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Early Diagnosis of the Chromosomal Deletion 5q14.2-q21.3 in a Preterm Newborn: Case Report

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ABSTRACT The researchers report a case of a premature baby diagnosed early in the postnatal period with an exceptionally long chromosomal deletion 5q14.2-q21.3 associated with dysmorphic features, epilepsy, cerebellar hypoplasia, psychomotor retardation, ventricular septal defect and a horseshoe kidney. According to clinical signs a standard cytogenetic examination on peripheral blood was performed and revealed an interstitial deletion of chromosome 5. A single nucleotide polymorphism array (SNP) analysis subsequently confirmed the 22.3 Mb long deletion of the long arm of chromosome 5. Within the deleted region 59 RefSeq genes were identified. Thirteen of these were expressed in specialized brain regions during fetal or adult stages of brain development. Among these the *MEF2C* gene seems to be the most limiting in relation to the normal development of brain and muscle. Only a few cases with this deletion have been reported in the literature to date. All cases manifested with severe mental retardation. Epilepsy and dysmorphic features in a newborn should lead to further genetic examination. New molecular genetic techniques such as the SNP array provide a quick and accurate diagnostic tool.

CASE PRESENTATION

This premature baby girl was born by normal vaginal delivery at 32+6 weeks of gestation after a preterm premature rupture of membranes (PPROM). Antenatal corticosteroids had been administered. During the course of pregnancy the mother was observed for polyhydramnios and hypertension. This was a second child of healthy parents with a negative family history for congenital malformations. Their first child was healthy. Consanguinity was denied. Apgar scores were 6, 8 and 8.

After delivery the baby developed signs of RDS and required nasal CPAP with FiO2 0.21-0.25. The baby was CPAP dependent for the first 25 days of life while also requiring caffeine for apnoea. On X-ray there were mild changes in transparency typical for RDS. Echocardiography performed because of a heart murmur in the first week of life revealed a small ventricular septal defect (VSD).

Priming was commenced on day one, she tolerated feeds well. During the first 5 days of life partial parenteral nutrition was also administered. Hyperbilirubinaemia was treated with phototherapy. Infection markers were always negative and congenital infections were excluded.

As a result of persistent apnoeic episodes and desaturations, despite the adequate caffeine treatment, further investigations were performed, including blood tests, lumbar puncture, EEG and metabolic workup. Infection, meningitis and metabolic disorders were excluded. An EEG showed severe pathology with frequent epileptiform abnormalities and slow EEG background pattern. Based on this phenobarbitone treatment was commenced. Due to progressive worsening of the baby's neurological status with more frequent seizures and apnoeas topiramate was then added to the treatment.

On MRI diffuse hypoplasia of the cerebellum, wide subarachnoid spaces, a mild degree of cerebral hypoplasia and abnormal gyration were described (Fig 1).

Finally, standard cytogenetic examination from peripheral blood revealed an interstitial deletion of chromosome 5 described as

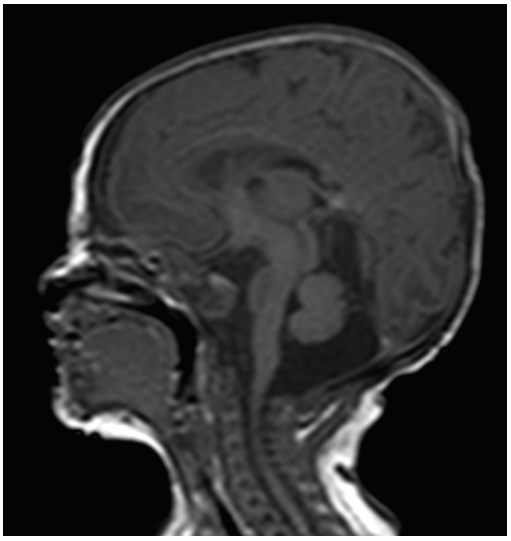

Fig. 1. MRI, T1/SE, sagittal plane-Cerebellar atrophy in our patient

46,XX,del(5)(q14.3;q22). SNP array analysis confirmed 22.3 Mb long interstitial deletion of the long arm of one chromosome 5 with precise localisation of the chromosome 5 breaks: arr5q14.2q21.3 (82,514,528-104,863,539)x1dn (Fig 2). Within the deleted region 59 RefSeq genes were identified. The deletion overlapped the chromosome 5 disease causing critical region known as the 5q14.3 deletion syndrome (OMIM613443).

