Approach to Genetic Diagnosis in Developmental Delay

Introduction

- This document does not replace input from a clinical geneticist, but given that many regions are underserved by clinical genetics, this document may assist primary care providers in conducting an initial diagnostic evaluation.
- Patients with new-onset seizures, developmental regression, concern for increased intracranial pressure or other acute concerns should be referred to the appropriate specialty.
- This document will change over time with new developments in genetic testing.

Initial considerations

- The American Academy of Pediatrics has published their statement on appropriate genetic evaluation of children with developmental delay: see Moeschler et al Pediatrics 2014.
- Much of the following is adapted from that source, with updates based on changing technology for genetic testing in the intervening years.
- Reasons to pursue diagnostic genetic testing:
    - A definitive diagnosis (reduced uncertainty, access to support groups, reduction in invasive diagnostic testing)
    - Ability to provide a more detailed prognosis for the child
    - Potential for treatment or management specific to the diagnosis
    - Determination of recurrence risk for the parents and other family members
- History and physical examination
    - Is there a known family history of a specific genetic condition?
    - Does the history or physical exam implicate a specific genetic diagnosis based on physical features or characteristic history (e.g. Down Syndrome, Prader Willi)?
    - Is there an aspect of the history that makes a genetic diagnosis less likely (e.g. extreme prematurity, prenatal exposure to alcohol, history of traumatic brain injury, history of meningitis)?
        - A reference for non-genetic considerations for etiological diagnosis in patients with developmental delay can be found in the attached documents.
    - If targeted testing is indicated then can contact genetics for advice on the logistics of testing or refer at that time.
    - If no specific diagnosis is considered likely then consider the untargeted approach presented below.
- MRI of the brain
    - Not necessarily indicated in all patients with developmental delay
    - Higher yield for providing actionable information in the following settings:
        - Epilepsy
        - Macrocephaly
        - Microcephaly

        - Focal neurological findings (e.g. asymmetry, ataxia, hypertonia, dystonia, concern for elevated intracranial pressure, etc.)
        - Developmental regression
    - If MRI findings are specific (e.g. Leigh syndrome, cerebellar atrophy, cortical dysplasias, etc.) then consider targeted testing for that indication with advice from genetics or refer at that time.
    - If MRI is not obtained or if findings are normal or nonspecific then consider the untargeted approach presented below.

<u>Untargeted approach to genetic testing for developmental delay</u>

- Tier 1
    - Chromosomal microarray
        - Provides copy number of most clinically significant genes (eg deletion, duplication, triplication); can diagnose aneuploidy
        - Roughly two-week turnaround time
        - Insurance authorization should be obtained prior to sending (or use a lab that will complete insurance authorization for you).
        - Informed consent for the following should be discussed prior to testing:
            - Diagnostic yield for the indication of developmental delay is about 10%-30% depending on the setting
            - Test will reveal if parents are related to one another
            - Test may have clearly diagnostic, clearly normal or ambiguous results
            - Ambiguous results may require testing of parents or other family members for follow-up; in other cases ambiguity cannot be resolved
            - May have secondary findings that are clinically-significant but unrelated to the reason for testing (e.g. cancer predisposition)
    - Fragile X trinucleotide repeat expansion analysis
        - Caused by a trinucleotide repeat that cannot be detected by methods other than targeted testing
        - X-linked disorder, but symptomatic females are not uncommon and thus testing is indicated in both sexes
        - Insurance authorization and informed consent should be obtained prior to testing
        - Diagnostic yield is 1%-2% in boys, lower in girls
        - Informed consent:
            - With diagnostic results, mother may be a full mutation or premutation carrier, results may have implications for her fertility and potential for adult-onset neurological disease in premutation carriers
- Tier 2
    - Large gene sequencing panel of developmental delay-associated genes

        - Ideally trio-based including both biological parents to reduce the likelihood of uncertain variants; if not trio testing initially, then parental samples are likely to be needed subsequently for confirmation of diagnosis
        - Insurance authorization and informed consent should be obtained prior to testing (or use a lab that will complete insurance authorization for you).
        - Informed consent includes:
            - Any time child and parents are tested, there is the possibility to reveal that one of the parents is not the biological parent of the child
            - Diagnostic yield is probably about 30%, but depends on many factors
            - Ambiguous findings are common; some can be resolved with further testing, others cannot
            - Secondary findings are possible - detection of a diagnosis that does not account for the patient's entire presentation but still has clinical relevance
            - A parent could also receive the same diagnosis as the child as a result of testing
- Tier 3
    - Whole exome or whole genome sequencing can be considered.
    - See www.treatable-id.org for a testing algorithm and information on diagnoses that have specific management and can be detected with biochemical testing
    - Samples should ideally be obtained 3-4 hours after eating
    - Informed consent:
        - There are often abnormal but nonspecific findings in metabolic testing and further testing is often required as a result.
    - Algorithm includes:
        - Serum amino acids
        - Serum homocysteine
        - Urine creatine metabolites
        - Urine organic acids
        - Urine purines and pyrimidines
        - Urine oligosaccharides
        - Urine mucopolysaccharides

<u>Genetic testing laboratories that currently offer patient insurance benefit verification service:</u>

- Patient insurance benefit verification may be available at other labs as well and the availability of this service may change.
- Some laboratories have subsidies available to limit out of pocket cost to families.
- We recommend assessing the availability of these services with the specific lab that will be used at the time that testing is obtained.
- Most genetic tests can now be performed with buccal swab sample kits from the labs.
    - GeneDx

- Ambry
- Invitae
- Baylor
- Lineagen
- Centogene

Return of results

- Labs will classify each reported genetic variant as either benign, likely benign, variant of uncertain significance (VUS), likely pathogenic or pathogenic.
- Likely pathogenic or pathogenic results can usually be reported as diagnostic to families if clinical features are compatible with that diagnosis.
- A VUS may require interpretation from a geneticist and additional testing of the child and family members.
- If there are questions about the significance of a result, then we recommend discussion with a geneticist prior to disclosing to the family.

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