Infant developmental profile of Crisponi syndrome due to compound heterozygosity for *CRLF1* deletion

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List of key features

Cold-induced sweating syndrome 1
Camptodactyly
Thin corpus callosum
Hyperekplexia
Feeding difficulties
Periodic fever

Summary

A 37-week gestation infant with fetal growth restriction weighing 2400 g (8th centile) who was the first-born child to nonconsanguineous Sicilian parents was referred to our institution on 23rd day of life for feeding difficulties, vomiting, and apnea requiring noninvasive ventilation and oxygen supply.

On physical examination, he showed a distinctive facial appearance (Fig. 1), right head tilting caused by left sternocleidomastoid muscle hematoma, bilateral camptodactyly of III and IV fingers (Fig. 2a and b), talipes calcaneovalgus, mild central-type hypotonia and decreased spontaneous motricity. Gavage feeding was required for absent sucking, swallowing, and neck muscle contracture after minimal orofacial stimuli. His father had suffered from mild feeding problems during infancy and now continues to have paradoxical sweating.

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At 2 months of age, he showed intermittent hyperthermia and brain MRI showed a thin corpus callosum (Fig. 3). One month later, a sleep EEG showed normal spindles maturation; a gastrostomy was performed for persisting feeding difficulties. At 5 months old, he was discharged with intermittent hyperthermia, improved muscular tone and resolution of trismus. Nevertheless, he showed developmental delay involving fine motor skills and balance reactions. At 11 months, the gastrostomy was removed. At 12 months, he weighed 9 kg (25th centile), was able to walk, had mild kyphoscoliosis and normal hearing. Improved manipulative skills were acquired after individualized physiotherapy (Fig. 2c–h).

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Investigations

We ruled out trisomy 18 by karyotyping, and mevalonic aciduria (MEVA) by molecular analysis of mevalonate kinase gene, and we hypothesized that he may have

Fig. 1

Frontal facial picture shows low-set ears, epicanthus, broad nose, anteverted nostrils, thin and pursed lips, long philtrum and micrognathia.

Fig. 2

(a and b) Bilateral camptodactyly of III and IV fingers. (c and d) Use of thumb and forefinger for grasping and holding the cube. (e and f) Single-pellet grasping using thumb and forefinger. (g and h) Manipulations and exploration of the object at 13 months.

Sohar-Crisponi syndrome/cold-induced sweating syndrome 1 (CISS1), (#272430). The array-CGH detected a paternal deletion of 44 kb in a chromosome 19 [19p13.11 (18,695,989_18,740,580)x1 in the GRCh37 coordinates], encompassing the cytokine receptor-like factor-1 (*CRLF1*, #604237), the brain-specific transmembrane protein 59-like (*TMEM59L*, #617096) and the chromosome 19 open reading frame 60 (*C19orf60*) genes. Direct sequencing of all nine exons and exon-intron boundaries of *CRLF1* gene in the patient and his parents identified a

Fig. 3

Midsagittal T2-weighted MRI of the brain shows a thin corpus callosum. Microretrognathia is an additional finding.

second maternally inherited microdeletion from intron 4 to the end of *CRLF1* [NM_004750.4: c.(697 + 167_?) del], and specific haplotypes of polymorphic variants.

Discussion

Crisponi syndrome/CISS1, is an autosomal recessive ciliary neurotrophic factor receptor (CNTFR)-related genodermatosis caused in 95% of cases by mutations in *CRLF1* on chromosome 19p13. The CNTFR pathway is important for CNS development. Crisponi syndrome/CISS1 can be suspected in the presence of the following clinical triad: camptodactyly with fistled hands, intermittent hyperthermia and muscular contractions with feeding difficulties. Considering the overlapping symptoms, differential diagnosis to be made are as follows: CNTFR-related genodermatoses affecting other receptor ligands (CLCF1, LIFR, and KLHL7), neonatal tetanus, Pierre Robin sequence, hereditary hyperekplexia, oculoauriculovertebral syndrome, Bowen-Conradi syndrome, Pena-Shokeir syndrome, Freeman-Sheldon/Sheldon-Hall syndromes, trisomy 18, and MEVA (Crisponi, 1996; Shires and Chow, 2015).

We first report Crisponi syndrome/CISS1 in an infant due to compound heterozygosity for two *CRLF1* deletion mutations: a maternal partial deletion encompassing exons 5–9 and a paternal 44 kb deletion involving also the neighboring genes *TMEM59L* and *C19orf60*. Although these two other genes have been implicated in normal neurodevelopment (Zheng *et al.*, 2017), haploinsufficiency has not so far been reported to result in specific phenotypes.

The relation of father's symptoms (mild feeding problems during childhood, sweating problems in adulthood) to the deletion is unclear since carrier signs are not known for *CRLF1* variations (Piras *et al.*, 2014). Another Sicilian boy with a similar clinical phenotype has been described (Di Leo *et al.*, 2010). He was a compound heterozygote for a smaller deletion mutation of 20kb encompassing exons 6–9 of the *CRLF1* and *C19orf60* and the missense point mutation c.935G>A.

So far, large deletions account for about 11% of total variations and usually occurred in a homozygous condition or in compound heterozygosity with missense mutations (Piras *et al.*, 2014).

Whilst deletions of a similar size have not been reported previously, the possibility still remains that this may be a further founder mutation in the Sicilian population.

Small subcortical white matter lesions on MRI were reported in patients with c.31_53del23 and c.413C>T mutations (Yamazaki *et al.*, 2010; Tüysüz *et al.*, 2013). Thin corpus callosum (Okur *et al.*, 2008), psychomotor delay (Piras *et al.*, 2014) as well as neurosensorial impairment (Alesi *et al.*, 2019) were reported. In our patient, normal polysomnography confirmed a relative sparing of brainstem functions, though the presence of stimulus provoked paroxysmal muscular contractures and autonomic dysfunction with hyperthermia suggest brainstem involvement (Della Marca *et al.*, 2008).

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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