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Rhombencephalosynapsis: embryopathology and management strategies of associated neurosurgical conditions with a review of the literature

Clinical article

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Object. Rhombencephalosynapsis (RS) is a rare congenital posterior fossa malformation characterized by dorsal fusion of the cerebellar hemispheres, hypogenesis or agenesis of the vermis, and fusion of the dentate nuclei and superior cerebellar peduncles. The objective of this institutional study is to review the clinical conditions associated with RS and analyze the varied biological profile of this unique condition.

Methods. The study data were collected retrospectively from the medical records of patients at Rainbow Babies and Children's Hospital. After required institutional review board approval, the authors obtained information regarding the cases of RS reviewed by the Departments of Radiology, Genetics, and/or Pediatric Neurology. Medical charts were systematically reviewed, and 9 patients were analyzed in detail.

Results. The authors describe 6 cases of RS and 3 cases of partial RS. This case series demonstrates an association between RS and symptomatic hydrocephalus (7 of 9 patients) and RS and Chiari malformation (5 of 9 patients). Patients with symptomatic hydrocephalus underwent endoscopic third ventriculostomy or ventriculoperitoneal shunt insertion. One of the patients with an associated Chiari malformation underwent foramen magnum decompression.

Conclusions. The authors present a large case series of RS. Patients with RS often had hydrocephalus and/or a Chiari Type I or II hindbrain malformation. Neuroimaging findings of RS are presented along with hypotheses to explain the embryopathology of this unusual condition.
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Key Words • **rhombencephalosynapsis** • **embryology** • **hydrocephalus** • **posterior fossa malformation** • **congenital malformation**

Rhombencephalosynapsis is a rare congenital posterior fossa malformation characterized by dorsal fusion of the cerebellar hemispheres, hypo- or agenesis of the vermis, and fusion of the dentate nuclei and superior cerebellar peduncles. Rhombencephalosynapsis commonly presents with hydrocephalus resulting from concomitant brain abnormalities. A multitude of cranial and extracranial abnormalities have been found in conjunction with RS. Clinical presentation and prognosis are mainly dependent on associated anomalies, and isolated cases are often diagnosed as incidental findings. Isolated RS often presents as only slight ataxia. Rhombencephalosynapsis was first described by Obersteiner[15] in 1914 in a postmortem examination of a 28-year-old man who had committed suicide. The first RS case in a living patient was diagnosed by MRI in 1991.[27,34] The estimated frequency of RS is 0.13%; however, the increased use of MRI for screening has increased this frequency.[29] With the advent of MRI, more in vivo diagnoses were made between 1991 and 2003 than all postmortem examinations from 1914 to 1991.[11] Magnetic resonance imaging is recognized as the best diagnostic tool that can unequivocally

Abbreviations used in this paper: ETV = endoscopic third ventriculostomy; RS = rhombencephalosynapsis; VP = ventriculoperitoneal.

diagnose RS;[35] however, ultrasound diagnosis is generally suspected after 22 weeks of gestation.[18] The pathogenesis and etiology of RS remain largely unknown, but RS is embryologically thought to arise at Days 28–41 of gestation.

Methods

The study data were collected retrospectively from medical records of patients at University Hospitals Case Medical Center Rainbow Babies and Children's Hospital in Cleveland, Ohio. After obtaining required institutional review board approval, we obtained information regarding the cases of RS seen by Radiology, Genetics, and/or Pediatric Neurology at the hospital. Medical charts were systematically reviewed, and 9 patients were analyzed in detail with a data record sheet.

Results

A summary of the 9 patients included in this study can be found in Table 1.

