Rhombencephalosynapsis: new findings in a larger study

Rhombencephalosynapsis is a developmental midline defect affecting the cerebellar vermis. The absence of the vermis in rhombencephalosynapsis may be compared to the other condition in which the vermis is largely absent. In Joubert syndrome, the cerebellar hemispheres are close to normal in volume; the intervening vermis is largely absent. In Joubert syndrome, the cerebellar vermis. The absence of the vermis in rhombencephalosynapsis is small and much shortened, leaving a gap between the cerebellar hemispheres. Although the vermis may also be totally absent in rhombencephalosynapsis, remnants such as the nodule may often be found in their normal place with respect to the adjoining hemispheres. Allowing a simplification, one can describe the vermis in Joubert syndrome as shortened and in rhombencephalosynapsis as narrowed.

The debut of the rhombencephalosynapsis story is credited to Obersteiner in 1916 with a detailed case report entitled ‘Ein Kleinhirn ohne Wurm’ (‘A cerebellum without vermis’) describing the autopsy findings in a 31-year old male. The original study is still worth reading for its wealth of detail such as absence of the mesencephalic trigeminal nucleus and misrouting of tracts at the lower mesencephalic level. Over 100 cases have since been published, mostly as case reports or small series. A review lists 58 published cases before 2005 (Barth, 2008). Hydrocephalus due to aqueductal stenosis is often present at birth. Other cerebral malformations typically affecting the midline may be found including aplasia of the septum pellucidum, fusion of the fornices and holoprosencephaly. Morphological studies reported by Pasquier et al. (2009) in 40 foetuses after medical termination of pregnancy showed fusion of colliculi, forking and/or atresia of the aqueduct, fusion of the thalami, callosal agenesis, lobar holoprosencephaly and neural tube defects as associated findings. Attention was drawn to the frequent occurrence of ‘Vertebral anomalies, Anal atresia, Cardiovascular anomalies, Trachea-oesophagus fistula, Renal anomalies, Limb defects’ (VACTERL) as associated findings. The cognitive outcome in patients with rhombencephalosynapsis may be normal; ataxia was the most frequent physical finding in a

References
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series of non-syndromic rhombencephalosynapsis (Poretti et al., 2009).

Two syndromes may be seen in association with rhombencephalosynapsis: Gómez–López-Hernández syndrome (MIM 601853) and VACTERL association (Pasquier et al., 2009; Ishak et al., 2012, see page 1370 of this issue). Especially the association with Gómez–López-Hernández syndrome, also known as cerebello-trigeminal-dermal-dysplasia, is relatively frequent. Typical symptoms are parietal skin alopecia, often accompanied by trigeminal anaesthesia, which may cause keratitis and masseter weakness. Brachyurriccephaly is often present, caused by craniosynostosis (Gómez, 1979; López-Hernández, 1982). The criteria have been recently evaluated by Sukhudyan et al. (2010). Trigeminal dysfunction is inconstant, and parietal alopecia together with rhombencephalosynapsis remain the core symptoms. No familial cases are on record. As a challenge to developmental neuroanatomists this syndrome appears to link the development of the embryonic trigeminal placodes to development of the cerebellum. Apart from the fact that the developing cerebellum and trigeminal placodes develop in close proximity an explanation is lacking. Gene associations with rhombencephalosynapsis or Gómez–López-Hernández syndrome have not yet been found. Recurrent cases, parental consanguinity and diverse chromosomal abnormalities point to a genetic origin as discussed by Ishak et al. (2012).

Multicentre studies on a rare disease may serve as a magnifying glass, confirming findings from smaller series. If so, the study by Ishak et al. (2012) is an exception in more than one regard. In a series of 42 cases studied by MRI, they observed a spectrum of severity with a gradient ranging between total absence of the vermis and retained parts of the anterior and posterior vermis including the nodulus. The retained anterior part of the vermis i.e. the part of the vermis rostral to the primary fissure in some partial cases has not previously been reported. The study confirms that ‘partial’ rhombencephalosynapsis is relatively frequent. Many of the patients have obstructive hydrocephalus due to aqueductal stenosis or atresia associated with a malformed tectum. This finding prompted the authors to review previous cases from their hospital records diagnosed as congenital hydrocephalus due to aqueductal stenosis, allowing a retrospective diagnosis of rhombencephalosynapsis in another five cases. The study also showed an association with other midline defects. A surprising finding was the absence of the olfactory bulbs in no less than 30% of the subjects, adding strength to the vision of rhombencephalosynapsis and holoprosencephaly as parts of a single spectrum. Also in this study a significant proportion of cases was found as part of Gómez–López-Hernández syndrome. For its size and detail this study may be expected to serve as a useful reference for clinicians, geneticists and neuroradiologists dealing with rhombencephalosynapsis.

Most studies regard rhombencephalosynapsis as whole or partial absence of the vermis with fusion or near-fusion of the hemispheres. Implicit in this view is a notion of the vermis and the hemispheres arising separately during ontogeny and being zipped together at a later stage. However, no such zipping takes place in reality. On the contrary, when the folial chains of a normal cerebellar cortex are followed across the midline there is continuity without break, only marked by a gentle depression between the hemispheres caused by the vermis. In the words of Voogd (2003): ‘the cortex is continuous between the successive segments (lobules) of the folial chains of vermis and hemispheres, with the exception of the cortex of the flocculus which is not continuous with the tonsilla’. Lack of differentiation and outgrowth in the developmental field near the midline may explain the morphology of rhombencephalosynapsis. Some of the patients in the series of Ishak et al. (2012) also show diminution in size of the hemispheres mainly in transverse direction, suggesting that the cerebellar hemispheres may become involved in this arrested development. No proper animal models are available yet to study the dynamics of rhombencephalosynapsis and the finding of associated gene(s) as a next step is keenly awaited.

References


