Severe craniosynostosis syndrome associated to salt wasting congenital adrenal hyperplasia

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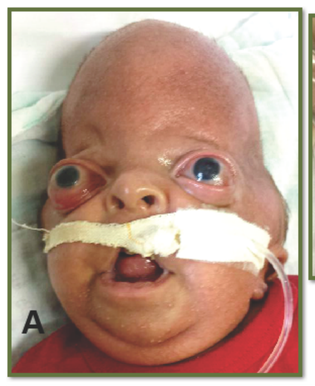
Background: Craniosynostosis, defined as the premature fusion of the cranial sutures, presents many challenges in etiology. One known form associated to steroid biosynthesis impairment is the Antley-Bixler Syndrome (ABS). ABS-phenotype with normal steroidogenesis have FGFR mutations, whereas those with ambiguous genitalia and altered steroidogenesis should be recognized as possibly having P450 oxidoreductase deficiency (PORD), a rare cause of congenital adrenal hyperplasia (CAH) with mild do moderate 17 OH progesterone (17HOP) elevation and basal normal cortisol levels.

CASE PRESENTATON

A term newborn, 46 XY, normal weight, male phenotype, with a severe craniosynostosis (turribrachycephalic skull shape), extreme ocular proptosis (unable to close eyelids) (Figures A, B), hand an feet malformation (Figures C, D) presented early respiratory insufficiency and needed mecanic ventilation. At 15 days of life, had clinical suspicion of adrenal insufficiency due to skin pigmentation and lowering of serum sodium. Hydrocortisone (HC) was iniciated and 3 days later also fludrocortisone, with further normalization of eletrolytes. Neonatal screening was collected after 1 dose of HC and 17 OHP levels were 733 ng/ml. Salt-wasting congenital adrenal hyperplasia (CAH) diagnosis was made. At 42 days of life, do to upper respiratory distress, was transferred to a tertiary complexity hospital. At the admission, signs of macrogenitossomia and cutaneous hyperpigmentation were seen (Figure E), with improvement after glucocorticoid adjustment (Figure F). No signs of radiohumeral or oder joint synostoses or skeletal fractures were clinical or radiological observed in this patient. Cranial CT and MR showed severe medium face hypoplasia, corpus callosum and septum pellucidum absence, posterior fossa with Arnold -Chiari type 1 and cloverleaf skull, suggesting Crouzon or Pfeiffer Syndrome aspects (Figures G to L). To avoid compressive complications of craniosynostosis, an early neurosurgical approach was performed (Figure M).



Figures A and B: craniosynostosis, turribrachycephaly and eyes proptosis

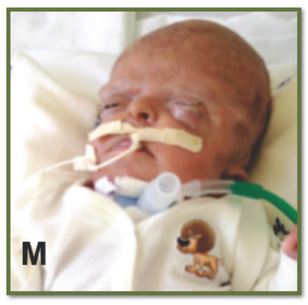
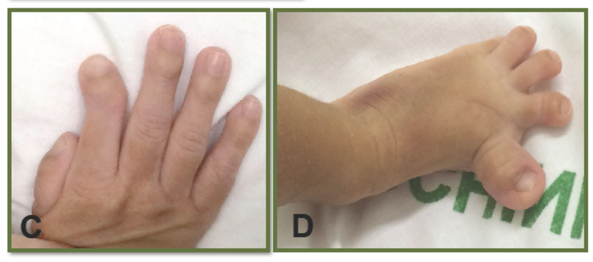


