The Restoration Act (INGO) is proudly offering virtual seminars on various clinical topics of inborn errors of metabolism, genetics, and neurology in collaboration with the Ministry of Health Kurdistan Regional Government, Directorate General of Health Duhok, Iraqi & Kurdistan Boards for Medical Specialization/Pediatric, University of Duhok College of Pharmacy and Pediatric Department of Medicine, Kurdistan Pediatric Society, Hevi Hospital, and the Iraqi Pediatric Society.

Questions & Answers from:

"Common Neurological Presentations of Metabolic Disorders"

Held 21 November 2024

Watch the recorded Virtual Clinical Seminar

Passcode: **BsW.?6?n**

Presented by Metabolic Specialist:

Dr. Brian Shayota, MD, MPH

Dr. Shayota written answers to the questions as written during the live seminar:

QUESTION: Why choosing lactate as 1st test in case 1

Answer: Lactate should always be assessed in a case of suspected mitochondrial disease. Although a normal lactate does not rule-out a mitochondrial disease, have an elevated lactate level in the absence of any other identifiable cause (ie. Cardiac disease/poor perfusion, etc) can be helpful by providing additional evidence to suggest a metabolic or mitochondrial disease.

QUESTION: What about Moyamoya Disease (MMD), is there specific gene relation with their stroke presentation?

Answer: Moyamoya is a very different situation that the conditions I discussed in the lecture. Studies suggest that ~10% of moyamoya in Asian populations have a primary cause, usually involving the genes R179, RNF213, and ACTA2. More common are secondary moyamoya conditions, where moyamoya is associated, but not the underlying pathological mechanism of the disease. This includes conditions like sickle cell anemia, neurofibromatosis type 1, and Trisomy 21.

QUESTION: Does Leigh syndrome relate to a specific race or it can affect people of all race and ethnicity?. for case 1

Answer: All races and ethnicities.

QUESTION: why you did WGS no WES

Answer: The yield of WGS over WES remains quite low, but most major US institutions have already moved towards WGS simply because the stored data will be more beneficial to review in the future as technologies improve and new mechanisms of genetic diseases are discovered. At the current time, I would consider WES + microarray to have a nearly equal diagnostic rate compared to WGS.

QUESTION: you mentioned that the pompe disease can lead to stroke?

Answer: It is a very very rare complication, but has been reported a couple times. Current guidelines for Pompe do not recommend screening for strokes. [Laforêt et al 2008, Sacconi et al 2010].

QUESTION: So MELAS causes stroke like episodes which we can differentiate from other types of stroke because it is non-vascular, you mentioned increased levels of homocysteine in a particular case and homocysteine can induce endothelial damage inducing thrombosis and potentially lead to vascular obstruction. Does that mean that some cases can present with vascular strokes?

Answer: A condition like classic homocystinuria will lead to vascular thromboembolic strokes if left untreated. The MELAS stroke-like episodes however, have a different finding on imaging that characteristically does not follow a vascular region.

QUESTION: Are physiotherapy interventions for individuals with homocystinuria can begin at any age ? and the risks that a physiotherapist should avoid during physiotherapy treatment?

Answer: Physiotherapy can be helpful in those recovering from a stroke, but will not do anything to help prevent them. The only known way to prevent a stroke in classic homocystinuria is to reduce homocysteine levels. This can be achieved by supplementing vitamin B6 (pyridoxine) if found to be B6 responsive. If the patient is B6-non-responsive, then a combination therapy including protein restricted diet, methionine-free amino acid formula, folate and vitamin B12 supplementation, and betaine.

QUESTION: Posterior reversible encephalopathy syndrome-like presentation has been observed with some metabolic disorders like OTC deficiency, MSUD, mitochondrial disorders. Have you observed this in your career?

Answer: I have seen patients that were initially misdiagnosed as having posterior reversible encephalopathy syndrome, but eventually were found to have a metabolic disease like OTC deficiency. Not sure about some of the others, but it would seem possible.

QUESTION: as a nursing student i wanna know what the key points should you teach a patient with epilepsy to help them manage their condition and avoid triggers?

Answer: It depends on the underlying cause of the seizures. If it is a metabolic condition like a mitochondrial disease, it is important to avoid metabolic stressors like prolonged fasting, fevers, and infectious illnesses in general. If a patient does have an infectious illness that includes poor nutritional intact of difficult to manage fevers, we do recommend those patients get admitted to the hospital for dextrose containing IV fluids until the infectious symptoms resolve.

QUESTION: in which age we can diagnose that the baby has CP (regardless of the CP type)?

Answer: CP should be diagnosed clinically within the 1st year of life. Classic CP is non-progressive, so if symptoms are not obvious within the first year, or more often in the first few months of life, then to neurological findings should be considered a new symptom, which goes against the very idea of what CP is.

QUESTION: I have seen a case of CP in Heevi, and according to the mother that were her third child with this condition and she have had married to her cousin. In this case can we relate all three case as having one common cuase, hereditary or can it be related to cousin marriage?

Answer: Consanguinity increases the risk of all autosomal recessive genetic conditions. So having multiple children affected and knowing the parents are blood relatives means that there is almost certainly an underlying genetic cause for the children's condition.

QUESTION: What are some common treatments used to help manage symptoms of cerebral palsy? since it's not curable

Answer: If it is uncomplicated CP without an underlying genetic cause, than the treatment is just physical and occupational therapy to help overcome the obstacles of their disability. However, if there is a genetic cause, than it will depend heavily on what that diagnosis is, though few of these conditions on the differential have targeted therapies.