Follow-up

At four weeks of age our patient was stable in terms of respiratory and cardiovascular system. However, despite the combined anticonvulsive therapy subtle seizures were present. General hypotonia and poor eye contact were noted. Her facial appearance was abnormal (Fig. 3) with nonspecific dysmorphic facial features. She tolerated feeding by nasogastric tube but did not suck. Therefore percutaneous endoscopic gastrostomy (PEG) was inserted to allow long term enteral nutrition in the home environment. EEG recordings remained grossly abnormal. A renal ultrasound uncovered a fusion anomaly of the kidneys - horseshoe kidney.

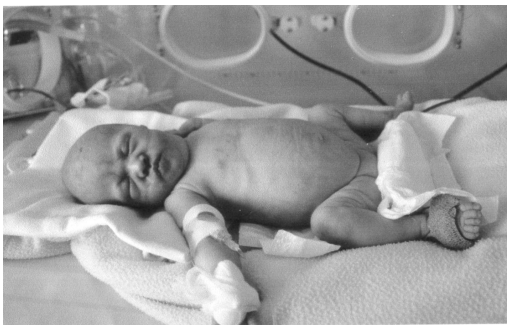

Fig. 3. Our patient at the age of 3 weeks. Dysmorphic facial features are present, a high and wide forehead, pronounced eyebrows, a wide nasal root and down-turned corners of the mouth, abnormal ears and a short neck

The baby was discharged home at the age of 2 months. She was hypotonic with subtle seizures such as yawning, increase in salivation, chewing, eye twitching, and facial grimacing. Medication on discharge from hospital was phenobarbitone and topiramate. She tolerated feeds by PEG and she was thriving.

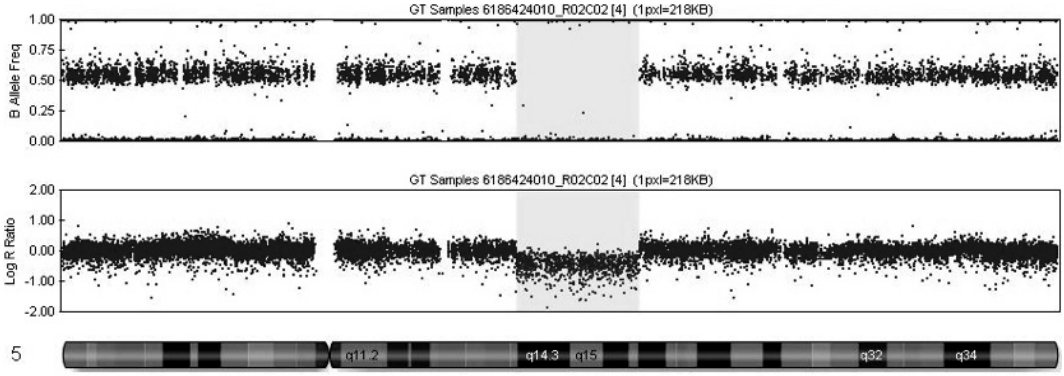

Fig. 2. SNP-array profile of chromosome 5 showing the 5q14.2-q21.3 deletion (highlighted red). The SNP genotypes are shown in the top panel (B allele frequency values AA=0/AB=0.5/BB=1), and the copy number in lower panel (LogR ratio of zero corresponds to a diploid copy number, decreased LogR ratio corresponds to a deletion)

At 7 months of age she was admitted to the paediatric intensive care unit of our hospital for acute bronchopneumonia with atelectasis. On admission she required immediate intubation and inotropic support. She required mechanical ventilation for 14 days. After successful antibiotic treatment she recovered and was discharged home after 30 days in hospital.

At 8 months of age the child was assessed by a consultant neurologist. At that time severe developmental delay was already apparent. She was hypotonic with hypertonic limbs, lying in a cot with little spontaneous muscle activity. She was not turning, sitting or crawling. She was able to suck and most of the time she fed from a bottle and PEG feeding was used only occasionally. Seizures were not observed however on EEG persistent epileptiform abnormalities were present repeatedly despite the treatment. Absent BAEP suggested hearing impairment.

Prognosis

Based on the current literature available the prognosis for this child is poor. Complications such as repeated aspirations and periods of decompensation of the baby's health status and epilepsy during infections might be expected. In terms of life expectancy the prognosis is uncertain.

