PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on "Evaluation of the child with global developmental delay and intellectual disability – CPS Podcast." These podcasts are designed to give medical students an overview of key topics in paediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

Evaluation of the child with global developmental delay and intellectual disability – CPS Podcast

Developed by Dr. Stacey Belanger, Dr. Joannie Caron and Dr. Meghan Pike for PedsCases.com.
November 15th, 2017

Introduction:

Hi everyone, my name is Dr. Meghan Pike and I am a second year Paediatrics resident at the IWK Health Centre at Dalhousie University in Halifax. This podcast was produced by PedsCases and the Canadian Paediatric Society (CPS), and will be discussing the new CPS statement on **Evaluation of the child with global developmental delay and intellectual disability**. This podcast was created under the guidance of Dr. Stacey Belanger, a Child Development Specialist at the University of Montreal and Dr. Joannie Caron, a general paediatrician who completed a fellowship in Developmental Paediatrics at the University of Montreal. They are the lead authors of this CPS statement.

Learning Objectives:

Today, our goal is to:

(1) Review the diagnostic criteria for Global Developmental Delay (GDD) and Intellectual Disability (ID);
(2) Develop a differential diagnosis of the causes of GDD and ID;
(3) Learn an algorithmic approach to the investigation of GDD and ID; and
(4) Apply this algorithm to a clinical case.

Clinical Case:

You are a fourth-year medical student doing an elective in community paediatrics in rural Nova Scotia. Your preceptor asks you to see a 3-year-old girl, Sara, who is accompanied today by her father. At her last visit, she was diagnosed with Global Developmental Delay of unknown etiology. This is her first follow-up visit.

Making the diagnosis of GDD and ID:

The first presentation of GDD or ID can vary, and it is important for a paediatrician to have an organized approach to the evaluation of developmental delay. Although the diagnosis of GDD is limited to children under 5 years of age, children with GDD can develop ID and the etiology behind these conditions often overlap. GDD and ID affect up to 3% of the paediatric population, and a cause of these conditions can be identified in 40-80% of cases.

The diagnosis of Global Developmental Delay is reserved for children **less than 5 years** old and requires significant delay (defined as at least two standard deviations below the mean with standardized tests) in at least two developmental domains:

- Gross or fine motor
- Speech/language
- Cognition
- Social/personal
- Activities of daily living

The diagnosis of Intellectual Disability (or Intellectual Developmental Disorder) require that three criteria be met:

(1) Deficits in intellectual function (reasoning, problem-solving, planning, abstract thinking, judgment, academic learning, learning from experience) confirmed by both clinical assessment and individualized, standardized intelligence testing.
(2) Deficits in adaptive functioning that results in failure to meet developmental and socio-cultural standards for personal independence and social responsibility. Without ongoing support, the adaptive deficits limit functioning in one or more activities of daily life across multiple environments.
(3) Onset of intellectual and adaptive deficits during the developmental period.

Causes of GDD and ID

Generating a concise list of the potential causes of GDD and ID helps limit tests that are time-consuming and costly. It is best to develop this list by thinking of broad categories: when could there have been an insult to the child's development that could have caused developmental delay? What is the most likely cause of this insult during this time?

Developmental insults could occur in the prenatal, perinatal or postnatal periods. In the prenatal period, causes of GDD/ID include genetic or metabolic, CNS malformations, teratogens or toxins (for example, drugs of abuse) or infections. In the perinatal period, neonatal asphyxia, prematurity or other neonatal complications could also impact development. Causes of GDD/ID in the postnatal period include infections, neglect, trauma or toxins. It should be noted that up to 55% of cases of GDD/ID can be attributed to perinatal causes.

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In evaluating children for a cause of GDD/ID, a 'clinical pearl' is to **consider clinical characteristics pointing toward a specific etiology, and ordering tests for that diagnosis first**. When no specific etiology is apparent, a stepwise approach to investigations is recommended. We'll review this next.

