Genetic testing for benign non-familial infantile seizures

Seizures are rather common during the neonatal period and during infancy. Benign infantile seizures are afebrile in nature, and characterized by the first seizure appearing between 3 and 12 months of age with a peak at 5-6 months. These seizures are idiopathic and affect infants that are otherwise normal. The outcome is favorable; and both familial and non-familial cases have been described.

Epidemiology - After West syndrome and symptomatic focal epilepsies, benign infantile seizures constitute the third most common type of epilepsy in the first two years of life, with the incidence being much higher in developing countries (Fejerman and Caraballo). In an Arab population, 14 out of 275 (12%) infants were concluded to have benign infantile seizures, out of which the majority (11 out of 14) were non-familial (Saadeldin et al., 2010). In our clinic, we see approximately 50 cases / year of benign infantile seizures, and other pediatric neurologists in Gujarat also see a similar number of cases. Out of these cases, approximately 10-20% of this is familial, and the rest (80-90%) is non-familial.

Presentation and management - The clinical manifestations of benign infantile seizures (also known as Watanabe–Vigevano Syndrome) are seizures that occur in clusters of 5 to 10 per day for 1-3 days and may recur after 1-3 months. A single isolated seizure episode may be seen in a third of the patient population 1-2 weeks before the clusters appear. Seizures are brief and focal, and consist of decreased responsiveness, motor arrest, impairment of consciousness, staring, automatisms and unilateral clonic convulsions (Panayiotopoulos, 2005) which may secondarily generalize (Specchio and Vigevano, 2006). The EEG is normal inter-ictally; ictal EEG shows focal discharges of very fast activity, and the side and location may vary between seizures even in the same patient . By definition, seizures remit 1-2 years from the onset and development is normal. During the active period, anti-epileptic drugs are effective, and withdrawal of the drug 1-3 years after onset of the seizures does not usually lead to relapse.

Etiology - As expected, the cause for benign familial infantile seizures is autosomal dominant and an association with Chromosomes 2 and 16 (16p12-q12) have been found (Callenbach et al., 2005). Mutations in KCNQ2 and KCNQ3 have been found in benign familial neonatal seizures (Grinton et al., 2015).

Hence, substantial evidence exists for possible genes involved in the familial cases of infantile seizures. On the other hand, not much is known about the etiology of non-familial cases of benign infantile seizures, but since these patients also constitute a considerable proportion of cases, we **would like to investigate possible genes for benign non-familial infantile seizures, and some candidates are PRRT2, SCN2A, SCN3A, KCNQ2 and KCNQ3.** The reasons for doing this research are multifold:

1. Finding a genetic component to the seizures will allow the neurologist to be more confident communicating to parents the exact cause of epilepsy.

2. A task force report for the ILAE recommends imaging, preferably MRI as standard of care for infants presenting with seizures (Wilmshurst, et al., 2015). Knowing that there is a genetic basis for this benign condition will enable the neurologist to omit this costly procedure.

3. Benign infantile seizures respond remarkably well to medication. The course of action for sporadic cases is to administer AEDs, wait and follow the evolution. Once the benign nature of the disease is established, the treatment is stopped. Confirmation of the diagnosis by genetic testing will allow the neurologist to tailor treatment accordingly which would be different from treatment for a symptomatic cause.

Patient recruitment and procedure - Patients from Paediatric Neurology Clinic, Ahmedabad will be recruited based on the following criteria: 1). First seizure during the first 28 days of life; 2). No family history of epilepsy; 3). Normal MRI taken before start of anti-epileptic medication, and 4). Normal EEG taken before the start of medication

A blood sample will be taken from approximately 40 patients over the course of one year and will be sent to Med Genome in groups of 5.

Genes to investigate - The choice of the genes to investigate is based on previous studies of benign familial infantile seizure and benign neonatal infantile seizures. The gene for benign familial neonatal seizures was showed to be located on the long arm of Chromosome 20, and since Chromosomes 2 and 16 have already been described for familial seizures, we will investigate those in the non-familial cases.

1. PRRT2 or proline rich transmembrane protine 2 is gene located on Chromosome 16. The PRRT2 mutation c.649dupC has been found to be the most frequent cause of benign familial infantile convulsions (Steinlein et al. 2012), but another study (Specchio et al., 2013) found a de novo mutation (c.649_650InsC) in 2 out of the 7 non-familial benign infantile seizure cases as well. Another mutation c.981C>G (I327M) in the PRRT2 gene has also been found in a Japanese cohort (Okumura et al., 2013). Expression of the PRRT2 protein is limited only to the brain and spinal cord and has a critical role in synaptic transmission (Ebrahimi-Fakhari et al., 2015). The expression of the protein peaks during postnatal development perhaps highlighting its role in infantile seizures (de Vries et al., 2012; Heron and Dibbens, 2013).

2. SCN2A - A syndrome where the first seizure episode occurs between 2 days and 3.5 months has been described and named benign familial neonatal – infantile seizures. A missense mutation in SCN2A – the gene that codes for alpha2 subunit of the Na channel was found in this condition (Berkovic et al., 2004). SCN2A is a gene that is located on Chromosome 2q24. Two other mutations were discovered in SCN2A - E430Q; I1596S in benign familial neonatal – infantile seizures (Herlenius et al., 2007) as well. Another mutation in SCN2A is c3003T – A (Striano et al., 2006).

3. KCNQ3 – Mutations in the KCNQ2 and KCNQ3 genes have been implicated in benign familial neonatal convulsions (Singh et al., 2003).

4. CHRNA2 - A novel missense mutation in the nicotinic acetylcholine receptor CHRNA2 has been found in benign familial infantile seizure. A single nucleotide substation in the CHRNA2 gene (c.1126 C > T; p. Arg376Trp) has been found (Trivisano et al., 2015).

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