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Short communication

De novo trisomy 20p characterized by array comparative genomic hybridization: Report of a novel case and review of the literature

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ABSTRACT

We report on a boy with speech delay, mental retardation, motor clumsiness, hyperactivity, dysmorphic facial features, brachytelephalangy and short stature. Electrocardiogram, echocardiography, renal ultrasound, electroencephalogram, fundoscopic exam and auditory brainstem responses were all normal. Brain magnetic resonance imaging showed a left temporal arachnoid cyst and a small pineal gland cyst.
High resolution karyotype and FISH analysis detected a de novo duplication of the short arm of chromosome 20. A molecular characterization of the chromosomal anomaly was performed by array-CGH, confirming a 17.98 Mb duplication of the short arm of chromosome 20 associated with a small duplication on chromosome 3p, that was shown to be maternally inherited.
This is one of the few cases of de novo trisomy 20p with extensive workup, characterization at molecular level and close follow-up from the neonatal period to age 30 months. We also compared the phenotype of our patient with that previously reported in literature, therefore contributing to better define the trisomy 20p syndrome and helping pediatricians and geneticists to better counsel families about the developmental prognosis of these children.

1. Introduction

Approximately forty cases of trisomy for the short arm of chromosome 20 have been reported so far (Kearney et al., 2011; London et al., 2007; Miller et al., 2010; Van Norstrand et al., 2007). The vast majority of them involves only partial trisomy associated to partial monosomy of another chromosome and, to our knowledge, only two patients with apparently pure trisomy 20p have been described (Grammatico et al., 1992; Oppenheimer et al., 2000). This fact, along with the limited number of cases characterized at molecular level, accounts for the complexity in defining a trisomy 20p syndrome. We describe a new case of de novo trisomy 20p in a boy with speech delay, mild mental retardation, motor clumsiness, hyperactivity, dysmorphic facial features, brachytelephalangy and short stature, characterized at molecular level and therefore particularly helpful to better define the phenotype of a trisomy 20p syndrome.

1.1. Clinical report

Our patient was referred at age 15 months to our clinic for the evaluation of developmental delay. He was the first child of non-consanguineous parents. The father, aged 31, was healthy, whereas the mother, aged 28, suffered from generalized epilepsy. She was treated with lamotrigine also during pregnancy and she was free of seizures for more than four years. The patient was born via C-section at 36 weeks' gestation; birth weight was 3100 g (90th percentile), length was 48 cm (75th percentile) and head circumference was 34.3 cm (75th percentile), according to the Italian Neonatal Study (INeS) growth charts.

Abbreviations: FISH, fluorescence in situ hybridization; Array-CGH, array-comparative genomic hybridization; INeS, Italian Neonatal Study; ALTE, apparent life-threatening event; ABR, auditory brainstem responses; MRI, magnetic resonance imaging; UCSC, University of California Santa Cruz; OMIM, Online Mendelian Inheritance in Man; DECIPHER, DatabasE of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources; ISCA, International Standards for Cytogenomic Arrays Consortium; ECARUCA, European Cytogeneticists Association Register of Unbalanced Chromosome Aberrations; HEK, Human Embryonic Kidney 293 cells; NHEJ, Non-Homologous End-Joining; FoSTeS, Fork Stalling and Template Switching model; MMBIR, microhomology-mediated break-induced replication.

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Apgar scores were 4 at 1 min, 7 at 5 min and 9 at 10 min. At the age of one month he presented an apparent life-threatening event (ALTE). He was admitted to our department and an extensive workup, including a comprehensive metabolic panel, endocrine screening, electrocardiogram and electroencephalogram resulted negative. At that time the neurological examination was normal.

Developmental delay became evident at the age of 10 months, when he was still unable to sit without support, to crawl and showed poor vocalizations and relation in general. Physical examination at 15 months revealed normal growth, with weight at 50th percentile, length at 25th percentile and head circumference at 50th percentile, according to the Italian Society of Pediatric Endocrinology growth charts. A dysmorphological examination revealed the following craniofacial features (Fig. 1): round face with full cheeks, a narrow bifrontal diameter with wide forehead and high frontal airline, mild epicanthic folds and up-slanting palpebral fissures; mild ptosis with strabismus of the right eye, synophrys, arched and medial-thick eyebrows with long eyelashes; depressed nasal root, with broad nasal tip and anteverted nares; slight micrognathia and open mouth appearance with featureless philtrum and normal palate. Examination of the hands showed bilateral brachytelephalangy, confirmed by an X-ray.

