

Congenital Unilateral Facial Nerve Palsy Due to Chromosome 22q11 Microduplication (SMARCB1, SNRPD3)

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Abstract

The chromosome 22q11.2 region has long been implicated with genomic diseases, DiGeorge Syndrome being the most common deletion syndrome.

Chromosome 22q11.2 Deletion Syndrome (DS) is one of the most known human genetic deletion disorders with a frequency of 1 in every 4000 births and resulting in a diverse clinical picture.

The 22q11.2 duplication syndrome (DupS) has been recently characterized as a new entity with features overlapping the 22q11.2 DS. Microduplications 22q11 syndrome showing an extremely variable phenotype ranging from normal or mild learning disability to multiple congenital defects. This variability could be responsible for many undetected cases. We report on a patient with a microduplication at 22q11.2 including SMARCB1 and SNRPD3 genes, congenital unilateral facial nerve palsy and cardiac septal defect.

This child would need a long term multidisciplinary follow up, when you consider that the syndrome is now known to have a heterogeneous presentation that includes later-onset conditions such as behavioural phenotypes and psychiatric illness.

Keywords: *Congenital; Chromosome 22q11; Deletion Syndrome; Duplication Syndrome*

Case Presentation

A term male baby, born to non-consanguineous parents through normal vaginal delivery, with birth weight of 3.2 kg. Baby had normal Apgar score of 8/9. Fetal bradycardia, positive vaginal and rectal swab (SBG) in maternal history.

At the time of birth was discovered a lack of mobility of the labial commissure on the left side with asymmetric crying faces and deviation of angle of mouth to right side. It was associated with absence of blinking in the left eye. Baby had normal faces while sleeping or at rest.

There were no obvious malformations in the cleft lip or palate except left minimal ear dysmorphology.

There was no hemifacial microsomia or other cranial nerve paralysis.

During hospitalization, we observed brief episodes of cyanosis with apnea and bradycardia in spontaneous resolution and altered PCR. A course of an antibiotic therapy was administrated.

Baby was investigated with echocardiogram, electrocardiogram, EEG, brain and renal ultrasound, fundus examination, audiometric exam with TEOAE, neurological examination and genetic counseling.

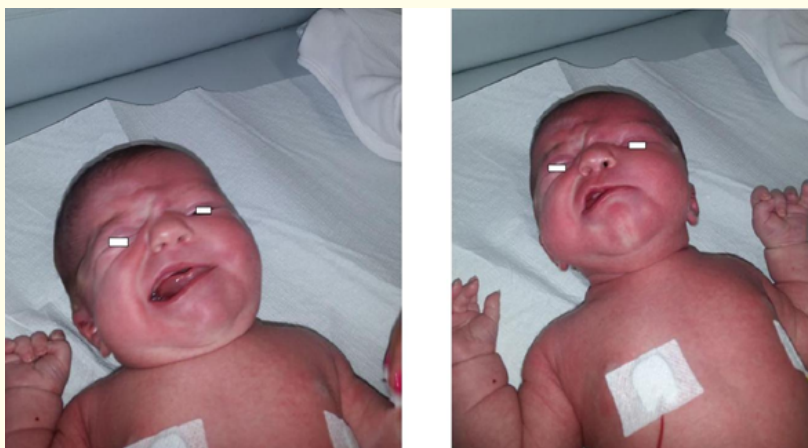
Echocardiography showed a DIA ostium secundum and a slight increase in speed in the aortic arch. The audiometric exam and EEG were normal.

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The initial diagnosis was congenital paralysis of the left facial nerve. Genetic investigations were extended to parents.

On the baby blood sample the PLPA analysis on 22q-region was performed and has shown the presence of heterozygous duplication of 22q11.2 region comprising SMARCB1 and SNRPD3 genes, inherited from the mother and was diagnosed with a chromosomal micro 22q11.2 duplication syndrome.

The infant was discharged in good general condition and is now on follow up.



Discussion

Facing an infant with facial asymmetry [32,37] while crying the diagnostic possibilities are numerous which range from unilateral congenital hypoplasia of the depressor muscle of the mouth (birth prevalence of 6.3/1000) to the so-called 22q11.2 deletion syndrome (DS) [1,4,6,19].

