PedsCases Podcast Scripts

This is a text version of a video from Pedscases.com on "**Fragile X syndrome.**" These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

Fragile X syndrome (Case video)

Developed by Jose Lopez-Vera and Dr. Neelkamal Soares for PedsCases.com.
Sept. 13, 2018.

Introduction:

Hi, my name is Jose Lopez-Vera, a fourth-year medical student at the Western Michigan University Homer Stryker MD School of Medicine (WMed) in Kalamazoo, Michigan, USA. This PedsCases video on approach to a child with intellectual disability was developed with the help of Dr. Neelkamal Soares, a Developmental-Behavioral Pediatrician and Professor of Pediatric & Adolescent Medicine at WMed.

Objectives:

After this podcast/discussion, the learner will be able to:

- Distinguish between developmental delay (DD) and intellectual disability (ID)
- Articulate the rationale for genetic testing in children with DD or ID
- Discuss some of common symptoms and signs in patients with Fragile X syndrome

Clinical Case:

Let's start this podcast with a case. A 5-year-old boy comes to the pediatric outpatient clinic with his mother for a school physical. He is new to the clinic and his mother brings his previous medical and educational records with her. His previous pediatrician, who he had been seeing since birth, found him to have developmental delays at age of 4 years and referred him for educational testing and ordered genetic lab-work. He was found to meet criteria for intellectual impairment, based on an IQ composite score of 61, and an adaptive rating of 63.
The genetic testing done showed a negative chromosomal microarray and a Fragile X molecular test result of 240 CGG triple repeats. After seeing this patient, and reviewing the documentation, the medical student presents the case to the attending physician. Here is the outline of the discussion around the case.

Medical Student (MS)
Attending Physician (AP)

MS: Hi doctor, I just encountered a patient with developmental delay in clinic.

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AP: Thank you for seeing the patient, I'd be to glad to hear about it! Where should we start? Would you like to present the patient formally to me?

MS: Absolutely. The patient is a 5 year old boy who presents to our clinic with his mother for a school physical. He is new to our clinic, but his mother brings his previous medical and educational records with her. From these records, he has a history of developmental delay at age 4, and was subsequently referred for educational testing and lab work was ordered. He was found to meet criteria for intellectual impairment, with an IQ of 61, and an adaptive rating of 63. The genetic testing done showed -....

AP: - Wait! Let's stop there and discuss the tests and results later. That was very good. We can also discuss your physical exam findings later. Now, let's talk about "intellectual disability". First off, what does the IQ of 61 already tell you, and what is your differential diagnosis for this in a 5 year old?

MS: hmmmm, an IQ of 61 indicates mild mental retardation. The differential diagnosis for that includes autism spectrum disorder (ASD), cerebral palsy (CP), Fragile X syndrome, learning disorder, Rett syndrome, seizures…and I'm sure there are more, but I can't remember the rest right now.

AP: Good, now let's talk about intellectual disability.

MS: Sure, what about it?

AP: What does it mean?

MS: According to the American Association on Intellectual and Developmental Disabilities, or the AAIDD, Intellectual disability is characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills. This disability originates before the age of 18.

AP: Do you know what term they used to use? You just said it earlier.

MS: Mental retardation?

AP: Exactly. Try not to use that term anymore, as it has been replaced. Mental retardation used to be the preferred term, but in 2007, the AAIDD substituted it for intellectual disability. They changed the name according to certain criteria. First, it reflects the changed construct of disability described by the AAIDD and WHO. It aligns better with current professional practices that focus on functional behaviors and contextual factors, provides a logical basis for individualized supports provision due to its basis in a social-ecological framework, is less offensive to persons with the disability, is more consistent with international terminology.

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MS: Interesting...so let me get this straight. Developmental delay is still different from intellectual disability...right?

AP: That's right! And Global developmental delay (GDD) is failure to attain expected developmental milestones in 2 or more areas of functioning. Not all children with GDD are found later to have ID

MS: And ID is usually identified later than GDD (after age 5), and is usually chronic in nature. A child may be delayed in a certain area, but later catch up and have no delay or disability.

AP: Very good. GDD is diagnosed when children are too young or too impaired to undergo systematic assessment of various levels of functioning So, let's say you suspect a child in your clinic to have ID. How are you going to go about diagnosing it?

MS: I know there are DSM-5 criteria for the diagnosis of intellectual disability, but I can't remember exactly what they are.

AP: You are correct. There are. The DSM-5 specifies that there should be deficits in intellectual function (reasoning, problem-solving, planning, abstract thinking, judgment, academic learning, and learning from experience, and practical understanding) confirmed by clinical assessment and standardized testing. There should also be deficits in adaptive functioning that require ongoing support, as they interfere with functioning in one or more activities of daily life, such as communication, social participation, and independent living, across home, school, work, and other settings. Also, these deficits occurs during the developmental period (generally childhood and adolescence)
Are you qualified as a pediatrician to diagnose ID?

