New SCN1A Mutation in Libyan Nonidentical twin

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Introduction:

As Charlotte Dravet described a new severe epilepsy syndrome in young children in in the end of the of the seventies of last century , she never imagine that the syndrome named after her would be one of the most studied epileptic syndrome by molecular genetic diagnostic tests , Dravet syndrome which is also known in many books as 'Severe Myoclonic Epilepsy of Infancy' or 'SMEI'or polymorphic myoclonic epilepsy of infancy (PMEI) , but Dravet syndrome is preferable because the myoclonic element can be absent or late , Dravet et al have named a seizure type "obtundation status" implying impairment of consciousness with variable intensity lasting hours to days.

Fully developed syndrome clinical picture:

Normal psychomotor development during the first months of life; earliest presenting symptoms of seizures, mostly starting during the first year of life; slowing of psychomotor development later on and other neurological deficits such as a peculiar clumsiness resembling cerebellar ataxia, finally leading to severely disabled individuals who are unable to live independently. Seizure types are multiple and include clonic and tonic seizures, either generalized or unilateral; myoclonic seizures; atypical absences of short duration; and complex partial seizures. Initially, seizures are often associated with fever, but afebrile seizures occur later in the course of the disorder. The syndrome is notable for its frequent occurrence of status epilepticus, either convulsive or as an obtundation status, and its resistance to a wide variety of anti-epileptic drugs. Photosensitivity is also a frequent finding eye blinking which myoclonic or partial siezures as we will describe in the two girls with the new SCN1A mutation.

As is the fate of most clinically and electrophysiologically defined syndromes, the uniqueness and delineation of Dravet syndrome were challenged by the observation that some patients present most of the cardinal features but lack others. These atypical cases led to the introduction of other designations such as SMEI-borderline or ‘Intractable Childhood Epilepsy with Generalized Tonic-Clonic Seizures’ (ICE-GTC) and started heated discussions as to whether these atypical cases represent true Dravet syndrome. Over 20 years passed till modern molecular genetic technologies provided the tools to reach a conclusion.

Initial EEGs are usually normal, epileptiform activity appears over time , EEG may shows diffuse dysrhythmia of slow waves with focal and diffuse spikes or poly spike wave or multifocal spikes.

2008 ILAE classification revisions:

In the 1989 ILAE classification, Dravet syndrome was listed as a cryptogenic disorder with both focal and generalized features. the 2008ILAE revision classifies Dravet syndrome as an epileptic encephalopathy with onset during the first year of life and of a fundamental genetic basis, most frequently a sodium channelopathy (what might have been called "idiopathic" in 1989), and also perhaps a part of the GEFS+ spectrum. Dravet syndrome is also classified in the , 2008 revision as a Genetic and Developmental Epilepsy syndrome .

There are many types of voltage gated channels and receptors which can be involved in the epileptogenesis of many encephalopathies and epileptic syndromes includes :

A) the neuronal nicotinic acetylcholine receptors (nAChRs) (CHRNA4/CHRNB2) which are pentamers, with each subunit containing four transmembrane domains. At least ten nAChR subunits, which can assemble into heteromeric (α2–α6, β2–β4) or homomeric receptors (α7, α9), are expressed in the human brain. The binding of two agonist molecules is required for channel opening. The channel itself shows little selectivity among monovalent cations.

B) The $GABA_A$ (γ-aminobutyric acid, subtype A) receptors (GABRG2/GABRA1) are ligand-gated ion channels that probably evolved from the same ancient genes as the nAChRs, with whom they share several features, such as four transmembrane domains per subunit and a pentameric structure. $GABA_A$ receptors are selective for small anions and allow both chloride and bicarbonate to permeate.

C) Voltage-gated sodium channels (SCN1A/SCN2A) are built from onelarge central poreforming glycosylated α-subunit, which contains four tandem domains, each resembling the structure of a voltage-gated potassium channel subunit. Sodium channels are associated with two accessory β-subunits, which accelerate the gating kinetics of the channel.

D) Voltage-gated potassium channels (KCNQ2/KCNQ3) are tetramers made up from homologous subunits. Each subunit contains six transmembrane domains. The fourth transmembrane domain carries several positively charged amino acids, which cause a conformational change on membrane depolarization. The linker between transmembrane domains 5 and 6 contains the selectivity filter that lines the ion pore.

E) Voltage-gated chloride channels of the CLCN type comprise a gene family with nine mammalian members. They build homodimeric proteins, which probably contain two separate pores. CLCN channels conduct chloride ions across cell membranes, governing the electrical activity of cells

Other disorders associated with SCN1A mutation includes:

Febrile convulsion in the mild side to a Genetic (generalized) epilepsy with febrile seizures plus; GEFS+, Severe Myoclonic Epilepsy of Infancy Borderland2 (SMEB), Intractable childhood epilepsy with generalized tonic-clonic seizures (ICE- GTC) to the most sever which is Dravet syndrome .