Chromosome 22q11.2 DS [33] is one of the most common human genetic deletion disorders with a frequency of 1 in every 4000 births, involves microdeletions (approximately 0.7–3 million base pairs in size), resulting in a heterogeneous clinical presentation [11,12,18,28,31], including facial dysmorphism, cardiac and palatal abnormalities, feeding difficulties, hypocalcemia, skeletal and renal anomalies, immunodeficiency [3,27], endocrine [26], genitourinary and gastrointestinal problems, developmental and speech delay, learning disabilities [20], cognitive deficits and neuropsychiatric illnesses [2,13,15,21], such as schizophrenia [14,15] (22q11.2 DS includes various diseases known in the past as diGeorge Syndrome, Conotruncal Anomaly Face Syndrome, Velocardiofacial syndrome, Cayler Syndrome, Opitz Syndrome, Takao Syndrome, Sedlackova Syndrome, third and fourth gill arch Syndrome, Shprintzen Syndrome, CATCH22 Syndrome ...).

Phenotypic expression is highly variable and ranges from severe life-threatening conditions to only a few less-severe associated features. Additional complexities include considerable interfamilial and intrafamilial variability [17].

There have been called into question modifier genes [29] present on the chromosome 22q or on other chromosomes.

More recently [23], duplication of the same chromosomal region has been associated with a distinct syndrome [24,25], but with several features overlapping with 22q11.2 deletion syndrome including velopharyngeal insufficiency, congenital cardiac anomalies, and also cognitive deficits [2,10], intellectual disabilities, behavioural problems [5], and psychiatric disorders like autism [8,38] and attention-deficit hyperactivity disorder.

There are far fewer reported cases of 22q11.2 Duplication Syndrome (22q11.2DupS), the reciprocal duplication syndrome involving the exact same set of genes [16], even of 22q11.2DupS [29] identification are clearly increasing due to the widespread use of microarray testing. Nevertheless, our current understanding of the 22q11.2DupS phenotype remains quite limited.

However, microduplication 22q11.2 [16] is primarily characterized by a highly variable clinical phenotype, which ranges from apparently normal or slightly dysmorphic features (with or without learning disorders) to severe malformations with profound mental retardation.

In a study the authors [22] discuss the complexity of genetic counseling for microduplication 22q11.2 and comment on possible explanations for the clinical heterogeneity of this syndrome.

In another work [25] the authors investigated a group of 295 patients with clinical features of DiGeorge/Velocardiofacial syndrome and valuated microdeletion and microduplication 22q11.2 screening and they did not identify 22q11.2 microduplication, suggesting that this is a rare event in patients with DG/VCFS features. This information probably stresses the importance of reports like this.

Individuals with 22q11.2DS have elevated rates of medical problems and birth defects that necessitate extensive medical screening and of community diagnoses of autism spectrum disorder (ASD) [36].

Prospective studies [13] of large cohorts of individuals with 22q11.2DS suggest that about 30 % of individuals with 22q11.2DS have attention-deficit/hyperactivity disorder [34] and roughly 25 % develop psychosis. There are also reports of an increase in features of ASD in this population, with estimated rates of ASD diagnoses in clinically ascertained samples ranging from 10– 40% [35].

Some children with 22q11.2DS exhibit deficits in social-emotional reciprocity, nonverbal communication and developing relationships [34]. 22q11.2 duplication has been found in absence epilepsies [7].

In another report [28] the patient with a 1.2-Mb microduplication at 22q11.2 spanning LCR22-F and LCR22-H which harbor the SMARCB1 and SNRPD3 genes presented healed cleft lip, mild facial dysmorphism, cognitive deficit, and delayed language development associated with severe behavioral problems including learning difficulties and aggressive behavior.

Some authors [9,30] have described the ocular features of the chromosome 22q11.2 DupS and have recommended that children with 22q11.2 DupS have a complete ophthalmological examination on diagnosis and regular vision screenings by their primary care physician thereafter.

In conclusion, this report gives further confirmation of the complexity and the incomplete knowledge of the pathology that concerns the 22q11.2 region both as deletion and as duplication. To this is added the remarkable expressive variability of syndromes related to this chromosomal region.

There is therefore the need for diagnostic testing in all newborns with asymmetric crying faces with deviation of angle of mouth to left or right side at the time of birth with genetic testing. This should be extended to parents to identify a parental derivation, however, much less common than the de novo forms. It also needs to be planned a multidisciplinary follow-up [32,37,38,39] for these infants lasted for many years.

Moreover, this case illustrates the importance of reporting unusual 22q11.2 duplications to further evaluate the incidence of these rearrangements in the general population and to improve genotype-phenotype correlations and genetic counseling.

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