Illustrative Cases

Case 1

This boy was prenatally diagnosed with myelodysplasia and hydrocephalus. The patient underwent closure of the lumbosacral myelomeningocele on Day 1 of life. On Day 5 of life, he had a right frontal VP shunt placed for hydrocephalus with a subsequent revision 7 months later. At 6 years of age, eye examination revealed a moderate amount of distant vision impairment and astigmatism. He remained symptom free for hydrocephalus at the time of follow-up. Cranial MRI showed abnormalities including cerebellotonsillar herniation to the upper C-4 level consistent with Chiari malformation Type II, flattened fourth ventricle, syrinx on the upper cervical core, tectal beaking, mild interdigitation of gyri along the interhemispheric falx, stenogyria, "towering cerebellum," left hypothalamus slightly smaller than right, and an intact corpus callosum (Fig. 1). The cerebellar hemispheres were not well defined, and the diagnosis of RS was considered.

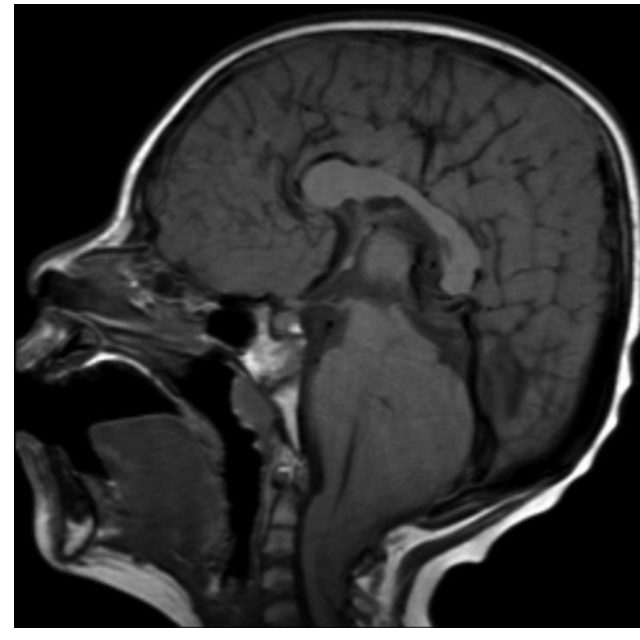

Fig. 1. Case 1. Sagittal T1-weighted image showing partial RS in the setting of Chiari malformation Type II. The cerebellar tonsils extend through the foramen magnum to approximately the C-4 level, and there is flattening and caudal displacement of the fourth ventricle. Additional findings associated with Chiari malformation Type II included tectal beaking and stenogyria.

Case 2

This 9-year-old boy presented with a history remarkable for mental retardation/cerebral palsy, complex partial seizures, congenital hydrocephalus, and Lesch-Nyhan self-mutilation syndrome. At 15 years the patient underwent right occipital VP shunt tap placement; revision was performed 1 year later. His hydrocephalus is currently controlled, but he still suffers from complications associated with his Lesch-Nyhan self-mutilation syndrome. His MRI abnormalities included corpus callosum dysgenesis with stenogyria of the fourth ventricle and brainstem, small fusion of cerebellar hemispheres, absent vermis and anomalous vertical orientation of straight sinus, prominent CSF collection from the lateral ventricles to the posterior fossa where it interfaces the superior aspect of cerebellum, and fused thalami and fused colliculi of the

TABLE 1: Summary of patients included in this study

Case No.	Sex	Diagnosis	Chiari Malformation Type	Hydrocephalus	VP Shunt Placement
1	male	RS	II	yes	yes
2	male	RS	no	yes	yes
3	male	RS	no	yes	yes*
4	male	RS	no	yes	yes
5	female	RS	I	no	no
6	male	partial RS	II	yes	yes
7	male	partial RS	II	yes	yes
8	female	partial RS	II	yes	yes
9	female	RS	no	no	no

* The shunt was placed 6 months after a failed ETV.

quadrigeminal plate (Fig. 2). The cerebellar malformation was found to be consistent with RS. This patient did not have a Chiari malformation.