Hundreds mutation have been described in this gene leading to abnormalities in voltage gated sodium channels, and now we present a **new pathologic mutation in a Libyan nonidentical twins**

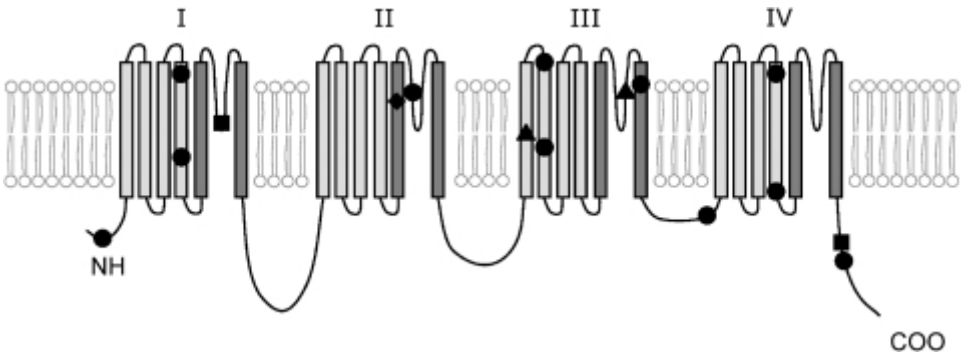

Figure 1 :

Schematic diagram of the SCN1Scoded voltage gated Na channel and the location of some abnormalities.

The story of Samar and Sahar :

They are two Libyan twin girls delivered on (9.12.2005) as normal vaginal delivery after full term normal pregnancy and without any peri-post or natal problem , with average weight and height and head circumference the parents are nonconsanguinous , fed artificial feeds with good hygienic and proper preparation , vaccinated according to the Libyan program of vaccination without side effects . The developed normally up to the age of 11 months when the seizures started as atonic irresponsive states first affected Sumer who kept in hospital for three days and discharged in good condition with a diagnosis of febrile convulsion . After one month her twin Sahar got the same attack, and also diagnosed the same since the attack in bath associated with febrile upper respiratory illness , after three months

again Sumer and after few days Saher got other attack with generalized tonic clonic picture taken to Tunisia EEG was done and they started them on valproate 200 mg three times daily after 45 days they got other similar attack with Sumer first followed by Saher who went in status epilepticus admitted to ICU for three days , the attacks becomes more frequent with some psychomotor regression (all attacks is induced by fever or exposure to hot weather or heavy exercise) adding to them carbamazepine which causes them to go in semi coma state fore few days removed and started on Phenobarbital 100 mg and increased the dose of valproate to 300 mg thrice daily when I saw them for the first time the convulsions was still there and so frequent and they were severely drowsy I stared them levetiracetam (keppra) and stopped Phenobarbital , they become active fully conscious , regained their activity but with eye blinking which could be a myoclonic attacks, they have also mild intellectual impairment.

They have (brother and sister of their father) with same history , the Uncle and Aunt now in mid thirties and severely handicapped mentally and physically.

MRI normal EEG focal spikes with generalized slowing , Dravet was suspected in this family (they refuse family genetic counseling) because of social problems but agree for genetic testing of the two girls , I requested the test for the SCN1A mutation which come positive with new unrecorded mutation affecting this gene in the location (c4511 A>T) .

As usual for most of these syndrome miss diagnosis and delayed diagnosis is the role specially in areas lacking experted physicians in many speciality not only pediatric neurologists .

We have a family with two affected adults who were not diagnosed yet and two girls who are also delayed in diagnosis , compined with poor education and bad social circumstances which prevent us from family screening of the whole family which may declare some mendlian inheritance with may be poor gene penetration in the parents or silent carrier state , in opposite to the usual way of De Novo mutions seen in this type of diseases

Exclusion of other disorders with similar convulsion behavior like lennox Gastaut , which is excluded by the age of presentation , Doose syndrome (which usually presented astasia – myoclonic association in 100 % of cases) with nearly same age of presentation but the clinical picture is in favour of Dravet , other disorders sharing same gene mutations and listed above also can be excluded with the exception of the borderline variant of Dravet syndrome height possibility of diagnosis in these two girls .

These two girls were investigated metabolically including sodium ,potassium calcium , sugar , chloride , blood gases , amino acids , organic acids and all wre normal .

MRI done and it was normal which make some metabolic disorder like mitochondrial disorders less likely beside other disorders that gives specific and suggestive disorders .