QUESTION: Does the genetics testing for cerebral palsy is recommended for all types of CP even with non idiopathic one? Which type of genetic testing is advisable WES\WGS?

Answer: It depends on the availability of genetic testing in your practice. At most centers in the US, if there is a clear environmental cause like prematurity or birth trauma, and the patient course is non-progressive CP, than we will not pursue genetic testing. However, in the absence of this type of history or if the neurological disease is progressive with time, then we do routinely pursue genetic testing, previously with WES but more so with WGS more recently.

QUESTION: How long it takes to get the result for WES?

Answer: WGS is more typical in our practice and we can order rapid WGS that will give us results in 1-2 weeks, ultra-rapid WGS in ~5 days, or standard WGS in 3-4 weeks. The quicker the test, the more expensive the cost. For WES, I believe the timing is similar.

QUESTION: as you now consaguinas marriage is very common in our community and it's not preventable, any action during pregnancy or Ealy neonatal period for early diagnosis and stablish management

Answer: It is important to know the diagnosis as early as possible for some conditions because starting treatment for certain metabolic conditions from birth can make a huge difference. So you need to know the diagnosis first, which sometimes you might learn of from an older sibling who has been diagnosed. Most of these metabolic conditions will not have anything suggestive during the prenatal period, so even for some of the more severe conditions I discussed, the babies are born looking perfectly healthy. If there is a known genetic condition in the family that you learn of because of an affected older sibling, you can perform genetic testing on the fetus with an amniocentesis sample, which can help the medical team and parents prepare for the extra care the baby may need once born. Even if there is not a treatment available, a diagnosis can also help with counseling for the family to understand the reason for the patients condition, help them make family planning choices, and may also inform if other family members are at risk for having a child born with the same condition.

QUESTION: some oral medications contain ARGININE ,do you recommend their presicription for patients with CP

Answer: No, arginine in standard doses is relatively harmless for anyone to take, but it is only a proven therapy used in the case of stroke-like episodes for MELAS.

QUESTION: Any need for anti coagulation in metabolic or genetic stroke , as you know the stroke is recurrent

Answer: Only for the metabolic conditions that cause thromboembolic strokes. In the case of inborn errors of metabolism, these are primarily the homocystinuria conditions, in which case anto-coagulations therapies can be helpful, but still more important is reducing the homocysteine levels.

QUESTION: In case one why you did WGS, whole genome sequencing not WES, whole exome sequencing?

Answer: Answered above:
"The yield of WGS over WES remains quite low, but most major US institutions have already moved towards WGS simply because the stored data will be more beneficial to review in the future as technologies improve and new mechanisms of genetic diseases are discovered. At the current time, I would consider WES + microarray to have a nearly equal diagnostic rate compared to WGS."

QUESTION: What are the latest insights into the role of mitophagy in clearing dysfunctional mitochondria, and are there therapeutic approaches to enhance this process?

Answer: Manipulating the controls of mitophagy offers a promising approach to treating mitochondrial conditions. I have seen reports that involve mitophagy stimulation, particularly by targeting the PINK1-Parkin pathway. Rapamycin is another drug that has

been found at least in mouse models to have a beneficial effect on Leigh syndrome. I am not aware of studies that have been performed on humans with mitochondrial diseases, though I would suspect they will be coming soon.

QUESTION: Is micoarray test is better than WES for the diagnosis of genetic causes of CP

Answer: No. Microarrays are good for picking up copy number variants (ie. large deletions or duplications on chromosomes) which generally present with a more complex phenotype as often there are multiple genes involved. However, much small deletions that may only involve a single gene can occur and importantly, these would not be picked up on WES, but can be found with a microarray, gene panel that includes sequencing and del/dup (read the fine print of the testing methods), and WGS.

QUESTION: What are (if there are) the latest advances in enzyme replacement therapy or gene therapy for metabolic diseases

Answer: I am actively involved in many of these trials. There are FDA approved drugs that our neurologist and neuromuscular specialists typically like spinal muscular atrophy (SMA), Duchenne muscular dystrophy, and metachromatic leukodystrophy. For traditional metabolic conditions, we are currently conducting human clinical trials on patients with glycogen storage disease type 1a, Pompe disease, Fabry disease, OTC deficiency, methylmalonic aciduria, and proprionic aciduria. Some of these are traditional gene therapies with AAV vectors to incorporate a copy of the gene, while other companies are investing in mRNA therapies. Enzyme replacement therapies are available for conditions like Fabry, Pompe, several of the mucopolysaccharidoses, and Gaucher along with clinical trials for argininemia and homocystinuria (that I am aware of).

QUESTION: What if epilepsy targeted gene panel was selected for genetic testing instead of WES?

Answer: Gene panels are okay as an initial step for epilepsy and what our neurologist had been doing for a very long time up until very recently. The challenge with gene panels for epilepsy is that you very frequently get variants of uncertain significance, which if you do not have much experience with interpreting genetic test results, it can be challenging to know what to do and how to counsel the family regarding the findings. Especially because a lot of these genes can have autosomal dominant inheritance patterns with decreased penetrance, so they can sometimes be hard to rule out even if you get follow-up parental testing. This can of course be true for WES results too. If resources are limited though, I would reserve sending WES/WGS for the epilepsy patients that have other medical concerns as well like dysmorphic features, developmental regression, or CNS anomalies, or some other more complex presentation.