Case 3

This 2-year-old boy presented with developmental delay and hydrocephalus. Surgical management included an ETV and strabismus surgery, both done in Puerto Rico at 2 years of age. The patient underwent VP shunt placement 6 months later. His hydrocephalus has remained asymptomatic since then. There was no Chiari malformation in this patient. The patient's MRI abnormalities included bowing of the corpus callosum and bowing of the third ventricle floor, mild elevation of quadrigeminal plate with widening of the proximal aqueduct (likely from stenosis or webbing in the aqueduct), moderate hydrocephalus involving lateral and third ventricles, and fusion of cerebellar hemispheres consistent with RS (Fig. 3).

Case 4

This Amish boy presented at birth with hydrocephalus. The patient's hydrocephalus required VP shunt placement at infancy and revision at 10 months. He was born with multiple congenital anomalies including sagittal synostosis, shunted hydrocephalus, and intractable epilepsy. Magnetic resonance imaging abnormalities included turricephaly, ventriculomegaly of the lateral ventricles, dysgenesis of the corpus callosum with colpocephalic appearance of ventricles, absence of a septum pellucidum, and fused thalami. There was no associated Chiari malformation. In the posterior midline between temporal horns of the lateral ventricles, an encysted fluid collection abutted the falx superiorly. The fourth ventricle was distorted and flattened. There was no clear-cut vermis, and the cerebellar hemispheres were contiguous with one another, consistent with rhombencephalosynapsis. Temporal horns of the lateral ventricles were present (Fig. 4).

Case 5

This 8-year-old girl presented with minor closed head trauma after being struck by a car and suffering a questionable loss of consciousness. The patient's mother recalled that she had frequent spontaneous falls and poor coordination of extremities. She had no visible neurological signs and was doing well in school, except for poor handwriting. Magnetic resonance imaging abnormalities included a right temporal cyst, cerebellar tonsils extending 6.5 mm below the level of the foramen magnum consistent with a Chiari malformation Type I, and lack of vermian tissue with fusion of cerebellar hemispheres posterior to fourth ventricle, suggesting rhombencephalosynapsis (Fig. 5).

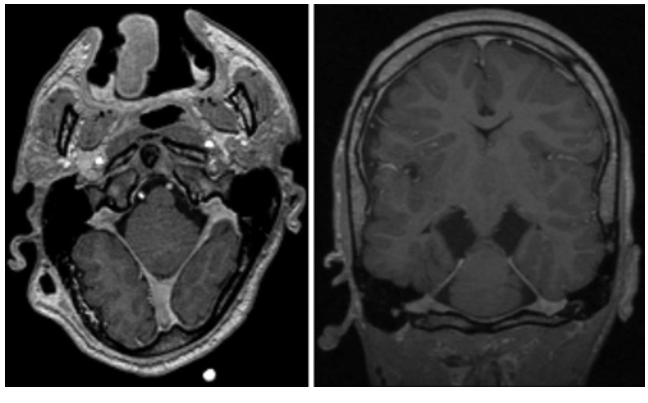

Fig. 2. Case 2. **Left:** Axial T1-weighted MP-RAGE (magnetization-prepared rapid acquisition gradient echo) image demonstrating fused, hypoplastic cerebellar hemispheres consistent with rhombencephalosynapsis. **Right:** Coronal T1-weighted MP-RAGE image including both fusion of the hypoplastic cerebellar hemispheres and fusion of the thalami.

