Open Access Case Report

Early onset familial relapsing polyneuropathy, mimicking CIDP; A lesson from clinical genetics

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Abstract

Background: In children, chronic immune-mediated neuropathies present with slowly progressive or relapsing episodes of gait difficulty, symmetric weakness and sometimes paraesthesia. Infancy and early childhood age of presentation and familial recurrence are believed to be atypical features.

Case presentation: Herein, we describe two brothers from a non- consanguineous Iraqi family, who presented with episodes of acute immune-mediated demyelinating peripheral neuropathy in early infancy that relapsed recurrently. Mild haemolytic anaemia was also reported. Inherited metabolic disorders were suspected and Whole Exome Sequencing of the youngest brother revealed homozygous frame shift mutation in CD59 gene, confirming the diagnosis of autosomal recessive hemolytic anemia, CD59-mediated, with or without immune-mediated polyneuropathy (HACD59).

Conclusion: The report highlights the advantage of genetic testing in such rare and inherited conditions. In the lack of necessary non-traditional diagnostic methods, it is substantial to maintain the accustomed medical practice and strategies, based on available clinical data.

Keywords: CD59 gene, Polyneuropathy, Paediatric, Iraq

Introduction:

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated disorder that is comparatively uncommon in the paediatric age group.1 In children, it may have acute manifestations and is misdiagnosed as acute inflammatory demyelinating polyneuropathy (AIDP). Upon subsequent relapses, the diagnosis is changed. A chronic course, often with subtle onset of symptoms can also be encountered. An acute presentation with severe symptoms and a relapsing course is more common in children when compared to adults.2 Furthermore, they exhibit a good response to therapy with better improvement and more promising prognosis.3 An informed consent was received from the family for the publication of these two cases.

Case 1

A three year old boy: He was first referred at the age of six months with acute symmetric muscle weakness accompanied by hypotonia and absent tendon reflexes, with the legs being involved to a greater extent. Lumbar puncture showed high protein level with normal cell count, while nerve conduction study (NCS) reported prolonged distal latencies, reduced motor conduction velocities and prolonged F-wave latencies with exclusive involvement of motor fibers. Both tests were performed few days after the onset of weakness. Intravenous Immunoglobulin (IVIG) was infused. He was discharged with partial improvement (he was able to move elbows, wrists and hands appropriately, but he had difficulty in lifting arms at the shoulder, while he could barely lift the right leg off bed and move the left leg horizontally). Because of the infantile onset of illness, the diagnosis of Guillain-Barré syndrome was doubted and congenital hypomyelinating neuropathy was suggested, which necessitated long term use of oral prednisolone (2 mg/kg, daily). Four months later, and while he was receiving oral prednisolone, a new attack of acute flaccid tetraparesis developed, which aggravated his muscle weakness and was accompanied by respiratory insufficiency that required artificial ventilation and IVIG (2 gram / kg over 3 days). He had preserved consciousness, hoarse voice, impaired swallowing, absent and reduced tendon reflexes in the lower and upper limbs, respectively, with more severely impaired strength of muscles of the lower limbs (grade zero versus grade - 2 in the upper limbs). He progressively, but partially improved and was discharged. At that time prednisolone was stopped as it exhibited no protective benefit. During the following months, he had similar but milder five attacks, where the weakness was aggravated by intercurrent infection. These attacks were treated by immunoglobulin (IVIG). Between episodes, the upper limbs' strength and function were partially regained, accompanied by persistent flaccid paralysis of the lower limbs. There was no significant

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difference in proximal/distal muscle involvement. The patient's cognitive level was age-appropriate. Blood transfusion was required twice, in the intensive care unit, because blood haemoglobin level decreased and blood smear showed polychromasia and high reticulocytes, while coomb's test was negative, which indicated haemolytic anaemia. Thenafter, the haemolysis was characterized by a chronic course. At the age of 30 months, Whole Exome Sequencing test revealed a mutation in CD59 gene. Since then, he and his brother (case 2) were placed on monthly IVIG program. His symptoms improved gradually and the muscle strength of the limbs recovered to the point where he could walk with assistance, yet contracture persisted in both feet, which necessitated orthopaedic intervention and orthosis. The family reported an unremarkable gestation and birth process. The parents are non-consanguineous. His older brother (case 2) is suffering of a similar illness. He has a positive family history (first-degree and remote kin on the paternal and maternal sides) of stillbirth, two abortions, childhood-onset strokes, psychomotor regression, neonatal death, and motor disabilities.

Case 2

A 15 year old boy: He presented with pain in the neck and back with acute symmetric muscle weakness of the lower extremities that were preceded by a flu illness. He suffered similar episodes at the second and third years of life, after which he improved with neurological deficits. Anaemia that needed blood transfusion was reported twice. His intellectual abilities were not affected and school performance was acceptable. In the current episode, systemic physical examination showed mild pallor, while neurological examination revealed an oriented adolescent boy, with multiple craniopathies (oculomotor, glossopharyngeal, and accessory nerves), distal wasting and contracture of the lower limbs, generalized hypotonia, areflexia, and muscles' strength profile of grade 4+/5 (equally distributed among proximal and distal muscles) in the upper limbs and 4+/3- (in the proximal and distal muscles, respectively) in the lower limbs. The nerve conduction study showed increased distal motor and sensory latencies, reduced conduction velocities in demyelinating range and prolonged F-waves latencies. Thus, symmetric sensorimotor peripheral polyradiculoneuropathy was confirmed with evidences of chronic neurogenic changes. He received IVIG, and later, a monthly program of immune suppressive medication was launched. Craniopathy disappeared and motor function recovered partially. The initial Modified Rankin Score (MRS) of score three gradually improved to a score of two.

