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Broadening of the phenotypic spectrum of Coats Plus Syndrome: a patient presenting with extreme short stature as a hallmark feature

Background and Aims

Coats plus syndrome (OMIM # 612199) is a highly pleiotropic disorder particularly affecting brain, eye, bone and gastrointestinal tract[1,2,3], caused by mutations in the CTC1 gene. We describe the phenotype of a patient with severe growth failure where whole exome sequencing (WES) revealed compound heterozygosity for two mutations in the CTC1 gene.

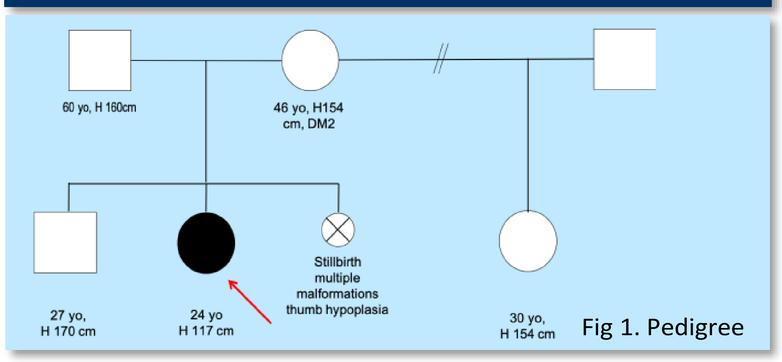

Fig 1. Pedigree

Patient

Medical history: Second child of healthy non-consanguineous parents with normal stature (**Fig 1**). Born SGA (length -5.0 SDS, weight -2.7 SDS) with thumb and feet malformations. Brother and half-sister healthy; a malformed sib died in utero.

Follow-up: Poor postnatal growth, severe deafness (narrow external auditory canal), multiple fractures, IQ 65, no secondary sex characteristics, primary amenorrhoea .

Examination at 23 yrs (Fig 2): Height 117.7 cm (-7.0 SDS) (**Fig 3**), BMI -2.3 SDS, upper/lower segment ratio 1.2, head circumference -2.0 SDS, Tanner breast and pubic hair stage 1, progeroid appearance, thin skin and hair, right thumb agenesis, left thumb hypoplasia, arthrogryposis, feet malformations (**Fig 4**).

Maxillo-facial status: microdontia/oligodontia, widespread root teeth dwarfism, agenesis of multiple permanent teeth, high palate.

Laboratory: hypergonadotropic hypogonadism (FSH 118, LH 49 IU/L, oestradiol <1 pg/ml); IGF-I 193 ng/ml (ref 133-366); stimulated GH-peak 22.5 ng/ml). Anaemia (11.2 g/dl). Triglycerides, total cholesterol, HDL-cholesterol elevated.

Radiology: osteopenia, bilateral radiohumeral luxofractures; agenesis of right thumb-metacarpal-scaphoid and hypoplasia of left thumb-metacarpal (**Fig 5**); feet malformations and fractures (**Fig 6**); Lumbar spine BMD T-score -1.8 SDS and Total hip BMD T-score -2.4 SDS; large bilateral calcifications in basal ganglia on skull X-Ray (**Fig 7**) and brain CT scan (**Fig 8**).

Sonography: bicuspid aortic valve; uterine size of 34x10x13 cm (no endometrial lining); left ovary 17x9x13 mm (right ovary not visualized).

ENT investigation: bilateral stenosis of the external auditory canal, left cholesteatoma (**Fig 9**).

Ophthalmological investigation: normal.

Treatment: Oestrogen, vitamin D. BMD normalized, and serum LH and FSH decreased on oestrogen treatment.


