NTPN Guideline for Investigations in CYP with Neurodevelopement concerns

May 2022



Developmental delay investigation guideline drivers

- 1. ~20% referrals to tertiary neurology
- 2. TAT for investigations (Micro array)
- 3. Access to MRI GA
- 4. Special Challenges
 - Regression
 - Severe behavioural issues
 - Epilepsy



Contributions

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Stakeholders

Parent and Patient -Via the YPF @ GOSH

Clinical Nurse Specialist

Advanced Nurse Practitioners



Pathway for assessment of children presenting with developmental concerns - definitions

ICD-11 (2021) - Disorders of Intellectual Development (6A00)

Disorders of intellectual development are a group of etiologically diverse conditions originating during the developmental period characterised by significantly below average intellectual functioning and adaptive behaviour that are approximately two or more standard deviations below the mean (approximately less than the 2.3rd percentile), based on appropriately normed, individually administered standardized tests. Where appropriately normed and standardized tests are not available, diagnosis of disorders of intellectual development requires greater reliance on clinical judgment based on appropriate assessment of comparable behavioural indicators.

In children under 5 years old and unable to engage with standardised tests, **Early developmental impairment (EDI)** may be an appropriate synonymous diagnosis and is coded the same in ICD-11

Commonly used synonyms

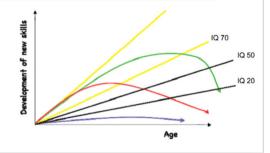
Mental retardation
Intellectual developmental disorder
Intellectual disability
intellectual disabilities
developmental delay
Global developmental delay

There are historical pifalls with these synonyms.

Definitions of these terms vary with time and some have proven potentially stigmatising or misleading.

Terms such as "delay" can give some families false hope about the overall developmental prognosis and do not capture the range of phenotypes each with varying trajectories of development.

Various phenotypes of developmental trajectory. From Horridge, 2011, Assessment and investigation of the child with disordered development. *ADCE&P*;**96**:9-20.





Pathway for assessment of children presenting with developmental concerns – initial assessment

History

Antenatal / perinatal / neonatal

Medical history

Developmental history

Plateauing or regression

Diurnal variation in symptoms

Family – 3 generation pedigree, enquire on consanguinity

History of foetal deaths

Vision & hearing

Functional "collateral" history from educators or other caregivers if available

Examination

Neurology

Gait

Gower's test

Dysmorphism

Inspection of skin (with Wood's lamp if available)

Organomegaly

Hearing & vision

Developmental status

Consider blood pressure if neurocutaneous stigmata

Growth chart

Height

Weight

Head circumference

BMI

Review past investigations

Newborn hearing screen (AOAE/AABR)

Newborn blood spot test (NBBST) – currently 9 conditions: N. Thames
Regional Newborn Screening