Discussion

The present cases were diagnosed as having chronic inflammatory demyelinating polyneuropathy (CIDP), based on the diagnostic criteria that were developed in 2010 and manifested as GBS-like episodes.4 The reported prevalence of CIDP is 0.48/100,000 in children, with a male predominance.5 Unusual manifestations in CIDP can cause diagnostic confusion, those include: Early age at presentation, presence of wasting/ contracture, cognitive impairment, seizures, delayed development, positive family history, elevated Creatine Kinase, impaired metabolic work-up and no benefit obtained by giving IVIG.6 In the present scenarios, familial recurrence, a positive family history (other relatives) of non-similar neurological disorders and the early presentation, raised suspicion of inherited disorders, particularly mitochondrial or respiratory chain disorders.7 Therefore, the youngest brother was genetically tested by Whole Exome Sequencing in Centogen lab (Germany). A previously unreported homozygous variant in Exon 4 (c. 183_184 dup, p.(Asn62Ilefs*19)) of CD59 gene was found, creating a shift in the reading frame starting at codon 62. The new reading frame ends in a stop codon 18 positions downstream. It has been confirmed by Sanger sequencing and was classified as likely pathogenic. The family could not afford the financial cost of doing genetic testing for the others members. CD59 gene encrypts CD59 glycoprotein, which inhibits the final step of Membrane Attack Complex (MAC) formation, and thus, named MAC-inhibitory protein (MAC-IP), or Protectin, that adheres to host cells via a glycophosphatidylinositol (GPI) anchor, safeguarding the cells from complement-mediated damage, by CD59.8 MAC deposits have been observed in areas of demyelination in disorders like Guillian-Barré syndrome, CIDP and multiple sclerosis. An observation, which suggested mediation of demyelination process in both peripheral and central nervous system by MAC activation.9 Both children had a chronic course of haemolysis which was exhibited as low haemoglobin, elevated reticulocytes and negative coomb's test. It has been found that increased susceptibility of erythrocytes to lysis in patients with paroxysmal nocturnal hemoglobinuria, is mainly mediated by CD59 deficiency.10 CD59-mediated haemolytic anaemia with or without immune-mediated polyneuropathy (HACD59) is an autosomal recessive disorder, which is caused by homozygous variant in the CD59 gene on chromosome 11p13. It causes relapsing-remitting polyneuropathy with infantile onset, often triggered by a febrile illness, and presents as hypotonia, hyporeflexia and limb muscle weakness.11 The expression of CD59 is analysed by Flow cytometry, which is an essential step in the diagnostic panel of CD59 deficiency.12 Yet, it was not available in the local labs. An autosomal recessive disorder results from biallelic variants (meaning two abnormal variants). This necessitates a consanguineous marriage, which is not the case in this family. Sometimes, this happens when the parents are distant relatives, or a founder (from the same village or ancestors), both of which most probably explain the inheritance pattern in the present cases. It could also be due to a hot spot for recurrent mutation (the area is prone to get mutations), or it is caused by compound heterozygous variants. To our knowledge, no case of HACD59 has been reported previously in Iraq.

Launching early diagnosis and using more extensive immuno-suppressive and immuno-modulating therapies like Eculizumab might have prevented relapses or reduced relapse severity and thus hindered the incapacitating trajectory in our patients.13,14,15 We did not have access to this medication for administering to our patients.

Conclusion

Our report highlights the atypical presentation of CIDP, where gene testing is essential to arrive to the diagnosis, comprehend the genetic mechanisms and guide toward convenient treatment option. It also emphasizes the importance of maintaining the traditional medical practice based on available clinical data, in areas deprived of non-traditional diagnostic tools like genetic testing.

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البدء المبكر لإعتلال الأعصاب المتعدد العائلي الناكس، محاكيا إعتلال الأعصاب المتعدد الإلتهابي المزمن المزيل للميلانين: درس من علم الوراثة السريرية

د. نبال وائل سعدي

الخلاصة

الخلفية: تظهرالإعتلالات المناعية المزمنة للأعصاب في الأطفال بشكل نوبات تصاعدية او ناكسة تسبب صعوبات في المشي، ضعف متناظر، وفي بعض الأحيان تنمل. يعتبر ظهور المرض في عمر الرضاعة والطفولة المبكرة والتكرار العائلي من المميزات غير القياسية.

عرض الحالة: نصف هنا شقيقين من عائلة عراقية لأبوين غير أقارب، حيث اصيبوا بنوبات حادة من إعتلال الأعصاب المحيطية المناعي المزيل للميلانين، في عمر الرضاعة المبكر والتي نكست بشكل متكرر. كما سجل فقر دم انحلالي خفيف. تم الإشتباه بأمراض التمثيل الغذائي الموروثة وكشف التحليل الجيني (التسلسل الكامل للإكسوم) للأخ الصغيرعن وجود طفرة إنزياح الإطار متماثلة اللواقح في الجين CD59، والتي تؤكد تشخيص فقر الدم الإنحلالي المتنحي الجسمي، بواسطة CD59، مع أو بدون إعتلال الأعصاب المتعدد المناعي (HACD59).

الإستنتاج: يبرز التقرير ميزة الإختبارات الجينية في مثل هذه الحالات النادرة والموروثة. في ظل غياب طرق التشخيص غير التقليدية الضرورية. من المهم الحفاظ على الممارسات والإستراتيجيات الطبية المعتادة، بناءً على البيانات السريرية المتاحة.