Fig 2. Patient (23 yr) and her mother

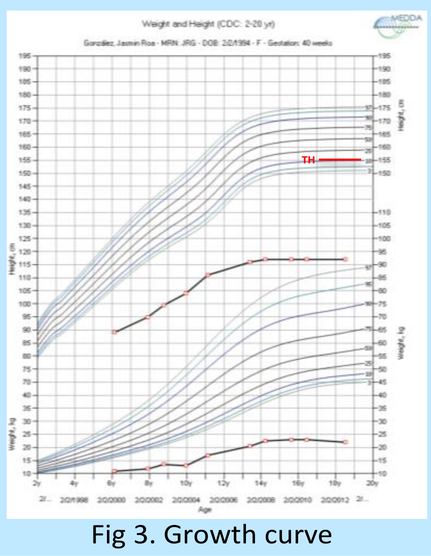

Fig 3. Growth curve

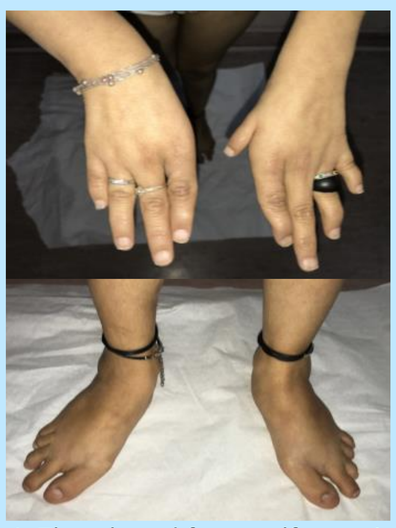
Fig 4. Thumb and feet malformations

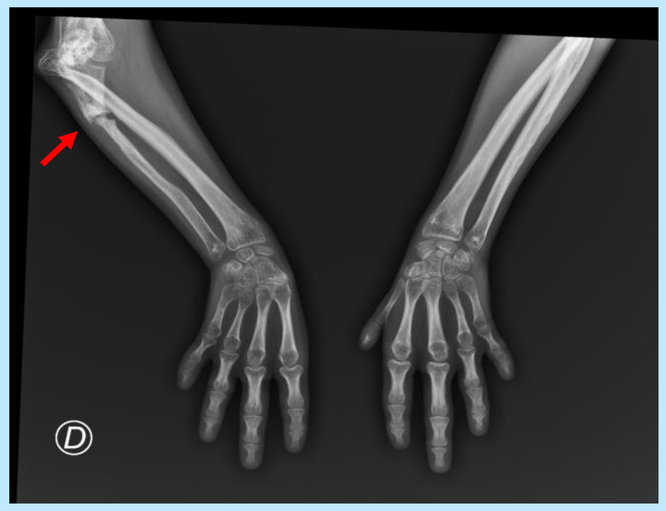

Fig 5. X-rays of the hands

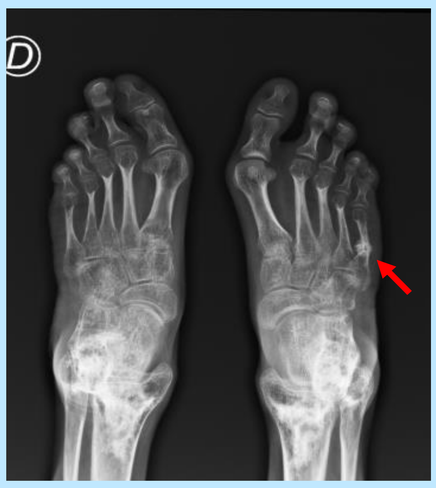

Fig 6. X-rays of the feet

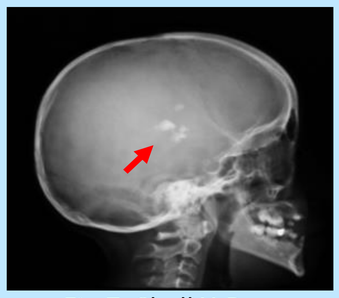
Fig 7. Skull X-Ray Intracranial calcifications

