetrahydrobiopterin (Kuvan) supplementation
- Enzyme replacement therapy (PEG-PAL)

Aminoacid disorders
- Histidinemia
  - Mental retardation
  - Speech disturbances
  - Autism
  - ...or completely normal
- Autosomal recessive, 1/12K
- Histidase deficiency
- Diagnose: Plasma amino acid analysis
- Treat: Diet?

Aminoacid disorders
- Urea cycle defects
  - Episodic illness (vomiting, lethargy, coma)
  - Autism, MR, hyperactivity, behaviour
- Many genes/enzymes
- Autosomal recessive and X-linked
- Diagnose: Plasma + urine amino acid analysis
  - Urine orotic acid, plasma ammonia
- Treat: Diet, drugs

Creatine deficiency disorders
- Guanidinoacetate methyltransferase deficiency
- Arginine-glycine amidinotransferase deficiency
- Creatine transporter defect
  - Autism, mental retardation, speech, epilepsy, extrapyramidal symptoms / signs

Creatine deficiency disorders
- Diagnosis: Creatine / creatinine ratio
- Treatment: Creatine supplementation

Index case
- Hypotonia at 9 m
- Dystonia at 22 m
- Creatine treatment since age 2y (for 5.5 y) - clinical improvement
Organic acid disorders
- Biotinidase deficiency
  - Autism
  - Ataxia, seizure, hypotonia, vision problems, hearing loss
  - Skin rash, alopecia
  - Autosomal recessive
  - Diagnosis: Serum biotinidase level
  - Treatment: Biotin supplementation

Organic acid disorders
- Succinic semialdehyde dehydrogenase deficiency
  - Autism, speech and language delay, motor, MR
  - Hypotonia, ataxia
    - Autosomal recessive
    - Diagnosis: Urine organic acids
    - Treatment: Vigabatrin

Purine & Pyrimidine disorders
- Adenylosuccinate lyase deficiency
  - Autism, mental retardation, epilepsy, motor
  - Autosomal recessive
  - Diagnosis: Purine metabolites
  - Treatment:

Purine & Pyrimidine disorders
- Dihydropyrimidine dehydrogenase deficiency
  - Highly variable
  - Seizures, motor, mental retardation
  - Autism, microcephaly, dysmorphic features
    - Autosomal recessive
    - Diagnosis: Pyrimidine metabolites (urine organic acids or specific screen)
    - Treatment: None, avoid 5FU chemotherapy

Lysosomal storage disorders
- Sanfilipo (MPS III)
  - Autism, severe MR, behavioural
  - Regression
  - Mild dysmorphic features
    - Autosomal recessive, 1/150K to 1/300K
    - 4 genes
    - Breakdown of heparan (+keratan) sulphate
      - Diagnosis: Urine glycosaminoglycans as screen; enzymes/DNA definitive
      - Treatment: None
Lysosomal storage disorders

- Neuronal Ceroid Lipofuscinosis (NCL)
  - Autism, seizures, myoclonus, chorea, vision, ataxia
  - Regression, mental retardation
  - Autosomal recessive, rare
  - Infantile: CLN1 (palmitoyl-protein thioesterase) *
  - Classical Late infantile: CLN2 (pepinase)
  - Juvenile (Batten): CLN3 (battenin)
- Diagnosis: Pathology, DNA
- Treatment: None

Cholesterol biosynthesis disorders

- Smith-Lemli-Opitz syndrome
  - Autism, poor expressive language, behavioural,
    mental retardation
  - Dysmorphic features
- Autosomal recessive, incidence 1/20K-80K
- 7-dehydrocholesterol reductase deficiency

Mitochondrial disorders

- Various mitochondrial DNA mutations, mtDNA depletion
  - Autistic regression, multiorgan symptoms
  - Diagnosis: Plasma lactate and amino acids, urine
    organic acids, creatine kinase
  - Treatment: ?
- Mitochondrial dysfunction postulated as one of the underlying
  pathophysiologies in autism

When to investigate?

- Consanguinity, family history
- Autistic / developmental regression
- Mental retardation, psychomotor retardation
- Language delay >> cognitive delay
- Seizures
- Dysmorphic features
Newborn screening

What to order: Plasma amino acids
- Diagnostic
  - PKU
  - Histidinemia
  - Many urea cycle defects
- Suggestive
  - Mitochondrial

What to order: Urine organic acids
- Diagnostic
  - Succinic semialdehyde deficiency
  - DPD deficiency
- Suggestive
  - Biotinidase
  - Mitochondrial
  - Urea cycle defects

What to order: Creatine* and Creatinine*
- Low creatine and creatinine suggestive for creatine synthesis defects
- High urine creatine/creatinine ratio suggestive for creatine transporter defect
* Included as part of urine metabolic screen

What to order: Purines* and Pyrimidines*
- Diagnostic
  - Dihydropyrimidine dehydrogenase deficiency
  - Adenylosuccinate lyase deficiency
- Suggestive
  - Urea cycle defects (orotic acid)
* Included as part of urine metabolic screen

What to order: Steroid profile
- Diagnostic
  - SLOS (7-dehydrocholesterol)
What to order:
Urine MPS/GAG screen
- Suggestive for MPS III

What to order
- Plasma lactate
  - Suggestive for mitochondrial
- Plasma ammonia
  - Suggestive for urea cycle defects, mitochondrial

Summary
- Good idea to include in general evaluation
  - Plasma amino acid, lactate, ammonia
  - Urine organic acid, metabolic screen
- Might be useful if high suspicion
  - Creatine + creatinine, purines + pyrimidines
  - If not included in a metabolic screening test
  - Steroid profile, urine MPS screen
- If doing MRI (e.g. MR) consider MRS (creatine, lactate)
- Don’t miss PKU