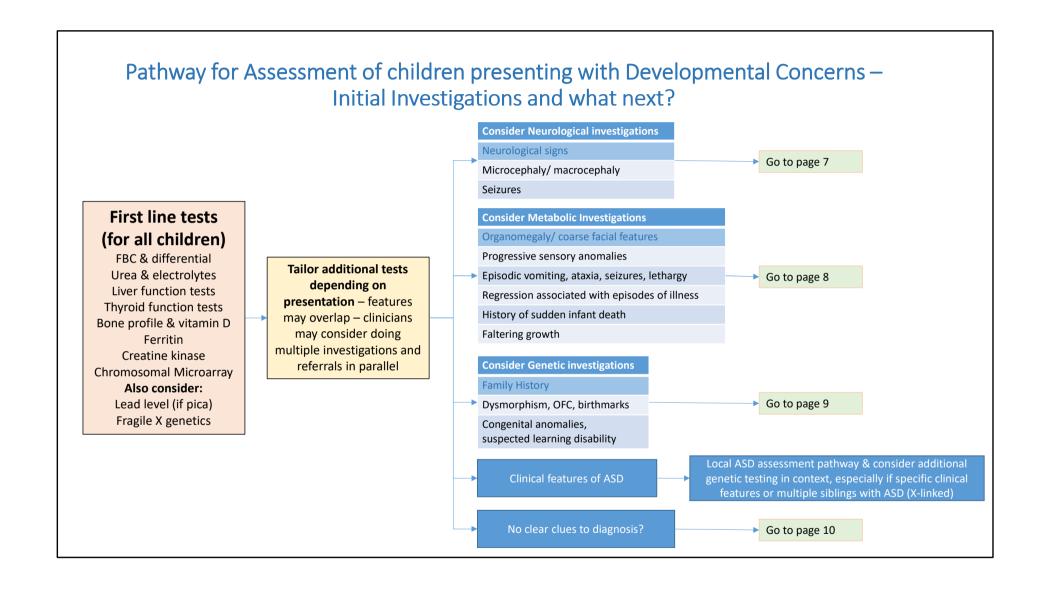
TORCH screen

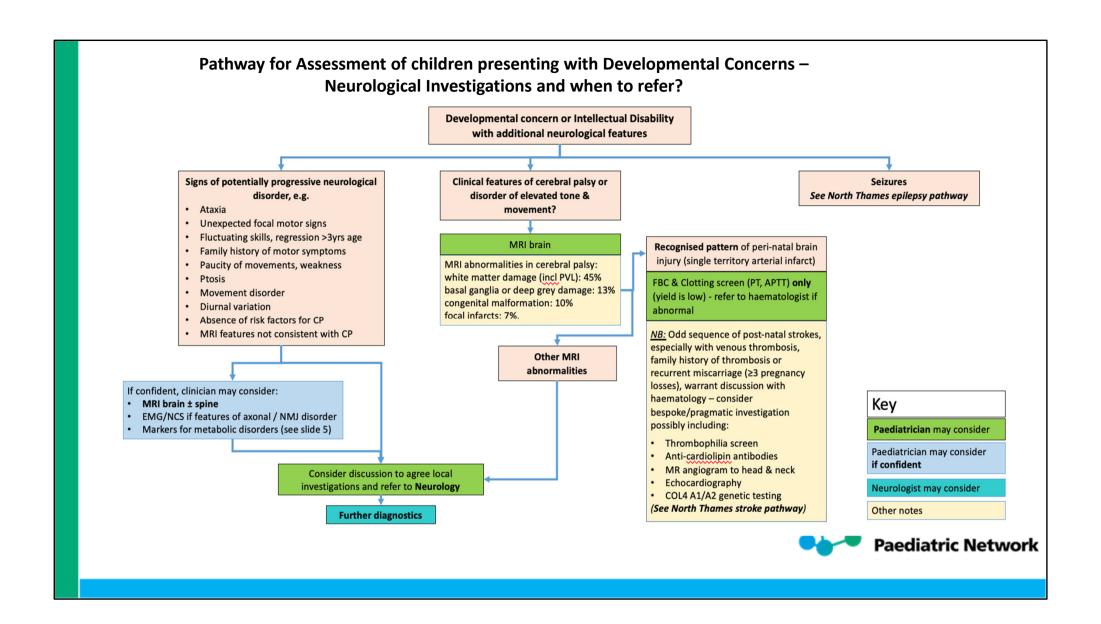
Prenatal genetic testing (including NIPT, or invasive CMA & qfPCR)

Previous imaging

Tests taken at other centres, e.g. inpatient ward, or neonatal unit







Pathway for Assessment of children presenting with Developmental Concerns – Metabolic Investigations and when to refer? Features highly suspicious for inborn errors of metabolism (IEM) Developmental impairment with possible features of IEM Conditions screened for by metabolic testing may be treatable. Organ dysfunction: Dysmorphia: Early diagnosis can be life-changing – it may halt unnecessary 1. Facial dysmorphism (e.g. coarse facial features) 1. Organomegaly investigations, aid genetic counselling and open up intervention 2. Cardiac dysfunction (e.g. arrythmia, 2. Congenital non-facial anomalies options that may improve the developmental prognosis 3. Non-congenital progressive spine deformities cardiomyopathy) Neurological features: 3. History of being severely symptomatic and The following metabolic screening tests can identify a wide range 1. Sensory deficits, especially if progressive (e.g., needing longer to recover with benign illnesses of the commonest conditions, including organic acidurias, fatty cataracts, retinopathy) (e.g. upper respiratory tract infection) acid oxidation defects, urea cycle disorders, amino acid disorders, Recurrent episodes of vomiting, ataxia, Behaviour: GSD and MPS.. These tests are relatively inexpensive and seizures, letharay, coma Behavioural or psychiatric problems (e.g. turnaround can be as quick as 24 hours. Stepwise regression in developmental psychosis at a young age) milestones associated with benign childhood 2. Unusual dietary preferences (e.g. protein or Blood: illnesses carbohydrate aversion) 1. Lactate Movement disorder (e.g. dystonia) **Growth abnormalities:** 2. Ammonia - deliver to lab quickly on ice 5. Severe hypotonia 1. Intrauterine growth retardation 3. Glucose Key 4. Blood gas 6. Pathognomonic neuro-imaging abnormalities 2. Failure-to-thrive and 5. Creatine metabolites (guanidinoacetate, paired with urine) Family history: Head circumference or stature growth 6. Amino acids Family history of IEM abnormality (>2 SD above or under the mean) Paediatrician may 2. Consanguinity (within 3-generation pedigree) request Urine: Family history of developmental disorder/ Features in italics indicate higher degree of 1. Urine ketones Metabolist to request unexplained neonatal/sudden infant death / suspicion 2. Creatine metabolites (guanidinoacetate, paired with blood) recurrent foetal death Urine GAGs (for mucopolysaccaridoses) - Advise to avoid excessive hydration prior to providing a urine sample as dilute Paediatrician may consider if confident samples are unsuitable Consider and discuss referral to metabolic team prior to local testing Other notes Discuss abnormal results with metabolic team, who may advise Bespoke panel of tests in specialist setting repeat testing locally or referral for testing in specialist setting **North Thames** Paediatric Network

