

A case of patient with severe Rubinstein-Taybi Syndrome type 2 with complete deletion of *EP300* gene and complex phenotype.



Elisa Santoro¹, Romana Marini¹, Antonio Novelli², Viola Alesi², Maria Lisa Dentici³, Marco Cappa¹

¹Unit of Endocrinology and Diabetes ;²Laboratory of Medical Genetics; ³Unit of Medical Genetics; "Bambino Gesù" Children's Hospital, IRCCS, Rome, Italy

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Background:

The Rubinstein-Taybi syndrome (RSTS) is a rare genetic syndrome (frequency 1 in 100,000 - 125,000 live births) characterized by postnatal growth retardation, intellectual disability, microcephaly, peculiar facial features, broad thumbs and big toes and other organs malformations. There are two forms: RSTS type 1 characterized by *CREBBP* gene mutations (16p13.3); RSTS type 2 due to mutations/ deletions in *EP300* gene (22q13.2). The type 2 is associated with a mild phenotype with possible absence of the typical diagnostic signs as broad thumbs and big toes.

Clinical Case:

We describe a boy (V.B.G.) who was referred at the age of 4 years for growth retardation, dysphagia for liquids, constipation, psychomotor delay with absent language and seizures controlled with sodium valproate. At the physical exam he presented dysmorphic features with microcephaly, characteristic long face with long thick eyelashes, pointed chin, high palate, and furthermore broad toes, post-axial appendix of left hand, limbs dystonia and hypospadias.

He was born at 36 weeks of gestational age by caesarean section for IUGR. The patient birth weight was 1,540 Kg and Apgar 5-7. His parents were healthy and not consanguineous with unremarkable family history. Karyotype in amniocentesis: 46,XY.

Postnatal echocardiography showed hypoplastic aortic arc; PDA and coronary ventricular fistula. The congenital heart features were corrected by surgery.

The neonatal cerebral echography showed choroidal cysts, dysmorphic corpus callosum, rostrum hypoplasia, agenesis of right olfactory bulb, enlargement of cerebral ventricles and CSF spaces.

At the age of 3 years V.B.G. started to present psychomotor regression with the onset of focal seizures.

The boy underwent to MNR which showed: choroidal cysts, dysmorphia of corpus callosum, rostrum hypoplasia, agenesis of right olfactory bulb, enlargement of cerebral ventricles and CSF spaces. Because the short stature a Test with arginine + GHRH was performed and a normal GH secretion was confirmed. Peculiar phenotype resembling RSTS has been proposed.

The array-CGH (Agilent, 180K) showed a 1.72 Mb deletion at 22q13.2 arr[hg19] 22q13.2(41,256,957-42,982,676)x1, encompassing 54 known genes, including 6 OMIM Morbid genes (*XPNPEP3*, *EP300*, *ACO2*, *TNFRSF13C*, *NAGA*, *CYP2D6*).

Conclusion:

To date, 34 cases of RSTS associated with *EP300* impairment were known. Of these, only one had complete gene deletion (del22q13.2) of 376 Kb and exhibited mild phenotype. Our patient harbors a larger deletion, encompassing *EP300* and 53 other genes and presenting with a severe and complex phenotype sharing many features of RSTS. Further cases are needed for evaluating common phenotypes determining a 22q13.2 contiguous gene deletion syndrome.

Pictures:



Testo



References:

- Simenson K et al. 2014 A Patient With the Classical Features of Phelan-McDermid Syndrome and a High Immunoglobulin E Level Caused by a Cryptic Intersitial 0,72-Mb Deletion in the 22q13.2 Region. Am. J. Med. Genet. A 164A, 806-809