Neurological examination revealed poor relation with the examiner, absence of speech and poor coordination in gross and fine motor skills. Electrocardiogram, echocardiography, renal ultrasound, electroencephalogram, fundoscopic exam and auditory brainstem responses (ABR) were all normal. A brain magnetic resonance imaging (MRI) showed a left temporal arachnoid cyst and a small pineal gland cyst. No other structural abnormalities were noted. During the stay he presented transient hyperphosphatasia, spontaneously resolved after one month.

At age 30 months cardio-pulmonary, genital and abdominal physical examinations were normal, whereas a short neck and mild kyphosis became evident; his height was between 3rd and 10th percentile, weight between 15th and 25th percentile and head circumference at 50th percentile. He started walking at 15 months. He had no history of seizures. Neurologic evaluation showed hyperactivity, good eye contact with fair interest in the environment and the examiner, fair gross motor development, poor fine motor skills and speech delay, with a vocabulary composed approximately of ten words and absence of sentences. A cognitive assessment was performed using Griffiths Mental Development Scale and revealed global developmental delay, with a global score of 25 (z score −2.3; <5th percentile). In particular, he scored below the 5th percentile in all sub-scales, except for sub-scale B (personal–social) where he scored 29.5 (z score −0.9; 16th percentile), and sub-scale F (practical reasoning), where he scored 21 (z score −0.8; 21st percentile).

2. Methods

2.1. Cytogenetic and molecular analyses

Chromosome preparations of the patient and his parents were performed from peripheral blood cultures using standard protocols.

Fluorescence in situ hybridization (FISH) analysis was performed with the whole chromosome painting probe of chromosome 20 (WCP20, Kreatech®, Amsterdam, The Netherlands) using standard protocols.

Genomic DNA of the patient and his parents was obtained from peripheral blood using the High Pure PCR Template Preparation Kit (Roche Diagnostics GmbH, Mannheim, Germany). Array-CGH analysis was carried out using a 44 K Agilent chip with a mean resolution of 75 kb (Agilent Technologies, Santa Clara, USA); the array was analyzed through an Agilent scanner (G2505C) and Feature Extraction software V.10.1.1.1. A graphical overview of the results was obtained using DNA Analytics software V.4.0.76. DNA sequence information refers to the public UCSC database [Human Genome Browser, February 2009, assembly hg19 (NCBI Build 37.1)]. Written informed consent was obtained from patient's parents.

2.2. Bioinformatic analysis

Breakpoint region sequences were analyzed using the UCSC Genome Browser and the Human Genome Segmental Duplication Database. We also employed the Pipmaker software to align the DNA sequences

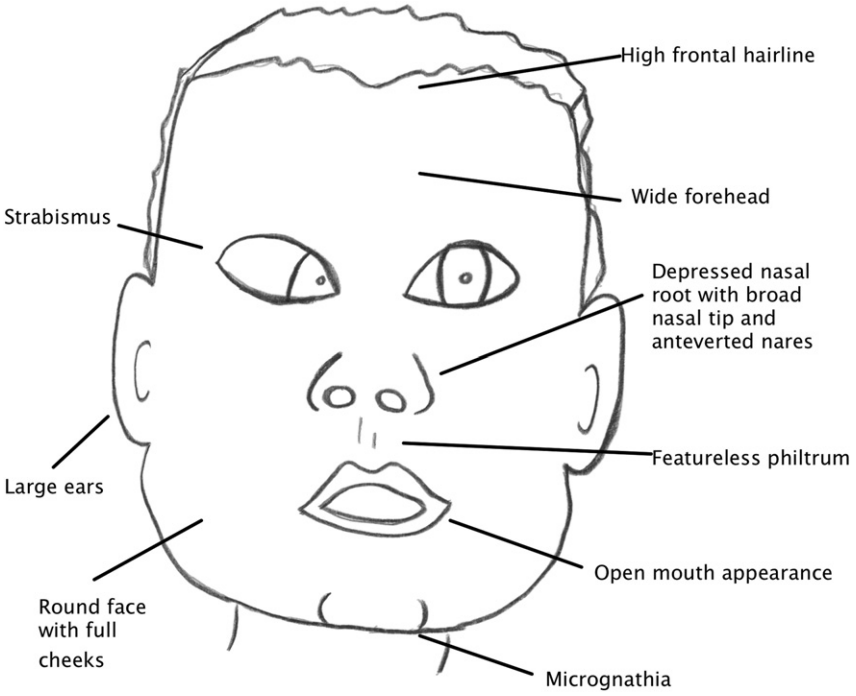

Fig. 1. Diagram of an idealized child representing the phenotypic abnormalities of our patient at age 15 months.