What do I do now?
The role of the pediatrician in the neurodiagnostic evaluation of children with neurodevelopmental disorders

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Let’s start with a case

- David is a 3 year 2 month old boy presenting for a well child check-up
- CC: Mom is concerned about speech
- HPI: not really talking, maybe has 5 words, used inconsistently
- PMH: born at term, no complications with pregnancy or delivery, no other health concerns
- TSH: no medications, up to date on immunizations
- EOS: no frequent ear infections
- FH: brother had speech delay
- Social history: parents both work full time; he attends daycare
Case (continued)

- In review of chart:
  - ASQ at 2, 4, 6 months all within normal range across all realms
  - ASQ at 9 months: borderline communication delay; recommended close follow-up
  - ASQ at 12 months: continued borderline communication delay; referred to Parents as Teachers
    (Lost to follow-up when this military family was relocated); no records available; no referrals were made to early intervention services or elsewhere
  - ASQ at 24 months (outside provider): frank delay in realm of communication and personal-social skills, borderline performance in problem-solving skills; record of referral to infant-toddler services made
    (Family moved again)

ASQ = ages and stages questionnaire

Going into the room

Further developmental history:

- Language:
  - Quiet baby, didn’t really coo, babble in infancy
  - First word, “Dada” at 15 months; specific name for items by 18 months
  - Slow word acquisition thereafter
  - By 2 could say “Baba” for cup/milk
  - New caps “Momma,” “Dada,” “Bubba” (for brother), “up,” “no,” “go”
  - Sparse two-word combinations “up, momma” or “no go”
  - Echolalic and palilalic speech “go go go”
  - No speech approximations, no stuttering
  - Hearing has been tested and is within normal range
Developmental history, continued

- Language (continued):
  - Doesn’t make very good eye contact
  - Doesn’t really point, really drag Mom to items of need/hot help
  - Doesn’t really follow gestures or understand body language
  - Paucity of facial expressions

- Social:
  - Plays off by himself at daycare
  - Doesn’t know the names of any of the kids in his class
  - No pretend play alone or alongside/with peers
  - Likes to build with blocks; gets very upset if others disrupt him
  - Doesn’t really smile much

Developmental history (continued)

- Gross motor:
  - Rolled 4 months
  - Sat 6 months
  - Crawled 9 months
  - Walked 11 months
  - Runs well, goes up and down stairs, rides a tricycle, can kick and throw a ball overhead

- Fine motor:
  - Can pick up small foods/feed self
  - Helps dress self
  - Can scribble
  - Cannot use scissors, does not like to string beads
  - Loves to stack blocks

Mother’s further concerns

- He often rocks while he’s watching TV
- He really only watches the same shows over and over
- He is bothered by the blender, automatic toilets
- He is a picky eater
Physical examination

- General: awake, in acute distress, crying
- HEENT: macrocephalic
- Heart: well-perfused
- Lungs: non-labored respirations
- Abdomen: nondistended
- GU: deferred
- Derm: one hyperpigmented macule on the left distal forearm
- Psych: poor eye contact, minimally interactive
- Extremities: no obvious deformities
- Lymph: no overt lymphadenopathy

Neurological examination:

- Mental status: awake, alert but minimally interactive with examiner, largely uncooperative with examination, no speech sound except for “Mama, mama” repeatedly
- Cranial nerves: red reflex bilaterally, PERRL, EOM, no ptosis, no nystagmus, normal facial symmetry, no fixed head tilt, tongue midline
- Motor: mild hypotonia throughout; frequent motor stereotypies observed
- Sensation: intact to light touch throughout as assessed by withdrawal
- Reflexes: unable to assess secondary to cooperativity
- Coordination: no obvious tremor or dysmetria
- Gait: normal straightaway toddler gait with good balance; walks on toes

Assessment

- 3 year 2 month old term toddler boy with macrocephaly and global developmental delay in the setting of a family history of speech delay
Differential diagnosis?

- Genetic
  - Fragile X, PTEN, NF1?
- Metabolic
  - Aminoacidopathies, organic acidurias, fatty acid oxidation disorders, etc.
- Structural
  - Septooptic dysplasia, lissencephaly

What does the pediatrician do?
Outline

- Why is this important?
- Define terms: global developmental delays vs intellectual disability
- How to identify delays in development
- What work-up can/should be started before a referral to a specialist?
- Interventions

Background

- Approximately 17% of children between the ages of 3-17 in the US have a neurodevelopmental disability
  - Most have a diagnosis captured by the DSM-V
  - Others include cerebral palsy, epilepsy, neuropsychiatric disorders
- Characterized by developmental deficits in either cognition, language, behavior, and/or motor skills that affect personal, social, academic and/or occupational functioning
- Present and are typically diagnosed in infancy and early childhood
- Non-progressive
- Comprehensive developmental care should include not only evidence-based treatments and supports but also a search for an underlying etiology

Background (continued)

- Population health concerns
  - Treatment for neurodevelopmental disorders is complex
  - Outcomes in education, employment, social participation, criminal activities
  - Caregiver emotional and financial burden
  - Conditions are not often life-limiting