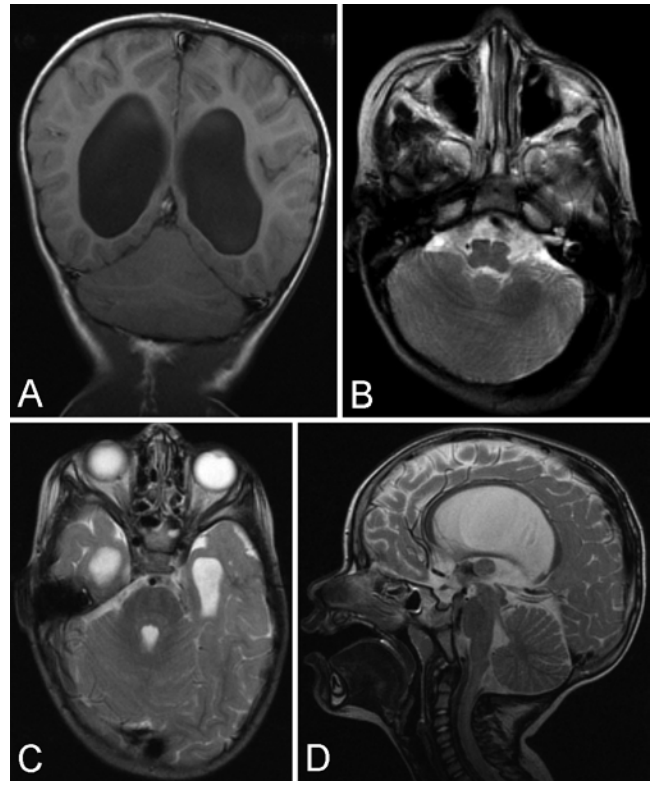

Fig. 3. Case 3. **A:** Coronal T1-weighted image showing fused cerebellar hemispheres indicative of RS. Note continuity of cerebellar folia across the midline, without a clear cleavage plane separating the hemispheres. There is ventriculomegaly involving the lateral ventricles. **B:** Axial T2-weighted image showing fused cerebellar hemispheres lacking an intervening vermis, consistent with RS. **C:** Axial T2-weighted images demonstrating pointing of the posterior aspect of the fourth ventricle characteristic of RS. **D:** Sagittal T2-weighted image showing hydrocephalus and elevation of the superior aspect of the tectum, in keeping with aqueductal stenosis.

Discussion

Rhombencephalosynapsis is a rare developmental anomaly of the cerebellum. It most commonly presents with hydrocephalus requiring surgical management. The hydrocephalus results from brain abnormalities that are often seen in conjunction with RS. A multitude of supratentorial abnormalities and extracranial anomalies have been found in conjunction with RS. Thus, the clinical presentation of RS is complicated as a result of associated abnormalities, and diagnosis is contingent upon MRI

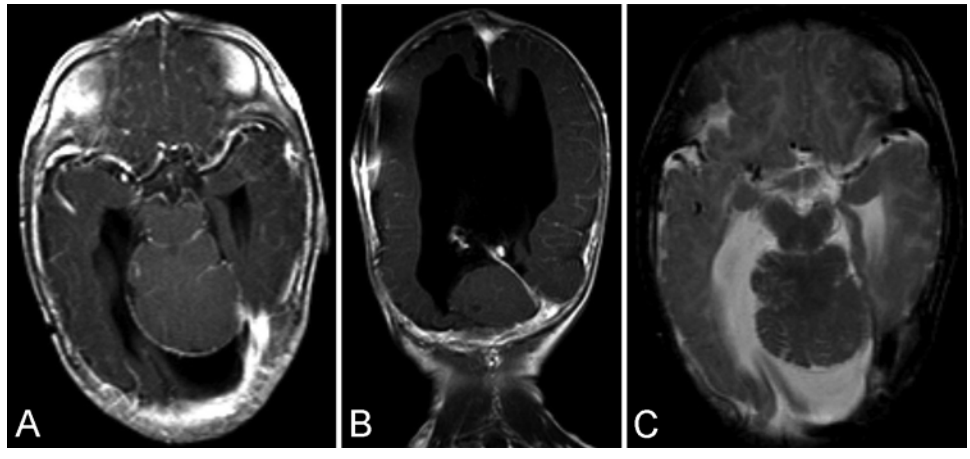

Fig. 4. Case 4. **A:** Axial Gd-enhanced T1-weighted image showing complete fusion of the cerebellar hemispheres, without a discernible vermis. **B:** Coronal Gd-enhanced T1-weighted image demonstrating fused cerebellar hemispheres in addition to enlarged, irregular lateral ventricles, absence of the septum pellucidum, overall paucity of supratentorial white matter, and callosal dysgenesis. **C:** Axial T2-weighted image demonstrating fused cerebellar hemispheres extending across midline without a discernible vermis. Note the partially visualized lateral ventriculomegaly, due in part to diminished supratentorial white matter.

findings. Isolated RS is usually diagnosed incidentally as patients are likely to be asymptomatic or suffer from only slight ataxia.