Figure M: after neurosurgical approach



Figures C and D: hand and foot malformation

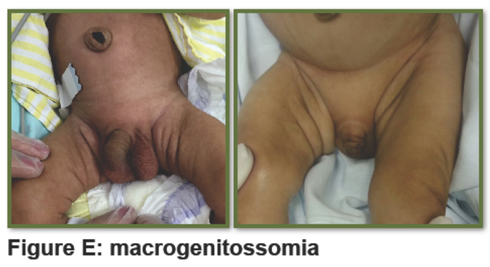
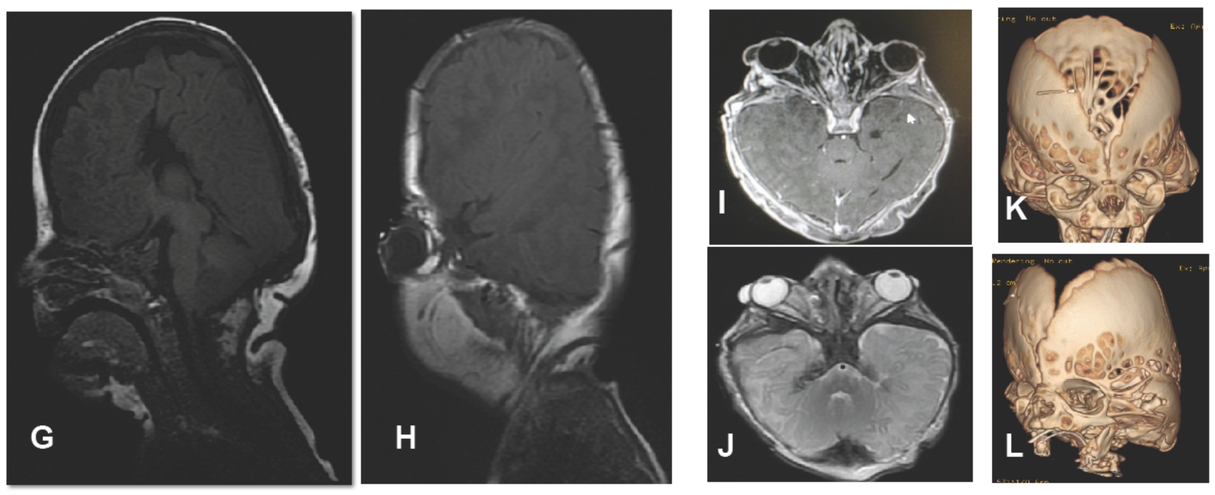


Figure E: macrogenitossomia

Figure F: genital appearence after GC adjustment



Figures G and H: turribrachycephalic skull shape

Figures I and J: brachycephalic shape and ocular proptosis

Figures K and L: early sutures closing and bone porosity

DISCUSSION

TABLE 1:Differential diagnosis of syndromes with craniosynostosis

Syndrome	FRGR MUTATIONS	THUMBS / TOES	HAND AND FEET	IMPAIRED STEROIDOGENESIS
CROUZON	YES	normal	normal	NO
PFEIFFER	YES	medial deviation	brachydactyly	NO
ANTLEY BIXLER	YES	arachnodactyly	arachnodactyly	NO
PORD/ANTLEY BIXLER	NO	arachnodactyly	arachnodactyly	YES

TABLE 2: Six domain scores associated to PORD malformations (MF)

DOMAIN/ SCORE	Midface hypoplasia	Craniosynostosis	Hand and Feet MF	Large joints synostosis	Femoral arching	Addicional MF
0	none	none	none	none	none	none
1	moderate (low implanted ears, pear shaped nose)	moderate	1	extension deficit	present	1 addicional MF
2	severe (structures compression, proptosis)	severe (2 or more sutures, turrincephaly)	2	fixed synostosis, contracture of a large joint	neonatal fractures	2 or more additional MF
3	complicated by stenosis or choanal atresia, tracheostomy	complicated by hydrocephalus, need for ventriculoperitoneal shunt	3 or more	various joints contracture	-	-

CONCLUSIONS

This patient has a severe syndrome with clinical aspects of FGFR mutations craniossynostosis (Table 1) and classical salt wasting CAH in a different clinical presentation than in ABS associated to PORD (Table 2) - the first possibility outlined, when features of craniosynostosis and adrenal steroidogenesis impairment are present.

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Adrenals and HPA Axis

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