MS: I believe so. Aren't physicians qualified to do so?

AP: Well, physicians (primary or subspecialists) may identify deficits in adaptive functioning, either by administering questionnaires for this, or by reviewing previously collected data. But generally, psychologists (clinical, educational, neuropsychologists) conduct the intelligence assessments, and also conduct adaptive assessments. This can vary in other countries based on regulations and standards of practice. One thing that should not happen is that ID should not be diagnosed purely on somebody's opinion, or non-standardized testing, or just a history of delays. Often, even after a diagnosis is made, it should be looked at again, or revisited, after a period of time, generally 2-3 years to ensure the stability of the diagnosis, and that the person still meets the criteria. The other thing to remember is that the educational qualification in school systems for intellectual disability might not be the same as the medical diagnosis because different systems use different criteria and different nomenclature. So, this is something for clinicians and families to be aware of.

MS: So, now that we have diagnosed intellectual disability, what about my patient? He does not have any “classic features” of any syndrome and I don’t want to jump to conclusions regarding a diagnosis, but I read that Fragile X syndrome is one of the most common genetic conditions associated with ID.

AP: Very good. Let’s dive into this. But before we get into the specific tests for the diagnosis, let's talk about the condition itself. What is Fragile X? Is it common?

MS: From the quick read I did last week, I learned that it has a prevalence of about 1 in 3,600 to 4,000 in males, and 1 in 4,000 to 6,000 in females. It is lower in females is because females with a full mutation also have another normal X chromosome. 1 in 151 females are carriers of the premutation, and 1 in 468 males are carriers of the premutation.

AP: Very good! Now, can you tell me what it is?

MS: From my reading, I learned that Fragile X is a genetic condition that causes intellectual disability, behavioral and learning challenges, and various physical characteristics.

AP: Great. Any physical characteristics that you can see?

MS: Now, our patient had no significant physical exam findings. In patients with Fragile X, depending on age, they can have typical physical features vary from patient to patient. Facial features include large ears, prominent jaw and forehead, and a long face. Other problems that can be found are connective tissue problems like strabismus, flat feet, high arched palate, mitral valve prolapse, double jointed fingers and hyper-flexible joints. In adolescence, there can be large testes.

AP: As we know, Fragile X isn't just associated with physical findings. What are some of the neuropsychiatric features? Can you name any?

MS: Sure! Kids with Fragile X can have ADHD, autism spectrum disorder, social anxiety, sensory disorders, and significant ID.

AP: Yes, also they can have hand-biting and/or flapping, poor eye contact, and aggression.

MS: And it is milder in females, right?

AP: Yes that’s correct. Females can have learning disorders more so than ID. Now let's talk about how you are going to go about diagnosing this child and narrowing down the differential diagnosis. What tests are you going to order?

MS: Hmmm, I might get a karyotype, maybe a PCR looking for a specific gene for Fragile X. I have the results he came with. His genetic testing showed a negative chromosomal microarray, which is a sensitive test used initially to investigate GDD and it consists of a computer chip analysis of DNA using molecular probes to diagnose deletions and duplications of whole chromosomes, portions of chromosomes, and specific locations associated with particular genetic diseases. The other is Fragile X molecular test which showed 240 CGG triple repeats. So it looks like he had PCR done, but why not a karyotype?

AP: Actually, the 2 most common genetic tests for Fragile X today, southern blot and PCR, have largely replaced karyotyping for the diagnosis of the disorder. Can you tell me what we are looking for in these specific tests?

MS: Well, I know that Fragile X is a triple repeat disorder, and the sequence is CGG in the FMR1 gene. I can't really tell you much else right now.

AP: That is an excellent base of knowledge to build off of. The FMR1 gene encodes the Fragile X mental retardation protein (FMRP), which is a regulatory protein that binds mRNA in neurons and dendrites. In a full mutation, FMRP is not made due to hypermethylation of FMR1, brain development is impaired due to abnormal synapse connections. It also can lead to excessive activity of the metabotropic glutamate receptor 5 (mGluR5) which results in many Fragile X symptoms in other tissues. Before we discuss the CGG repeats, let's go back and talk about how we test for Fragile X.

MS: You mean the southern blot and PCR?

AP: That's right. Southern blot tells if the gene has a full mutation, approximate size of the mutation, whether the gene has been methylated, and if there is mosaicism of the gene. PCR can determine the actual number of CGG repeats that are present in the FMR1 gene.

MS: ohhh now I remember from my reading. Certain numbers of repeats indicate different severities of the disease. The more repeats, the more severe the mutation. Right?

AP: That's right. 5-44 repeats indicates a normal unaffected individual. Patients with 45-54 repeats are unaffected, but are at risk of passing it onto their offspring, hence considered intermediate or grey zone. Patients with 55-200 repeats have a premutation, and >200 repeats indicates a full mutation. Males with a full mutation have Fragile X syndrome, and their mothers almost always have a premutation.

MS: Our patient had 240! That means he has the full mutation, and the disease.