The current study depicts a clinical series of 9 patients with complete or partial RS. In the accepted hypothesis of cerebellar embryonic development, 2 distinct rhombic lips give rise to the corresponding cerebellar hemispheres. These rhombic lips fuse at 12 weeks of gestation. Fusion begins with anterior vermis formation and is then followed by posterior vermis formation.[23,27] This hypothesis explains the origin of Dandy-Walker malformation as an insult taking place after the formation of the anterior vermis but before the formation of the posterior vermis.[1]

Cerebellar hemispheres arising from paired primordia conflicts with the current understanding of RS. In RS, the cerebellar hemispheres are fused despite the absence of the vermis. Thus, Utsunomiya et al.[36] proposed that the cerebellar primordium is, in fact, unpaired. This implies that the fusion of cerebellar hemispheres in RS is not due to a primary maldeveloped vermis but is a result of a primary failure of vermian differentiation.[36] According to this view, Dandy-Walker malformation likely results from secondary degeneration or regression of the median portion of the unpaired cerebellum primordium.[36]

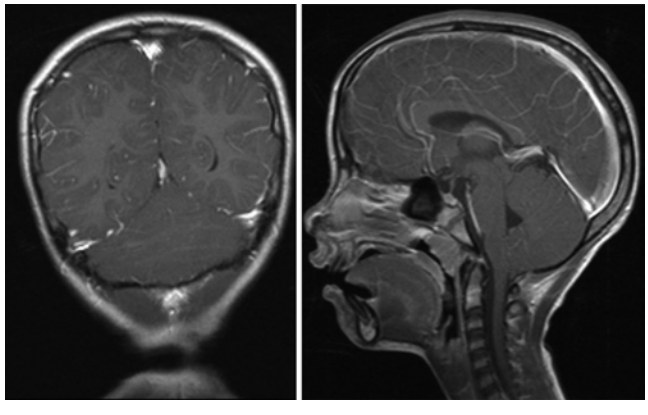

Fig. 5. Case 5. **Left:** Coronal T1-weighted Gd-enhanced image showing complete fusion of the cerebellar hemispheres, consistent with RS. **Right:** Rhombencephalosynapsis in conjunction with Chiari malformation Type I. Sagittal Gd-enhanced T1-weighted image demonstrating cerebellar tonsillar ectopia extending more than 5 mm below the foramen magnum. Although the cerebellar hemispheric fusion cannot be directly visualized, there is no recognizable vermis on this midline sagittal image.

In contrast to the above-mentioned hypothesis of primary failure of vermian differentiation, Sandalcioglu et al.[25] claimed that the malformation seen in their patient with RS could not have resulted from inadequate separation by rostral midline structures. They proposed a primary circular malformation of the cerebellar primordium and/or the rhombic lips prior to the cerebellar development or a form of fusion syndrome as a result of cerebellar expansion.

The isthmus is a strip of neuroepithelium at the mesencephalic-metencephalic border that has been implicated in the development of RS. The isthmus is an important region in cerebellar formation.[38] It acts as an organizing center for the development of the midbrain and hindbrain regions. Fibroblast growth factor and bone morphogenetic proteins Wnt1, Gbx2 and Otx are crucial for isthmus formation and differentiation.[1,13] These proteins are also necessary for the expression of genes such as *EN1*, *EN2*, *PAX2*, and *PAX5,* which are crucial for midbrain and cerebellar development.[13,16] Although multiple genes involved in midbrain-hindbrain patterning are known, mechanisms for the development of RS remain unknown. Animal models with knockouts for genes important in the isthmic organizer pathway have not been shown to have a direct relationship with RS development.[8,14,18] Sarnat[26] proposed that RS results from underexpression of dorsalizing genes. There is speculation that studying dorsalizing genes involved in regulating developmental events at the pontomesencephalic junction could result in the identification of mutations unique to the development of RS. One author claimed that recessive inheritance has been almost definitively excluded as a result of the rarity of sibling codiagnosis,[18] but recurrence in one family and

consanguinity in another suggest a genetically inherited cause.[4,24,25,33] Notable proposed environmental teratogenic effectors include insulin-dependent diabetes mellitus[30] and phencyclidine intake at the beginning of pregnancy.[12]