DSM-V: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
Background (continued)

- Early intervention is paramount
  - The underlying neural mechanisms for most of these disorders begin in utero or, generally, within the first weeks or months of life
  - Environment + experience may modify brain development

- Pediatricians may lack confidence in evaluating and managing neurodevelopmental disorders
- Provider ratio data from 2000: 20% deficit below demand for child neurology services
- Residents graduate feeling unprepared, uncomfortable, dependent on subspecialists, uneducated but motivated to learn

Definitions

- Developmental delay: failure to gain the skills expected of a child of the same age; generally refers to a single realm of development
  - Communication disorders
    - Mixed receptive-expressive language disorder
    - Speech apraxia
    - Speech sound disorder
    - Childhood apraxia of speech
    - Social pragmatic communication disorder
  - Motor disorders
    - Developmental coordination disorder
    - Stereotypic movement disorder
Definitions (continued)

- Global developmental delay: failure to gain the skills expected of a child of the same age across multiple realms of development
- Generally used before age 5-6 years of age, when intellectual testing is less reliable
- Intellectual disability: limitation in both intellectual functioning and adaptive behavior
- Specific learning disability: persistent impairment in at least one major area (reading, written expression, math)
  - Dyslexia, dysgraphia, dyscalculia

Definitions (continued)

- Neurodevelopmental disorders represent a spectrum that could include:
  - Attention-Deficit/Hyperactivity Disorder
  - Autism Spectrum Disorder
  - Neurological signs (hypotonia, spasticity, weakness, etc.) and/or symptoms (fatigue)
  - Other psychiatric conditions

How to identify delays

- Ages and Stages Questionnaire®
- Parents’ Evaluation of Developmental Status
- Modified Checklist for Autism in Toddlers
- Communication and Symbolic Behavior Scales
- Screening Tool for Autism in Toddlers and Young Children
Neurodiagnostic evaluation

- In 2014 the AAP released an updated guideline for the comprehensive evaluation for children with intellectual disability or global developmental delays.
- Appropriate evaluation for genetic etiologies, inborn errors of metabolism, and the role of imaging in this context.
- Benefits: clarify etiology, prognostication, recurrence risk, refined treatment, avoidance of redundant/unnecessary tests, surveillance for known complications, family support, research, multidisciplinary care coordinated by the medical home.

Chromosomal microarray

- Now considered the first-tier diagnostic test in all children with GDD/ID.
- Replaced G-banded karyotyping and FISH.
- Gold standard.
- Higher resolution genomic imbalances:
  - Gains: duplications
  - Losses: deletions
  - Rearrangements.
- Diagnostic rate is at least twice that of karyotyping at approximately 12%.
- Other names: array-based genomic copy number analysis, comparative genomic hybridization, single nucleotide polymorphism arrays.
Chromosomal microarray (continued)

- Possible results:
  - Pathogenic or likely pathogenic
  - Benign or likely benign
  - Variant of uncertain significance
  - Incomplete vs variable penetrance
  - Coverage
  - The role of the genetic counselor
  - Higher level testing is generally deferred to the specialist

Inborn errors of metabolism

- 1-5% of children with ID have an underlying metabolic disorder
  - Some are not included in the newborn screening blood spot panels
  - Potential for improved outcomes after diagnosis and treatment is high
  - Screening tests:
    - Blood: amino acids, acylcarnitine profile
    - Urine: organic acids
    - Others: homocysteine, creatine metabolites, purines and pyrimidines, mucopolysaccharides, oligosaccharides
  - Cost is relatively low

Diagnostic imaging

- There is no consensus on the role of neuroimaging neither by MRI nor CT
- Recommendation: to consider in children with abnormal clinical examinations
  - Macro or microcephaly, focal findings, history of seizures
  - CT: low diagnostic yield, exposure to radiation, often still need sedation
  - MRI: more sensitive, more expensive, often need sedation
  - Abnormal findings are found in ~30% of all children with DD/ID but often these are nonspecific/nonsyndromic
Recommendations:

- Chromosomal microarray should be performed in all
- Specific metabolic testing should be considered
- Fragile X testing should be performed in all
- Further testing could be considered based on gender:
  - XLID panel for boys if X-lineage is suggested by family history
  - MECP2 deletion/duplication/sequencing studies for girls
- If macro- or microcephaly or focal findings are present, consider neuroimaging
- If all are unremarkable consider referral to other specialists
- Make a plan for reevaluation

Summary

- Neurodevelopmental disorders are common
- Early intervention is paramount to ensure optimal outcomes
- Pediatricians are responsible for recognizing developmental delays
- At least cursory genetic and perhaps metabolic testing, with or without neuroimaging, can be initiated by the pediatrician
- Specialists can partner in further neurodiagnostic evaluation
Thank you!

Questions?

References
3. https://pubmed.ncbi.nlm.nih.gov/27027609/#:~:text=Early%20identification%20of%20infants%20at,weeks%20or%20months%20of%20life
7. https://pubmed.ncbi.nlm.nih.gov/pmc/articles/PMC5701958/