DISCUSSION

In the patient researchers identified an interstitial deletion comprising 22.3 Mb which includes 59 annotated RefSeg genes (http://genome.ucsc.edu/). Among those the MEF2C gene appears to be the most limiting one for the normal development of the brain and muscle. Our patient presented with dysmorphic features, epilepsy, cerebellar hypoplasia, a ventricular septal defect and a horseshoe kidney.

There are around 50 cases of 5q interstitial deletion reported in the literature to date (Baekvad-Hansen et al. 2006; Malan et al. 2006; Tzschach et al. 2006; Cardoso et al. 2009; Sobreira et al. 2009; Bienvenu et al. 2013; Carvill et al. 2013). The clinical features of individuals with these deletions include severe mental retardation, congenital malformations, and nonspecific facial dysmorphisms (Cardoso et al. 2009).

The missing part of the long arm of chromosome 5 in our patient compared to other cases is exceptionally long, 22.3 Mb. The deletion sizes previously reported in the literature were variable with a maximum of 8.8 Mb (Le Meur et al. 2010). In our patient the missing portion of chromosome 5 is the longest described to date. This suggests that the prognosis and clinical outcome, especially psychomotor retardation, in our patient may be worse than in the other cases.

Cardoso et al. identified a critical region of approximately 5.8 Mb (88,833,718-94,826,030) corresponding to 14 annotated genes within this region, 13 of those are expressed in specialized brain regions during fetal or adult stages of brain development.

Recently, the detection of the 216kb deletion of the 5q14.3 removing only the MEF2C gene (myocyte enhancer factor 2C isoform 2) in patients with severe mental retardation, epilepsy, cerebral abnormalities and facial stigmatisation identified the MEF2C gene as the most likely responsible gene (Le Meur et al. 2010).

MEF2C belongs to the evolutionary ancient MEF2 gene family of transcription factors, which are broadly expressed during the development and maintenance of muscle cells. Other important functions are the regulation of the cardiac morphogenesis, right ventricular development, myogenesis, vascular development, development of megakaryocytes and platelets and the regulation of the nervous system during both development and injury repair. MEF2C gene product plays an essential role in hippocampal-dependent learning and memory, in normal neuronal development, distribution and electrical activity in the neocortex (Martin et al. 1993; Barbosa et al. 2008; Wu et al. 2011). The Mef2c-null mice showed neocortical disorganisation, neuronal immature electrophysiological network, abnormal behaviour, with anxiety and stereotype and decreased cognitive function (Li et al. 2008). These murine phenotypes provide convincing arguments for the implication of MEF2C haploinsufficiency as the cause of mental retardation, epilepsy and cerebral malformations (Li et al. 2008).

SNP Array

SNP array is a type of DNA microarray which is used to detect polymorphisms within a population. In comparing individual DNA sequences unique genetic differences between individuals are identified. 99.9% of one individual DNA se-

quence will be identical to that of another person. Of the 0.1% difference, over 80% will be single nucleotide polymorphisms (SNPs). An SNP is a single base substitution of one nucleotide with another, and both versions are observed in the general population at a frequency greater than 1%. Current estimates are that SNPs occur as frequently as every 100-300 bases. This implies in an entire human genome there are approximately 10 to 30 million potential SNPs. More than 4 million SNPs have been identified. SNPs are not inherited independently, rather sets of adjacent SNPs are present on alleles in a block pattern commonly known as a haplotype. Many haplotype blocks in humans have been transmitted through many generations without recombination. This means although a block may contain many SNPs, it takes a few SNPs to identify or tag each haplotype in the block. An SNP array can also be used to generate a virtual karyotype using software to determine the copy number of each SNP on the array and then align the SNPs in chromosomal order.

CONCLUSION

To conclude, The researchers reported a unique case of a rare genetic disorder - deletion 5q14.2-q21.3 which The researchers diagnosed in a preterm baby early in the neonatal period at the age of only 3 weeks. Our patient, had an exceptionally long deletion of part of chromosome 5 (22.3 Mb), and as a result manifested dysmorphic features, epilepsy, cerebellar hypoplasia, psychomotor retardation, a ventricular septal defect and a horseshoe kidney. Among all haplotypes insufficiency of MEF2C seems to be the most important factor responsible for these manifestations. Molecular genetic methods such as SNP play an important role in early diagnostics of such genetic disorders.