Rhombencephalosynapsis is thought to arise at Days 28–41 of gestation. The supratentorial abnormalities that are often associated with RS are also thought to arise at this time. The most common abnormalities seen in conjunction with RS include hydrocephalus, absence of the septum pellucidum, and hypoplasia of the corpus callosum.[25] Hydrocephalus is the most frequently associated supratentorial anomaly and is attributed to the narrowing of the fourth ventricle or to stenosis of the sylvian aqueduct. Rhombencephalosynapsis can be associated with septoopticopituitary dysplasia, but it is not clear if this is a true malformation associated with RS or due to chronic hydrocephalus.[16] The most complete list of associated anomalies was found in a paper by Pasquier et al.[18] and included rupture or absence of septum pellucidum, dysgenesis or agenesis of the corpus callosum, fused fornices and thalami, atrophy of the white matter with gyral abnormalities, fusion of the inferior and superior colliculi, malrotated hippocampi, hypoplastic chiasm, fused cerebral peduncles and thalami, parietal and temporocortical dysplasia, and schizencephalic cleft.[3,6,9,10,18,20–22,29,33,34,36] Hypoplasia of the temporal lobes, olivary nuclei, anterior commissure, and optic chiasm, and agenesis of the posterior lobe of the pituitary are occasionally seen. Extracranial anomalies, although rare, include the musculoskeletal, urinary tract, cardiovascular, and respiratory systems.[5,17] Tetralogy of Fallot, autosomal-dominant polycystic kidney disease Type 1, and polydactyly have been seen in patients with RS.[7,18] Holoprosencephaly has been reported in conjunction with RS in 3 cases.[18,32] One of these cases involved a unique association of holoprosencephaly, RS, and VACTERL.

If a diagnosis of RS is made, a review of the patient must be performed to exclude Gomez-Lopez-Hernandez syndrome. This syndrome was first described by Gomez and Lopez-Hernandez in 1979. It is a rare syndrome consisting of the triad of RS, trigeminal nerve anesthesia, and alopecia often in the parietal and occipital region. Clinical findings often include mental retardation, skull asymmetry, ataxia, and a distinct facial appearance that includes low-set ears, hypertelorism, midfacial hypoplasia, and clinodactyly of the fifth finger and have been sporadic.[28]

Facial dysmorphisms associated with RS include prominent forehead, hypertelorism, small pointed nose with a large nasal bridge and anteverted nostrils, midface hypoplasia, smooth philtrum, small mouth with thin lips, and microretrognathism as well as posteriorly rotated low-set ears with a coarse up-sized lobule and deformation of the external auditory canal.[18] Typical symptoms of RS include swallowing difficulties, delayed motor acquisitions, muscular hypotonia, spastic quadriparesis, dysarthria, gait ataxia, abnormal eye movements, nystagmus, and seizures. Cognitive function is often impaired, and most patients die early in life, although life into adulthood has been reported. Clinical prognosis is contingent upon the severity of neurological signs and cognitive impairment.[18,22,33,34] In isolated cases of RS, motor skills may be only mildly affected, and cognition may be normal. Often times there is no correlation between MRI findings and clinical manifestations.[1] Magnetic resonance imaging signs of RS are fused cerebellar hemispheres, absent or hypoplastic vermis, narrow diamond-shaped fourth ventricles, and fused dentate nuclei. Because of abnormal configuration of the fourth ventricle, the fusion or apposition of dentate nuclei and middle cerebellar peduncles can be noted behind the pointed fourth ventricle.