Algorithm for investigating GDD or ID

The initial evaluation of any child with suspected GDD or ID involves four steps:

(1) History and physical examination
(2) Audiology
(3) Ophthalmology or optometry
(4) EEG if suspected seizures

The **history and physical examination** is the very first step, and is the most important phase of investigation. The history should include a detailed, three-generation family history, looking for recurrent miscarriages, birth defects, infant deaths, GDD/ID, neurologic conditions, genetic conditions, ethnic background and consanguinity. A psychosocial history should include parent language, education, employment, drug or alcohol abuse, child care arrangements and a history of abuse or neglect and involvement of child protective services. As the latter can be a very sensitive topic, I like to gain this information by asking "have you ever met with a social worker?" Thinking back to our list of causes for GDD/ID, an important prenatal and birth history is also important. Be sure to ask about prenatal ultrasounds, screening for fetal aneuploidy, a history of maternal diabetes or hypertension, infections or exposures in pregnancy. Document the patient's birth weight, length and head circumference, his or her APGAR scores and length of hospitalization. You should also ask about any red flags suggestive of inborn errors of metabolism (more on these later). Be sure to take a detailed history of developmental milestones, paying particular attention to regression or lack of milestones and the timing of parents' first concern about their child's development. I like to use the Ages and Stages Questionnaire to evaluate developmental milestones.

The physical examination should include growth parameters, head shape and palpation of fontanelles. An examination of the skin for cutaneous stigmata of neurodevelopmental syndromes as well as the spine for spinal cord abnormalities should be included. Listen to the heart for any evidence of cardiac anomalies and palpate the abdomen for organomegaly. Examine limbs and genitals for any abnormalities. A detailed neurodevelopmental exam should be completed, which includes a neurological exam, screening for congenital abnormalities or dysmorphic features, and an office assessment of current developmental level.

After the history and physical examination, patients should be referred for a formal assessment of **vision and hearing**, as identifying a deficit in these areas could alter management.

If the history suggests the patient may have had a seizure, a referral for an **EEG** should be considered.

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In about 12-38% of cases, the history and physical examination may be enough to point to a specific etiology of GDD/ID. At this point, specific testing for the suspected etiology should be considered. If confirmatory testing establishes a diagnosis, counsel the family on the implications of this diagnosis and refer the patient as necessary.

If the history and physical exam does not point towards a specific diagnosis, it is appropriate to move on to **genetic testing**.

In the majority of cases, a chromosome microarray should be ordered first, as it is the single test with the best diagnostic yield and is almost 50% more sensitive than standard karyotyping. However, if there is a clinical suspicion of aneuploidy (for example, Turner syndrome, trisomy 21) or a family history of chromosomal rearrangements, karyotyping should be ordered instead of microarray.

Two relatively common genetic causes of ID are Fragile X and Rett Syndrome. Fragile X DNA testing is recommended for all boys AND girls with ID and MECP2 molecular analysis should be ordered when there is a clinical suspicion of Rett Syndrome or for girls with moderate-severe ID.

In children with unexplained GDD or ID, testing for treatable **inborn errors of metabolism** can occur at the same time, or shortly after, genetic testing. Tier 1 testing for inborn errors of metabolism should occur even when clinical red flags are absent and even if the patient has had a normal newborn screen. Tier 1 is a group of tests that is capable of identifying 60% of treatable inborn errors of metabolism. Table 1 tests include a CBC, glucose, blood gas, lytes, creatinine, TSH, liver enzymes, creatine kinase, ammonia, lactate, plasma amino acids, an acylcarnitine profile, homocysteine, and urine organic acids, creatine metabolites, purines and glycosaminoglycans. Other tests should be ordered depending on the clinical presentation (see Table 5).

If clinical red flags for inborn errors of metabolism *are* present, then consultation with a metabolic specialist should be considered. Red flags include: family history of inborn errors of metabolism, consanguinity, IUGR, failure to thrive, growth abnormalities, severe hypotonia, sensory deficits, spine deformities and neuro-imaging abnormalities, among others.

Additional investigations that can be considered in the work up of GDD/ID include iron, vitamin B12 and lead in children with risk factors for lead exposure. Testing for congenital TORCH infections can be considered in certain clinical situations and should be done in consultation with an infectious disease specialist.

If, after performing all of the above investigations, a diagnosis is not established, consider a **Brain MRI and consult** Genetics/Metabolics and/or Neurology.