Hypoglycaemia indicates organic aciduria, FAO defects, GSD, or MSUD

Metabolic acidosis (raised anion gap) indicates organic aciduria, FAO defects, or MSUD

Elevated urine ketones indicates MSUD or organic acidurias

Absent urinary ketones indicates FAO defects. Abnormal plasma carnitine in organic acidurias and FAO defects

Elevated ammonia indicates Urea cycle disorder, Organic aciduria or FAO defect

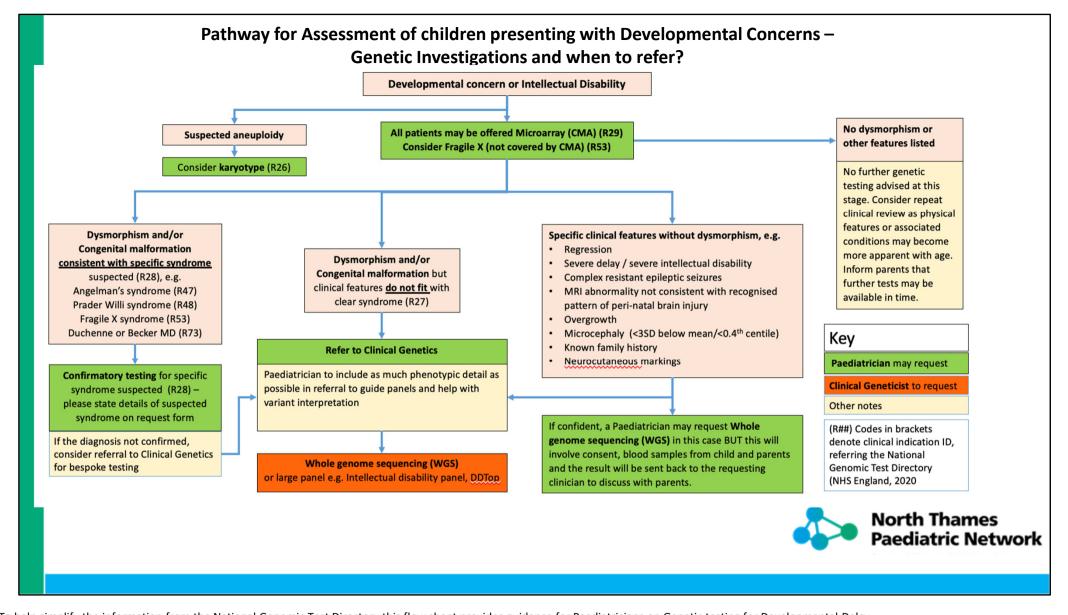
Elevated lactate indicates organic aciduria, FAO defect, or respiratory chain defect

Deranged LFT indicates FAO defects

Plasma Amino acids – high glycine indicates Non-ketotic hyperglycinaemia, or organic aciduria. High BCAAs indicates MSUD. AAs usually abnormal in urea cycle disorders

Abnormal urinary organic acids in MSUD, FAO defects, and organic acidurias

Elevated urine GAGS in MPS

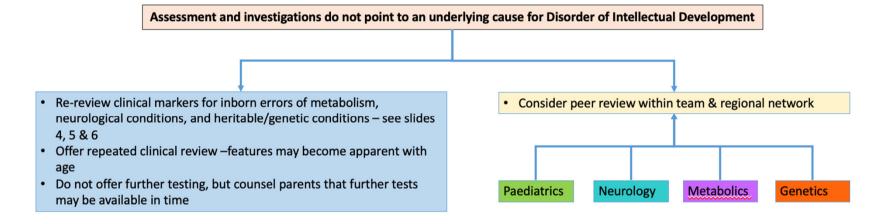


To help simplify the information from the National Genomic Test Directory this flow sheet provides guidance for Paediatricians on Genetic testing for Developmental Delay.

All children with Developmental delay, Intellectual disability and/or autism spectrum disorder should have a microarray. In all cases Fragile X should be considered as this is not covered by the microarray test. If the clinician has suspicion of a particular syndrome this should be specified at the time of the microarray test so that scientists are alerted to apply additional tests should these be required.

If the microarray is normal, further investigation is guided by the patient phenotype. For dysmorphic children or children with congenital malformations a referral should be made to a Clinical geneticist to assess and consider whole genome sequencing. For children who have no dysmorphism or congenital malformations no further genetic testing may be useful as there is very little specificity in the phenotype. Clinicians may wish to review over time as sometimes physical features or medical conditions become more apparent with age. For children with no dysmorphism who have features such as regression, more severe intellectual disability/developmental impairment, abnormal MRI brain or epilepsy, the Paediatrician may order a whole genome sequence (if confident) or refer to a Clinical Geneticist,

Pathway for Assessment of children presenting with Developmental Concerns – No clear clues to diagnosis?





Future work:

- 1. Operationalise the guideline Workshop ie where to send tests
- 2. Common pitfalls of metabolic tests (Proposal for an audit after implementation)