Shekdar[31] classified posterior fossa malformations into those with a large posterior fossa and those with a normal or small posterior fossa. Disorders associated with a large posterior fossa include classic Dandy-Walker malformation, a Blake pouch cyst, mega cisterna magna, and a posterior fossa arachnoid cyst. Disorders associated with a normal or small posterior fossa include Dandy-Walker variant, Joubert syndrome, tectocerebellar dysraphia, neocerebellar hypoplasia, and cerebellar atrophy. Rhombencephalosynapsis fits under the normal or small posterior fossa category. Among these malformations, Dandy-Walker malformations are more common than the others and are commonly associated with symptomatic hydrocephalus. Patel and Barkovich[19] created a classification scheme for cerebellar malformations contingent upon cerebellar hypoplasia versus cerebellar dysplasia with RS fitting the criteria of focal cerebellar dysplasia.

Magnetic resonance imaging is especially important in distinguishing RS from Dandy-Walker continuum (cystic posterior fossa malformations: Dandy-Walker malformation, Dandy-Walker variant, and mega cisterna magna), Joubert syndrome, tectocerebellar dysraphia, cerebellar dysplasia of lissencephaly Type II, and pontocerebellar hypoplasia. Rhombencephalosynapsis can present in conjunction with other posterior fossa malformations. For example, a fetal autopsy that revealed RS in conjunction with a ventriculocele (Dandy-Walker cyst) verified that RS and Dandy-Walker malformation can coexist.[30] Traditionally, RS is thought to result from fusion of 2 lateral cerebellar primordia at 28–41 days of gestation,[30,34] whereas Dandy-Walker malformation represents cystic dilation of the fourth ventricle due to obstruction of the outlet foramina at 49–70 days.[2,37] The vermian maldevelopment in RS is characterized by an absence of anterior vermis and a deficiency of the posterior caudal vermis. The nodulus tends to be formed. In Dandy-Walker malformation, the posterior vermis tends to be defective. There is an association between Dandy-Walker malformation and elevation of the confluence of sinuses. Elevation of the confluence of sinuses is not found in RS. From the standpoint of management, patients with RS do not typically require a cystoperitoneal shunting compared with a Dandy-Walker malformation. A posterior fossa cyst decompression is also not typically required in patients with RS. Ventriculoperitoneal shunting has been successfully used in RS with hydrocephalus similar to modern management of Dandy-Walker malformation with hydrocephalus.

Isolated cases of RS are often diagnosed incidentally. The clinical presentation of RS is mainly dependent on associated anomalies. Isolated cases of RS present with

only slight motor skill dysfunction, and cognition may be normal. Therefore, isolated cases of RS commonly do not require medical management. However, when associated anomalies are present, surgical management may be required. Most notably, associated hydrocephalus requires the placement a VP shunt or an ETV. In the current series, only 1 patient underwent ETV. However, ETV failed at 6 months, necessitating placement of a VP shunt.

Conclusions

We present one of the largest case series of live humans with RS, illustrating the association of symptomatic hydrocephalus (7 of the 9 patients) and Chiari malformation (5 of the 9 patients). It is important to recognize this clinical anomaly and the possibility of associated genetic conditions, such as Gomez-Lopez-Hernandez syndrome. We performed VP shunt placement to treat symptomatic hydrocephalus cases and never had to perform a posterior fossa cyst decompression or cystoperitoneal shunt. We have discussed the classic MRI findings of this condition, along with hypotheses regarding embryopathology. Rhombencephalosynapsis should be suspected in infants with congenital hydrocephalus and a cerebellum without formation of the cerebellar vallecula.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Cohen, Manjila, Bangert. Drafting the article: Weaver, Manjila, Bangert. Critically revising the article: all authors. Reviewed submitted version of manuscript: Weaver, Manjila, Cohen, Bangert. Approved the final version of the manuscript on behalf of all authors: Cohen. Study supervision: Cohen, Bangert.

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