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Applying the algorithm

So – let's apply this algorithm to our clinical case. We have Sara, a three-year old girl with a recent diagnosis of Global Developmental Delay.

Let's start with a detailed history. Remember that our differential diagnosis for GDD includes prenatal, perinatal and postnatal causes, and that we must consider each of these categories when taking a history and doing a physical examination.

Sara's parents tell you that they first started worrying about her development when she could not sit independently by 10 months of age. She also did not start walking until she was 22 months old. In addition to delayed motor skills, Sara also presented with an inability to draw a circle or turn a page of a book. Her words were only intelligible about 25% of the time, and her parents did not feel like she could correctly follow two-step commands. These findings prompted a referral to your preceptor, a consultant paediatrician in rural Nova Scotia, who arranged formal testing for vision and hearing, which were normal. At Sara's last visit, your preceptor diagnosed her with Global Developmental Delay of unknown etiology.

Today, a review of systems is unremarkable: in particular, Sara has never had a seizure. There were no red flags suggestive of an inborn error of metabolism.

Sara does not have any chronic medical problems. She has never been hospitalized and has never had surgery. There have never been any concerns about Sara's growth.

Sara was born to a 27-year old G1P1 via an uncomplicated vaginal delivery with an Apgar score of 9,9,10. Her mom was very healthy during her pregnancy, had normal prenatal ultrasounds and did not have any perinatal screening for fetal aneuploidy. There were no known infections or exposures during mom's pregnancy. At birth, your patient's growth parameters were between the 30-50th %ile for weight, height and head circumference. She was discharged home the next day with her mother.

Sara does not take any prescription or over-the-counter medications or supplements. Her immunizations are up to date.

A detailed, three-generation family history is unremarkable: there is no history of GDD/ID or genetic conditions. Sara's parents are not related.

On psychosocial history, you learn that the patient lives at home with her mother, who is a pharmacist and her father, who is a teacher. She does attend preschool from Monday to Friday. The family has never met with a social worker. The family has a drug plan.

On physical examination, Sarah is on the 50th%ile for height, weight, head circumference and BMI. She does not have any skin lesions. She has a soft, systolic murmur that is loudest when

she is sitting up and gets quieter when she lies down. There is no organomegaly, limb or genital abnormalities. A neurological exam is normal. She does not appear to have any dysmorphic features.

Sara is very quiet during the physical examination and does not seem interested in speaking to you. She requires help from her father to undress for the physical examination. She is able to point to your stethoscope when prompted and to her belly when asked. She can not walk down the stairs from the exam table to the floor with alternating feet and instead, asks her father to put her down.

Your history and physical examination does not point to a specific cause of Sara's Global Developmental Delay. Moving down the algorithm, you decide to order a chromosomal microarray and tier 1 metabolic testing, as well as make a referral to a Geneticist. Sara's bloodwork will include a CBC, glucose, blood gas, lytes, creatinine, TSH, liver enzymes, ammonia, plasma amino acids, an acylcarnitine profile, and urine organic acids, metabolites, purines and glycosaminoglycans. You also decide to include iron and vitamin B12.

This case illustrates that about 70-80% of causes of Global Developmental Delay cannot be identified by history and physical examination alone. The etiology of GDD takes time, and a large part of your role will be to support Sara and her family through every step down this algorithm.

Conclusion

Let's review the key points from today's Podcast:

- A thorough history and physical examination is the best first step for evaluating the cause of GDD or ID, as it will help guide further investigations. If the clinical assessment points toward a specific etiology, order tests for that diagnosis first.
- All patients with GDD/ID should have formal vision and hearing testing.
- If the history and physical exam does not point to an etiology of GDD/ID, chromosomal microarray and Fragile X DNA testing are first-line. EEG and/or Brain MRI should be considered in any patient with abnormal neurological findings or a history of seizures. Tier 1 metabolic testing should also be ordered.
- Clinical consultation with Genetics, Metabolics and Neurology could be considered at any time.

I hope you enjoyed this podcast on Evaluation of the child with global developmental delay and intellectual disability. I would like to thank Dr. Belanger, Dr. Caron and the team at PedsCases.com for this collaboration.

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