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Case Study

Infantile spasms and 15q11.2q13.1 chromosome duplication in two successive generations☆

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ABSTRACT

Familial cases of West syndrome have been reported only in Japan. In that study no chromosomal analyses were made. It has been suggested that microarray analysis should be included in the diagnostic evaluation of patients with infantile spasms and developmental delay, when an evaluation for structural brain lesions and metabolic disorders reveal no abnormal findings.

We report here the first case of infantile spasms and 15q11.2q13.1 chromosome duplication in two successive generations. The daughter and mother with infantile spasms, and the autistic son had the duplication. The clinical course of infantile spasms was very similar in the mother and daughter. The spasms were primarily considered to be of unknown aetiology.

Chromosomal microarray analysis revealed a 6.2 Mb size 15q11.2q13.1 duplication.

The duplication belongs to the 15q11q13 duplication syndrome (OMIM 608636) which when maternally derived is characterised by neuro-behavioural disorders like autism, hypotonia, cognitive deficit, language delay and epilepsy.

The proportion of patients with unknown aetiology for infantile spasms will decrease when more careful chromosomal studies are made. Our report expands the phenotype of chromosome 15q duplication syndrome and is the first report of this abnormality in two successive generations of infantile spasms.

☆ This work described is consistent with the Journal's guidelines for ethical publication.

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1. Introduction

The development of genetic technologies has led to the identification of many copy number variations (CNVs) in the human genome. The number of genes and genetic regions associated with infantile spasms are rapidly increasing (ARX, CDKL5, FOXG, GRIN1, GRIN 2A, MAGI, MEF2C, SLC25A22, SPTANI, STXBP1 and 15q11q13).[1] Tuberous sclerosis is the most common genetic disease in infantile spasms. The phenotypic expression of 15q11-13 duplication has expanded recently.[2]

We report here a family in which members of two successive generations - a mother and daughter-had infantile spasms and were found to have a chromosomal duplication in the long arm of chromosome 15 as well as high-lighting the importance of chromosomal analysis in cases of infantile spasms with no identified aetiology. Our cases suggest that the phenotypic spectrum of 15q11q13 duplication syndrome may be wider than previously considered and may include infantile spasms.

2. Case study

We report here a family with infantile spasms and 15q11.2q13.1 chromosome duplication in two successive generations. There was no previous family history of mental retardation, epilepsy or psychiatric problems like schizophrenia. There is no consanguinity in the family.

2.1. Proband

The girl was born at 40 + 5 weeks' gestation after a normal pregnancy and delivery. The birth weight was 3882 g, height 53 cm and head circumference 35 cm. The Apgar scored 8 at 5 min. The child was the second birth of the 30 years old mother. The father was 35 years old. The mother had taken valproate (1500 mg/day and folic acid substitution) for her epilepsy during pregnancy. Early development was normal except of slight delay in early motor milestones.

At the age of 8 months she was referred to the paediatric neurology clinic of Central Hospital of Kymenlaakso, Finland, for repetitive movements. The diagnosis of infantile spasms was promptly made at the admission. EEG showed typical hypsarrhythmic pattern. At the time of referral, she had flexor spasms and was slightly hypotonic. The head circumference, height, and weight were at 50 percentile. A physical examination was rather unspecific.

Careful aetiological investigations were made: MRI of the brain, determination of urine organic acids, blood glucose, lactate, thyroid function, cytomegalic and toxoplasma antibodies, analysis of cerebrospinal fluid including leucocytes, protein and glucose, and karyotype testing. All the results were normal. Tuberous sclerosis was first suspected because she had three hypomelanotic macules in the lumbar region. The kidney and heart ultrasound were also normal. Fundi of the eyes did not show any hamartomas, signs of congenital infections, or features of metabolic disease. Diagnosis of infantile spasms of unknown aetiology was made.[3]

Vigabatrin (up to 150 mg/kg/d) was started and given for five weeks without any response but ACTH (synthethic derivate) 0.5 mg had a rapid response. ACTH was given for 10 days and thereafter prednisolone 30 mg/d/5 days, 20 mg/5 days, 10 mg 5 days with a total dose of 300 mg. After that she started valproate medication.

At last visit at age of 17 months she maintained good eye contact. She had developmental delay. She was interested in toys and immediately put them in her mouth. She did not yet demonstrate any pincer grip. She did crawl and stood up with support. Muscle tone was low. The facial features of the baby and her mother were normal.

2.2. Mother

The mother was born after 41 + 6 weeks' gestation. Birth weight was 3260 g, height 50 cm, head circumference 34 cm. She scored 9 Apgar at 5 min. Early development was normal.

She had infantile spasms at the age of 9 months and typical hypsarrhythmia. She had a normal MRI. The etiological studies included careful clinical studies including eye fundi examinations, and laboratory studies: blood cell counts, vacuolated lymphocytes, urine metabolic screening. The CSF was studied for cell counts, glucose, protein, and immunoglobulin G (IgG) index. All were normal and she was thought to have infantile spasms of unknown aetiology. The response to ACTH was immediate.

Other than infantile spasms she was otherwise healthy and had no seizures until the age of 19 years when she developed partial and generalized seizures. Carbamazepine was started but it was not effective but valproate was effective. She used valproate during the both pregnancies.

In school she had learning difficulties and was given a special education.

The clinical course of the girl and mother with infantile spasms were very similar.

2.3. The older male sibling of the proband

During pregnancy mother had taken valproate 900 mg/day. He was born at 40 + 1weeks'gestation with normal delivery. The birth weight was 3830 g, height 52 cm and head circumference 34 cm. He scored 9 Apgar at 5 min. He was referred to the paediatric neurology clinic of Central Hospital of Kymenlaakso because of developmental delay at the age of two years. He had some facial features which might be interpreted for valproate toxicity in *utero*: epicanthic folds and a low-lying nasal bridge. He started walk at the age of 20 months. He used some words at the age of two years. Now at age of five years he has a diagnosis of autism and learning disabilities.

Microarray analysis using HumanCytoSNP-12(v2.1)chip (Illumina) revealed the 6.2 Mb size 15q11.2q13.1 duplication in Prader–Willi/Angelman syndrome region, (arr 15q11.2q13.1(22,754,322–28,941,318)×3, Hg19) (Fig. 1) in the daughter, mother and autistic brother. The father did not have any chromosomal abnormality.