Method :

Genomic DNA was screened for mutation in the SCN1A gene , the complete coding region and relevant parts of the gene were umplified by Polymerase Chain Reaction (PCR) and analysed by direct sequencing , the resulting sequence data was compaired with the reference sequence gene

ID NM_006920.

Sumar and Sahar carries the same SCN1A gene mutation c.4511 A>T (p.Gln150Leu) heterozygous state .

Interpretation :

The sequence analysed detected a nucleotide exchange A>T in heterozygous state at position c.4511 in exon 24 of the SCN1A gene , this alteration is first time detected .

All used bioinformatic programs predict this variant to be damaging , given the position of the transition of this evolutionary highly conserved nucleotide and the prediction by different bioinformatic algorithms it is most likely that this gene is pathogenic .

Conclusion :

These twins have new pathologic mutation involving the SCN1A gene which is should be added to the other mutations of this gene , the variation of clinical picture does not affect the diagnosis because it is usual in medicine in general and in Dravet disease and its varients .

N/B Testing for SCN1A was done in (BIO SCIENTIA) institute for medical diagnosis (Konrad-Adenauer st 17) 55218 , Ingelheim , Germany.

Reference :

1- *Dravet C, Bureau M, Oguni H. et al. Severe myoclonic epilepsy in infancy: In: Roger J, Bureau M, Dravet C, et al (eds) Epileptic Syndromes in*

2- *Infancy, Childhood and Adolescence, 3 ed. John Libbey, Eastligh, pp 81-103. 2002 Lossin. A catalog of SCN1A variants. Brain De2008:doi;16:1016/jbraindev.2008.07.011.*

3- *International League Against Epilepsy www.ILAE.org*

4- *Miller I, Sotero de Menezes M. SCN1A Seizure Disorders. Gene Reviews: NCBI Bookshelf 2007;www.ncbi.nlm.nih.gov/bookshelf.*

5- *Harkin LA, McMahon JM. The spectrum of SCN1A-related infantile epileptic encephalopathies.*

6- *Brain 2007 Mar;130(Pt 3):843-52.*

7- *Nabbout R, Gennaro E et al. Spectrum of SCN1A mutations in severe myoclonic epilepsy of infancy. Neurology. 2003; 60: 1961–7.*

8- *KIMURA K, SUGAWARA T, A missense mutation in SCN1A in brothers with severe myoclonic epilepsy in infancy (SMEI) inherited from a*

9- *father with febrile seizures. Brain & Dev(2005) ;27: 424-430.*

10- *Hurst D, Epidemiology of Severe Myoclonic Epilepsy of Infancy. Epilepsia 2001;42:796-803.*

11- *Gardiner M, Molecular Genetics of Infantile Nervous System Channelopathies. Early Human Development 2006;*

12- *1016jearlhdev.2006.09.013. 10. Scheffer I, Berkovic S, Generalized Epilepsy with Febrile Seizures Plus: A genetic disorder with heterogeneous clinical phenotypes. Brain*

13- *1997;120:479-490.*

14- *Scheffer I, et al., Neonatal epilepsy syndromes and GEFS+. Epilepsia 2005;46(10):41-7.*

15- *Iwasaki N, Nakayama J. Molecular Genetics of Febrile Seizures. Epilepsia 2002;43:32-35.*

16- *Scheffer I, Berkovic S. Generalized (genetic) Epilepsies with Febrile Seizures Plus. In: Engel J, Pedley T. Epilepsy: A Comprehensive Textbook.*

17- *Lippincott Williams & Wilkins 2007; 2553-2662.*

18- *2005;20(11):893-97.*

19- *Chiron C, et al., Lancet 2000;356:1638-42.*

20- *Yakoub M, et al., Early diagnosis of severe myoclonic epilepsy in infancy. Brain Dev 1992;14;299-303.*

21- *Laux, L. Personal communication.*

22- *Dravet C. Personal communication.*

23- *Korff C, Laux L. Dravet syndrome: a Retrospective study of 16 patients. Jour Child Neur 2007; 22:185-94*

24- *Epilepsia 2005; 39:508 – 512.*

25- *Ulrich S. Syndromes I: Dravet, West, Lennox-Gastaut, and Doose Syndromes*

26- *Maryse Lassonde and Ulrich Stephani. Epilepsia 2006; 47:53-55.*

27- *Nieto Barrera M, Candau Fernandez Mensaque R, Nieto Jiménez MD*

28- *John J. Millichap, MD, Sookyong Koh, MD, PhD, Linda C. Laux, MD, and Douglas R. Nordli, Jr, MD in NEUROLOGY*