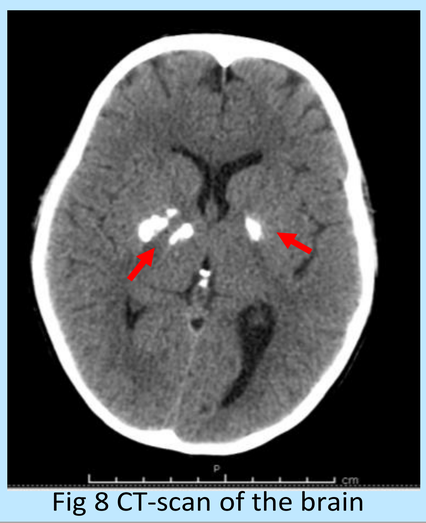
Fig 8 CT-scan of the brain

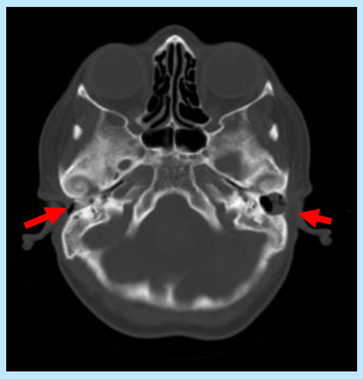
Fig 9 CT-scan: asymmetry of the external auditory canals, left cholesteatoma

Conclusions

Multiple characteristics (SGA, progeroid appearance, cerebral calcifications of the basal ganglia, osteopenia, bone anomalies, fractures, growth failure, anaemia, sparse hair) are consistent with Coats Plus Syndrome, but this patient is the first to present with extreme short stature, complete hypergonadotropic hypogonadism and thumb anomalies. Retinal and gastrointestinal features are absent. These observations confirm the large phenotypic variability of the syndrome and also illustrates the importance of performing WES in the diagnosis of children with extreme short stature.

Results

Sequencing data of WES of patient and parents were analysed with a stringent post-sequencing annotation pipeline including *de novo*, X-linked recessive and recessive modes of inheritance filters.

The recessive inheritance filter revealed a paternally (c.1617+5G>T) and maternally (c.724_727del, p.(Lys242Leufs*41)) inherited pathogenic variant in the CTC1 gene (NM_025099.5).

Mutations in this gene are known to cause Cerebroretinal Microangiopathy with Calcifications and Cysts 1 (CRMCC1; Coats plus syndrome; OMIM #612199).

The c.724_727del p.Lys242Leufs*41 variant has been described in various patients[2]. The c.1617+5G>T variant has not been reported. Splice Predict software predicts the loss of the splice donor site which probably results in an in-frame skip of exon 10 (**fig 10**).

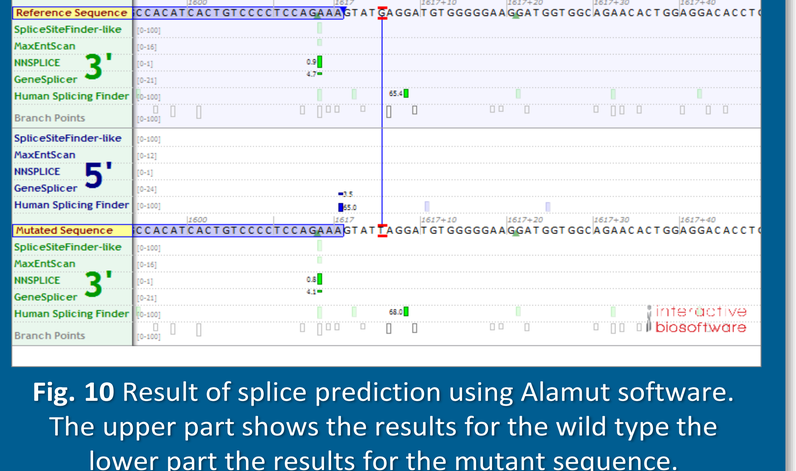

Fig. 10 Result of splice prediction using Alamut software. The upper part shows the results for the wild type the lower part the results for the mutant sequence.

References

1. Tolmie JL et al. A familial syndrome with Coats' reaction retinal angiomas, hair and nail defects and intracranial calcification. Eye 1988; 2: 297-303.
2. Anderson BH et al. Mutations in CTC1, encoding conserved telomere maintenance component 1, cause Coats plus. Nature Genet 2012; 44: 338-343.
3. Sargolzaeiaval, F et al. CTC1 mutations in a Brazilian family with progeroid features and recurrent bone fractures. Mol Genet Genomic Med 2018; 6: 1148–1156.

Acknowledgments

We thank the patient and her parents for their cooperation. The patient and her family authorized use of their pictures in this poster.

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