ABBREVIATIONS

PPROM preterm premature rupture of membranes, RDS respiratory distress syndrome, VSD ventricular septal defect, EEG electroencephalography, CPAP continuous positive airway pressure, NICU neonatal intensive care unit, Mb megabase, bp - base pairs, SNP a single nucleotide polymorphism, PEG percutaneous endoscopic gastrostomy, BAEP brain auditory evoked potentials

NOTE

Written informed parental consent was obtained for both print and online publication of this case and any accompanying images.

REFERENCES

Baekvad-Hansen M, Tumer Z, Delicado A, Erdogan F, Tommerup N, Larsen LA 2006. Delineation of a 2.2 Mb microdeletion at 5q35 associated with microcephaly and congenital heart disease. *American Journal of Medical Genetics Part A,* 140(5): 427-433.

Barbosa AC, Kim MS, Ertunc M, Adachi M, Nelson ED, McAnally J, Richardson JA, Kavalali ET, Monteggia LM, Bassel-Duby R et al. 2008. MEF2C, a transcription factor that facilitates learning and memory by negative regulation of synapse numbers and function. *Proceedings of the National Academy of Sciences of the United States of America,* 105(27): 9391-9396.

Bienvenu T, Diebold B, Chelly J, Isidor B 2013. Refining the phenotype associated with MEF2C point mutations. *Neurogenetics,* 14(1): 71-75.

Cardoso C, Boys A, Parrini E, Mignon-Ravix C, McMahon JM, Khantane S, Bertini E, Pallesi E, Missirian C, Zuffardi O et al. 2009. Periventricular heterotopia, mental retardation, and epilepsy associated with 5q14.3-q15 deletion. *Neurology,* 72(9): 784-792.

Carvill GL, Heavin SB, Yendle SC, McMahon JM, O'Roak BJ, Cook J, Khan A, Dorschner MO, Weaver M, Calvert S et al. 2013. Targeted resequencing in epileptic encephalopathies identifies de novo mutations in CHD2 and SYNGAP1. *Nature Genetics,* 45(7): 825-830.

Le Meur N, Holder-Espinasse M, Jaillard S, Goldenberg A, Joriot S, Amati-Bonneau P, Guichet A, Barth M, Charollais A, Journel H et al. 2010. MEF2C haploinsufficiency caused by either microdeletion of the 5q14.3 region or mutation is responsible for severe mental retardation with stereotypic movements, epilepsy and/or cerebral malformations. *Journal of Medical Genetics,* 47(1): 22-29.

Li H, Radford JC, Ragusa MJ, Shea KL, McKercher SR, Zaremba JD, Soussou W, Nie Z, Kang YJ, Nakanishi N et al. 2008. Transcription factor MEF2C influences neural stem/progenitor cell differentiation and maturation in vivo. *Proceedings of the National Academy of Sciences of the United States of America,* 105(27): 9397-9402.

Malan V, Martinovic J, Sanlaville D, Caillat S, Waill MC, Ganne ML, Tantau J, Attie-Bitach T, Vekemans M, Morichon-Delvallez N 2006. Molecular characterisation of a prenatally diagnosed 5q15q21.3 deletion and review of the literature. *Prenatal Diagnosis,* 26(3): 231-238.

Martin JF, Schwarz JJ, Olson EN 1993. Myocyte enhancer factor (MEF) 2C: A tissue-restricted member of the MEF-2 family of transcription factors. *Proceedings of the National Academy of Sciences of the United States of America,* 90(11): 5282-5286.

Sobreira N, Walsh MF, Batista D, Wang T 2009. Interstitial deletion 5q14.3-q21 associated with iris coloboma,

hearing loss, dental anomaly, moderate intellectual disability, and attention deficit and hyperactivity disorder. *American Journal of Medical Genetics Part A,* 149A(11): 2581-2583.

Tzschach A, Krause-Plonka I, Menzel C, Kalscheuer V, Toennies H, Scherthan H, Knoblauch A, Radke M, Ropers HH, Hoeltzenbein M 2006. Molecular cytogenetic analysis of a de novo interstitial deletion of 5q23.3q31.2 and its phenotypic consequences. *American Journal of Medical Genetics Part A,* 140(5): 496-502.

Wu W, de Folter S, Shen X, Zhang W, Tao S 2011. Vertebrate paralogous MEF2 genes: Origin, conservation, and evolution. *PloS one,* 6(3): e17334.