AP: Unfortunately, that's right. You got the diagnosis right! His mother has the premutation as well. Why do all of this? Why not just have Fragile X be a clinical diagnosis?

MS: Well, lately, the diagnostic yield has increased substantially from genetic testing, from 8% to 35%, according to a study I looked at, likely due to improved technology. Families get more educated about not only the diagnosis, but the process moving forward as well during treatment, and what to expect. The tests are for establishing diagnosis, not confirming them.

AP: I'm very impressed! Now, all this talk about trinucleotide repeats...what exactly are they? Can you think of other disorders of trinucleotide repeats?

MS: Sure! For starters, trinucleotide repeats are normally occurring repeats in several genes. When they are not replicated correctly, they result in disorders. When the repeats exceed normal stable threshold, consisting of unstable microsatellite repeats, it increases the number, making the gene defective. Other diseases that I can think of are Huntington's, Friedreich Ataxia, Myotonic Dystrophy, and I'm sure there are others as well.

AP: I'm impressed. There are others. Spinocerebellar ataxias, spinobulbar muscular atrophy (SBMA) just to name a couple. Ok. Now that we have a fundamental understanding of the disease, we need to treat this patient. What other medical workup is necessary for Fragile X patients?

MS: Well, I read that these patients can also develop other medical conditions, such as gastroesophageal reflux disease, obstructive sleep apnea, strabismus and refractive errors, recurrent sinusitis/otitis media, decreased visual acuity, scoliosis, and mitral valve prolapse. There is actually an American Academy of Pediatrics guideline on the appropriate health supervision of patients with Fragile X syndrome which is really helpful. The guideline breaks down the health supervision into ages. For the 1-5 year old group, the guidelines include evaluation for ophthalmologic and orthopedic problems, inguinal hernias, seizures, recurrent otitis media, as well as monitoring of receptive and expressive communication, emotion and behavior, psychopharmacologic interventions, linear growth monitoring, facial structural changes, sleep disturbance/apnea, delayed toilet training.

AP: Yes, these patients often develop other problems, and it is important to monitor these.
In addition, there are two late-onset conditions to be aware of, especially in those with premutations. One is called Fragile X Associated Tremor/Ataxia Syndrome (FXTAS) which involves white matter lesions on MRI with intention tremor or gait ataxia. The other, only seen in females, is FMR1 Related Primary Ovarian Insufficiency (FXPOI), which is cessation of menses before age 40 years.

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MS: Alright, I'll try to read more about that, but it is generally in adults, not children, right?

AP: Correct. Now on the topic of treating these patients, who else is involved? Are you going to do everything yourself? Does Fragile X have a cure?

MS: Unfortunately, like most other genetic disorders, there is no cure, only symptomatic treatment, of which I hope I don't have to manage all by myself! It seems like a lot. I'm not really sure, but I imagine these patients qualify for special education, and other types of therapies. Thanks to the help of many allied health professionals involved in the treatment, growth, and development of the patient, the job is made a bit easier. These include, speech language pathologists, occupational therapists, special teachers in school, the family, and so on… It is important to integrate the various roles together in the care of the patient throughout different settings like the school, home, medical home, and mental health and therapy.

AP: Absolutely. They usually have help from other professionals that aren't necessarily doctors. But of course, the majority of the care comes from the family. It is important that these patients receive the exact same health care and surveillance that any other child would, as mentioned earlier in the AAP guidelines for the age group. Do you have any questions about Fragile X that we haven't discussed yet?

MS: No, I think that just about covers it. We just have to also remember to make sure the family understands every step of the process of management! Thanks so much.

AP: Absolutely, the family is the cornerstone of all of this. I hope this was useful.

MS: Invaluable! Thanks!

AP: No problem. Now, let's go see the patient together...

Let's summarize with a few key points:

- The term "mental retardation" is archaic, now replaced with "intellectual disability" (ID)
- Global developmental delay (GDD) is the term used most often in younger children (and with less severity)
- Genetic testing is indicated in searching for diagnosis in ID and GDD
- Fragile X syndrome is the most common inherited cause of ID
- Fragile X has many disease manifestations: physical, cognitive, psychosocial, and has no cure
- An interprofessional approach is often required in the care of individuals with Fragile X syndrome with the family and patient at the center of it all.

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Thank you for listening to this PedsCases podcast on the approach to a child with intellectual disability. Stay tuned for more PedsCases podcasts!

References:

- Saul RA, Tarleton JC. FMR1-Related Disorders. [Updated 2012 Apr 26]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1384/
- Hersh JH, Saul RA, Committee on Genetics. Health Supervision for Children With Fragile X Syndrome Pediatrics May 2011, 127 (5) 994-1006
- FXS — National Fragile X Foundation. Retrieved March 28, 2018, from https://fragilex.org/learn/
- Home | Fragile X Syndrome (FXS) | NCBDDD | CDC. Retrieved March 28, 2018, from https://www.cdc.gov/ncbddd/fxs/index.html

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