Evidence Report: Genetic and Metabolic Testing on Children with Global Developmental Delay

Case Presentation
A 3-year-old boy is brought to your child neurology clinic due to concerns regarding his development. The parents state that the pregnancy, delivery, and early postnatal period were unremarkable and that concern about his development first arose because he was not speaking at 2 years of age. The pediatrician had ordered an audiological examination; basic laboratory evaluations for anemia, lead toxicity, and hypothyroidism; a karyotype; and a non-contrast head MRI. You are able to review these test results, including the MRI images, and you interpret them as normal.

The child’s past medical history is negative for any chronic illnesses, prior hospitalizations, surgeries, or episodes of head trauma. The parents deny consanguinity, prior miscarriages, or any family history of early childhood death or neurologic disease, going back three generations. They have three older children, two boys and a girl, who are healthy and developing normally. On 10-topic review of systems, the parents deny any concerns other than that he is often constipated, is not toilet trained, is easily frustrated and prone to aggression, and sleeps poorly at night.

On examination his vital signs and growth parameters are within normal limits for age. He is awake and alert and shows no signs of acute distress, though he is fearful and uncooperative with the examination. He has no obvious dysmorphism or signs of a phakomatosis. His general physical examination is normal. He makes contact with you and his parents and expresses desires to leave and for snacks through sounds and gestures but does not say any words. He turns when his name is spoken but does not follow any commands. His cranial nerve examination is normal. His motor examination reveals normal bulk, mildly decreased limb tone, and at least 4/5 strength. His sensory exam appears grossly intact, with withdrawal of all limbs from light touch. His deep tendon reflexes are normal and symmetric, and Babinski signs are not elicited. He reaches accurately for objects without tremor, though he uses a raking grasp and chews an offered pen rather than writing with it. He is able to sit, stand, and walk independently but runs slowly and clumsily, with his hands held above his waist.

You explain to the parents that their son shows evidence of moderate to severe global developmental delay (GDD), with development that is generally below that expected for children half his age. You further explain that his examination and family history do not clearly indicate a more specific diagnosis, but that you suspect a problem with brain function that may be genetic in nature. You review their options with them, and they express interest in further diagnostic testing to better understand his long-term prognosis and risk of complications. On the basis of the recent evidence review, you order a genomic microarray study. The total time spent in this evaluation is 1 hour, 30 minutes of
which was expended in counseling and coordination of care.

Questions
1. Microarray can be considered for this patient because:
   A. The normal karyotype does not exclude a genetic cause of GDD
   B. Both parents are available if follow-up testing is needed to interpret an ambiguous result
   C. The child has no dysmorphic features to suggest a specific syndromic diagnosis
   D. The child has no family history to suggest an X-linked inheritance pattern
   E. All of the above

The correct answer is E. Available evidence suggests that genomic microarray studies have the highest diagnostic yield in this clinical scenario (Class III studies).

2. What additional history would most increase your interest in testing this patient for mutations in X-linked intellectual disability (XLID) genes?
   A. The parents discover that they are second cousins
   B. The mother learns that her older sister has just given birth to a son with Down syndrome
   C. The father adds that he and his brothers all struggled in school and were in special education
   D. The mother reveals that her older brother and a sister’s son both have unexplained intellectual disability (ID)
   E. The child has a 9-year-old sister who has been diagnosed with dyslexia

The correct answer is D. A family history that fits possible or definite X-linked inheritance of ID greatly increases the likelihood that testing XLID genes will be diagnostic (Class III studies).

3. Which of these inborn errors of metabolism (IEM) is not inherited in an X-linked recessive manner?
   A. Creatine transport deficiency due to mutation of the SLC6A8 gene
   B. Menkes kinky hair disease
   C. Smith-Lemli-Opitz syndrome
   D. Ornithine transcarbamylase deficiency
   E. Hunter syndrome (MPS II)

The correct answer is C. Smith-Lemli-Opitz syndrome is inherited in an autosomal recessive manner, with mutations carried by 1 out of 30 persons of European descent. The other IEMs listed are inherited in an X-linked recessive manner and are thus most often found in males. Screening for IEMs in children with GDD/ID has a yield of between 0.2% and 4.6%, depending on the presence of clinical indicators (such as family history) and the range of testing performed (Class III). Testing for congenital disorders of glycosylation has a yield of up to 1.4%, and testing for creatine synthesis and transport disorders has a yield of up to 2.8% (Class III).
Diagnosis Coding
The documentation provides the diagnosis Global developmental delay (GDD). There is no index entry or specific numerical code in ICD-9-CM for GDD.1 A less specific code that best fits GDD and captures the concept without attributing undiagnosed deficits is:

783.42 Delayed milestones

If after the evaluation (or with time) more specific developmental delays or specific disease states are found, it is very important that the appropriate codes for those conditions be used instead of the above nonspecific code. Codes for several specific developmental delays are found in Chapter 5 of ICD-9-CM, which as of October 1, 2011, has been renamed “Mental, Behavioral and Neurodevelopmental Disorders.” Codes for both the cause and type of delay should be used when available, with the cause being listed first.

Evaluation and Management Coding
Since there is no reference in the history of a formal consultation request, the pediatric neurologist would code for a new patient. The comment at the end of the evaluation documents the expending of 60 minutes with the patient and 30 minutes in counseling and coordination of care. This would permit the use of code 99205, which is a level 5 new-patient visit.2 The coding is based on time and requires that 50% or more of time is spent counseling and coordinating care during a 60-minute visit.


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