Case Study

Rhombencephalosynapsis diagnosed in childhood: Clinical and MRI findings

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\textbf{ABSTRACT}

Rhombencephalosynapsis (RES) is a rare cerebellar malformation of unknown etiology characterized by vermal agenesis or hypogenesis, fusion of hemispheres and the dentate nuclei. Clinical presentation and prognosis are extremely variable and generally depends on the associated supratentorial anomalies. We report the first Tunisian case of RES diagnosed by magnetic resonance imaging (MRI) in a 3.5-year-old boy born to consanguineous parents. The child had spastic diplegia, facial dysmorphia, skeletal anomalies and normal intellectual development. Additional supratentorial anomalies were agenesis of septum pellucidum, moderate hydrocephalus and hypogenesis of corpus callosum. In this paper, the clinical and MRI findings and possible pathogenesis of this disorder are discussed.

\section{1. Introduction}

Rhombencephalosynapsis (RES) is a rare congenital malformation of the posterior fossa characterised by hypogenesis or agenesis of the vermis, dorsal fusion of the cerebellar hemispheres, fusion of dentate nuclei and superior cerebellar peduncles. The condition was firstly described by Obersteiner in 1914 from autopsy of a 28-year-old man who died by suicide. It was named RES by Gross and Hoff in 1959.\textsuperscript{1} The severity of clinical manifestations and prognosis of RES depends on the posterior fossa findings and supratentorial-associated anomalies. In this paper, we report a new case of RES diagnosed by MRI in a 3.5-year-old boy with spastic diplegia.

\section{2. Case report}

A 3.5-year-old boy was admitted for delay of acquirement of the walk. He was the fourth child of a consanguineous couple. He was born by normal delivery after uncontrolled pregnancy. There was no family history of congenital malformations or other notable medical problems. Weight was 11.5 kg (5th percentile), length 87 cm (<3rd percentile) and head circumference 49 cm (13th percentile). Examination at the time of admission revealed facial dysmorphia (low set ears and hypertelorism) and normal intellectual development (normal speech). Neurological examination revealed spastic diplegia, lower limb hyper-reflexia and bilateral sign of Babinski. The standing position and walking are not possible that with help.
General examination revealed scoliosis and genu valgum. Spinal radiography revealed segmentation anomalies of thoracic vertebra in T8 and T9 with mild scoliosis. Ophthalmologic examination showed clear corneas and normal fundi. Cranial magnetic resonance imaging (MRI) showed complete agenesis of the vermis with fusion of the cerebellar hemispheres, fusion of dentate nuclei and superior cerebellar peduncles, biventricular hydrocephalus, hypogenesis of corpus callosum and agenesis of septum pellucidum (Figs. 1 and 2). The pituitary gland and optic chiasm were normal. No other central nervous system (CNS) or extra-CNS anomaly was detected and chromosomal analysis revealed normal karyotype of 46, XY.

3. Discussion

We describe a new case of RES diagnosed by MRI in a living patient. It is only since 1991 with the advent of MRI, that the diagnosis of RES has been made during life. Prenatal diagnosis of this malformation by MRI is currently possible and has been made in some cases. To date, about 50 cases with RES have been described which approximately 36 cases diagnosed by MRI. Recently, partial RES was described in two pediatric patients presenting normal development of the anterior vermis and nodulus, but part of the posterior vermis.

Fig. 1 – Axial T2-flair images: (a) midline Fusion of cerebellar hemispheres, fusion of cerebellar peduncles and dentate nuclei. (b) Continuing of folia through entire width of cerebellum and abnormal shape of fourth ventricle.

Fig. 2 – Coronal T2-weighted images: (a) Abnormal transverse cerebellar folial orientation. (b) Fusion of the cerebellar hemispheres without intervening vermis. Note also the ventriculomegaly with absence of the septum pellucidum.
was deficient. These observations suggest that RES should be considered as a malformation with variable degree of severity.

Most reports are of pediatric patients, although there are some cases of adult subjects in the literature. Sener reported that the frequency of RES was 0.13% in a series of 3000 pediatric patients who underwent head MRI. Almost totality published cases have been sporadic. In our case, there was not familial history of malformation and chromosomal analysis was normal but parental consanguinity could suggest an autosomal recessive inheritance. However, consanguinity is a common constellation in our country. In two additional cases described in the literature, parents have also an ethnic background with common constellation of consanguinity. As no occurrence in sibs was ever observed, an autosomal recessive inheritance seems very unlikely.

