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Chromosomal microarray in unexplained severe early onset epilepsy – A single centre cohort

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ABSTRACT

Background: Severe early onset epilepsy may lead to impaired cognitive and motor development, and consists of a group of specific and overlapping electro-clinical phenotypes which may be the result of an inborn error of metabolism, congenital or acquired structural brain lesion, known chromosomal or mono-genetic disorder. A significant proportion of cases however remain unexplained, representing a major diagnostic and management challenge.

Methods: In this study we describe a cohort of children with severe early onset epilepsy and examine the clinical utility of chromosomal microarray (array-comparative genomic hybridisation, CGH) in this group of epilepsies.

Results: In 51 children with unexplained severe early onset epilepsy, all of whom had chromosomal array tested, copy number variants were detected in 17.6% and pathogenic variants in 5.9% of infants.

Conclusions: Chromosomal microarray is a useful investigation in early onset refractory epilepsy and epileptic encephalopathy. Detailed review of the precise array abnormality and phenotypes associated are important for determining significance.

1. Introduction

Severe early onset epilepsy may lead to impaired cognitive and motor development, and consists of a group of specific and overlapping electro-clinical phenotypes which may be the result of an inborn error of metabolism, a congenital or acquired structural brain lesion, or a known chromosomal/mono-genetic disorder.[1] However a significant proportion of such cases remain unexplained, which represent a considerable diagnostic and management challenge.[2] There is growing evidence that chromosomal copy number variants (CNVs) i.e. deletions or duplications are responsible for a proportion of cases. We describe a cohort of children with severe early onset

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epilepsy and examine the clinical utility of chromosomal microarray i.e. array-comparative genomic hybridisation (CGH) in this group of epilepsies.

2. Methods

Children referred (between the years 1998–2013) with unexplained early onset (<1 year) epileptic encephalopathy or unexplained refractory epilepsy with abnormal development were included in this study. Children with inborn errors of metabolism, brain structural abnormalities (including cortical dysplasia), previous causative genetic diagnoses or disease processes explaining their epileptic disorder were excluded. As six children died prior to the use of array CGH, one lost to follow up, and one family declined testing, these were excluded. All histories, examinations and previous metabolic, genetic, neuroimaging and epilepsy investigations were reviewed. Phenotypes were classified into known electro-clinical syndromes where possible. Chromosomal microarray testing was performed in all patients. Ethical committee approval was obtained from the Children's University Hospital, Temple St., Dublin.

3. Results

Fifty one patients were included. Table 1 outlines their collective phenotypes and chromosomal microarray detection rate. Nine patients (17.6%) had CNVs detected. In three (5.9%) the CNV identified was considered pathogenic (i.e. diagnostic), one of which was maternally inherited (Table 2). Uncertain and unlikely clinically significant CNVs are presented in Table 2.

Table 1 – Characteristics of cohort (n = 51 infants).

Male: Female	25 (49%): 26 (51%)
Electro-clinical phenotype	
Ohtahara syndrome	5 (9.8%)
Migrating partial seizures of infancy	1 (2%)
Dravet syndrome spectrum	4 (7.8%)
Infantile spasms	23 (45.1%)
Non-specific (focal)[a]	15 (29.4%)
Non-specific (generalised)[a]	3 (5.9%)
Average age of seizure onset (range)	4.7 months (day 1–12 months)
Average age of follow up (range)	5.8 years (12 months–14 years)
Good developmental outcome	3 (5.9%)
Number of CNVs detected by array CGH	10 (19.6%) (n = 9 patients)
CNV – likely pathogenic	3 (5.9%)
CNV – uncertain significance	2 (3.9%)
CNV – unlikely significant	5 (9.8%)

[a] Where a clear electro-clinical syndrome could not be determined, infants were classified as having epilepsy or epileptic encephalopathy with either generalised or multifocal features on electroencephalogram. All patients had at least 1 brain magnetic resonance imaging scan. All patients had baseline metabolic screens including serum amino acids, ammonia, lactate, urine organic acids and mucopolysaccharides, and many had further metabolic investigations of serum, urine, cerebrospinal fluid. Some had muscle & skin biopsy. No child had major dysmorphism or complex congenital anomalies.

4. Discussion

This study investigated the utility of array CGH in a cohort of 51 previously extensively investigated infants with unexplained severe epilepsy. We found CNVs in 17.6% of children; likely clinically significant or pathogenic CNVs in 5.9%, uncertain CNVs in 3.9% and unlikely significant CNVs in the remainder. The detection of both sporadic and inherited CNVs has important prognostic and disease management implications.

Patient 1 had a contiguous gene deletion (0.761 Mb) of 20q13.3 involving two important epilepsy genes *KCNQ2* and *CHRNA4*. While this deletion may result in benign familial neonatal seizures[3] it is important to be aware that children harbouring larger deletions (520 kb–6.8 Mb) may have more deleterious developmental phenotypes as seen in Patient 1 in this study. The deletion size and genes contained within the deletion are of clinical and prognostic relevance in contiguous gene deletion disorders.[4]

15q13.3 deletion is also associated with developmental delay and epilepsy.[5,6] Patient 2 had infantile spasms, the second patient reported in the literature with this phenotype. Remarkably both children had similar treatment responses and favourable developmental outcome, and this presentation may represent a phenotype which responds well to treatment, although further reports are necessary to support such findings.[6,7] Within the affected chromosomal region of 15q13.3 deletion, *CHRNA7* encoding a cholinergic receptor, is the primary candidate epilepsy gene.[5]

Deletions of 16p13.11 have been associated with genetic generalised epilepsy (GGE/formerly 'idiopathic generalised epilepsy') often with intellectual or psychiatric disturbance. Interestingly, the mother of Patient 3 carries the 16p13.11 deletion and had a convulsion at 9 months and onset of GGE at age 10 years, without intellectual or psychiatric disorder. There are three reported children with early onset epileptic encephalopathy (two had infantile spasms) with 16p13.11 deletion confirming infantile spasms as a sub-phenotype associated with this deletion.[8,9] In Patient 3 the deletion is inherited, there are no dysmorphic features and seizure-developmental outcomes at 16 months were favourable.

While certain CNVs are either directly pathogenic or confer risk for different neuro-cognitive, developmental and epilepsy phenotypes at both the population and individual levels, CNVs of uncertain significance were also detected in this study (Table 2). For these, the literature was also reviewed, in addition to a comparison of their chromosomal location and phenotypes to those present in the Decipher database (http://decipher.sanger.ac.uk - Sept 2014). The pathogenicity of 16p13.11 duplication (Patient 4), in contrast to 16p13.11 deletion has been debated, despite growing reports of its occurrence in association with various neurodevelopmental phenotypes including epilepsy.[8,10] Of those children reported