Additional abnormalities reported in association with RES are variable. Hydrocephalus or ventriculomegaly, dysgenesis of the corpus callosum and absence of the septum pellucidum are the most commonly associated anomaly.8 Fused thalami, tectum and fornices, hypoplasia of the temporal lobes, olivary nuclei, anterior commissure and optic chiasma and agenesis of the posterior lobe of the pituitary can occasionally be seen. Extracranial anomalies are very rare and may involve musculoskeletal, urinary tract, cardiovascular and respiratory systems. In our case, there were supratentorial anomalies (agenesis of septum pellucidum, moderate hydrocephalus and hypogenesis of corpus callosum) with skeletal abnormalities (spinal segmentation anomalies with mild scoliosis and genu valgum) exceptionally described in association with RES. However, musculoskeletal system seems to be the commonest site of associated anomalies in cases with RES. Clinical presentation and prognosis are extremely variable and generally depends on the associated supratentorial anomalies. Therefore, no correlation between MRI findings and clinical manifestations can be established. RES may be isolated and diagnosed incidentally in adulthood.5,13 Symptoms of severely affected children include mental retardation, spasticity and epilepsy. Delayed cognitive and mental retardation were reported in the majority of the case reports.

Children with isolated RES may have normal cognitive and clinical manifestations can be established. RES may be isolated and diagnosed incidentally in adulthood.5,13 Symptoms of severely affected children include mental retardation, spasticity and epilepsy. Delayed cognitive and mental retardation were reported in the majority of the case reports. Children with isolated RES may have normal cognitive and language function, at least in early school age. Adults with RES and no intellectual disability have been reported.13,14 Therefore, in our case, we observed normal cognitive development, previously reported in some pediatric and adult patients and spastic diplegia which has been exceptionally described. However, a long term neurodevelopmental followup is necessary to establish intellectual capacity. Non-specific dysmorphic features such as low set ears, hypertelorism and high arched palate were reported by several authors. Involuntary lateral movements (head rolling) without or with only mild cognitive delay are reported by several recent papers.

Because of its high resolution and multiplanar imaging, MRI is the preferred investigational procedure in the evaluation of the cerebellar anomalies. Axial images demonstrate fusion of the cerebellar hemispheres, dentate nuclei and superior cerebellar peduncles. Coronal images show horizontal folial orientation without intervening vermis. RES results from a disturbed development of the cerebellum between 28 and 41 days of gestation. The commonly associated supratentorial abnormalities are consistent with this gestational period. However, the pathogenesis of this midline defective malformation remains unclear and causative factors are controversial. In the traditional view, RES was considered as an abnormal development of the vermis with subsequent fusion of the hemispheres. In the more recent view, Utsunomiya et al. suggested that fused cerebellar hemispheres may be explained by the fact that the cerebellar primordium is essentially unpaired and not a pair of unconnected bilateral structure and concluded that fusion of the cerebellar hemisphere is not secondary to a primary maldevelopment of the vermis, but rather result from a primary failure of vermian differentiation. These authors suggested that this cerebellar malformation is due to undivided hemispheres instead of fused hemispheres. However, the hypothesis of genetic defects remains an interesting research track. In one case, it was reported an anomaly affecting chromosome 2q. Also, experimental studies on the genetic control of early regional specification of brain structures have identified a critical organizing center for cerebellar development, the “isthmic organizer” located at the junction between the mesencephalon and metencephalon and defined by caudal and rostral limits of expression of the homeobox-containing genes Otx2 and Gx2, respectively. Sarnat suggested that RES is probably due to an underexpression of a dorsalizing organizer gene. A possible animal model is the Dreher Lmx1a gene mutant mouse which shows agenesis of the vermis with fusion of the cerebellar hemispheres and inferior colliculi due to dorsal patterning defects in the hindbrain, closely resembling human RES. Lmx1a gene mapping to 1q21–q23 regulate early developmental events at the pontomesencephalic junction. Molecular analysis may reveal a mutation in the Lmx1a gene unique to RES. Lmx1a was also shown to regulate formation of the roof plate and specification of dorsal cell fates in the spinal cord and developing vertebra. So, mutation in the Lmx1a gene could explain spinal abnormalities associated with RES. Further study may reveal other candidate defective genes in RES.

In conclusion, clinical presentation of RES is extremely variable and spastic diplegia may reveal this malformation in children. RES diagnosed in childhood are more often associated with supratentorial than extracranial anomalies. The cause of RES is unknown; however, hypothesis of genetic defects remains possible. Further study and speculation of candidate defective genes may shed light on the pathogenesis of this rare cerebellar malformation.

REFERENCES