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MR Imaging of Rhombencephalosynapsis: Report of Three Cases and Review of the Literature

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We describe the clinical and MR findings in three cases of rhombencephalosynapsis, a rare congenital malformation of the posterior fossa consisting of vermian agenesis or severe hypogenesis, fusion of the cerebellar hemispheres, and apposition or fusion of the dentate nuclei. Associated anomalies include hydrocephalus, fusion of the inferior colliculi, deficiency or absence of the septum pellucidum, and hypoplasia of the anterior commissure. Fourteen previous cases of rhombencephalosynapsis have been reported, including Obersteiner's first report in 1914. The clinical presentation is variable, ranging from early death to variable degrees of cerebellar dysfunction and developmental delay. Patients may reach young adulthood. We report three additional cases and provide radiographic (MR) images of this unusual anomaly detected during life.

Diagnoses in three children with rhombencephalosynapsis were made on the basis of MR findings. To our knowledge, this is the first report of this disorder being diagnosed in living patients.

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Since the introduction of MR imaging, brain malformations have been shown to be much more common than were previously suspected. Anomalies of neuronal migration, the corpus callosum, and cerebral white matter are all identified and characterized by MR with unmatched sensitivity and specificity. Nowhere has the superiority of MR been more clearly shown than in the posterior fossa.

Recently, we had the opportunity to study three patients with vermian agenesis, fusion of the cerebellar hemispheres, and anomalies of the dentate nuclei. A search of the pathologic literature revealed 14 similar cases, including the original description by Obersteiner in 1914 [1–8]. We describe here the MR appearance and clinical manifestations of rhombencephalosynapsis. We also speculate on the embryogenesis of this disorder.

Case Reports

Case 1

A 4½-year-old girl was the product of a normal term pregnancy. At birth, she weighed 2552 g (10th percentile) and had a head circumference of 31 cm (2nd percentile). During infancy, she was believed to have a poor sucking reflex and slow motor milestones. She was a very irritable child and was prone to fits of crying and breath-holding, during which she arched her back. She reacted to sound but displayed no visual tracking. Because of questionably widened cranial sutures, CT was performed and revealed absence of the septum pellucidum, moderate ventriculomegaly, and cerebellar dysmorphism. Consequent to these findings, awake and sleep electroencephalography, ophthalmologic evaluation, visual evoked responses, and chromosomal analyses were performed and were all normal.

Head circumference at 3 months of age measured 38 cm (40th percentile). The anterior fontanelle was full, and the metopic suture was widely split. At 7.5 months, she had made considerable progress, although she displayed gross motor delay. At that time, she was no

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longer irritable, but rather very sociable. Head circumference was 42.5 cm (35th percentile). She began talking at 16 months and began walking at 2.5 years.

Cranial MR (Fig. 1) at 3.5 years revealed dorsal fusion of the cerebellar hemispheres, hypogenesis of the vermis, horseshoe-shaped apposition (and probable fusion) of the dentate nuclei, absence of the septum pellucidum, and ventriculomegaly consistent with hydrocephalus. The corpus callosum appeared thinned, but present. The pituitary gland, infundibulum, and optic chiasm were normal. No anomalies of cerebral neuronal migration were evident.

At 4 years 3 months, head circumference was 53 cm (98th percentile) and brachycephalic in shape. The child had dysmorphic facies with small midface, long filtrum, high palate, tent-shaped mouth, and low-set ears. She had balance problems with a tendency to fall. She could jump, walk backward, stoop, and navigate stairs in both directions, but was unable to hop, tandem walk, or heel- or toe-walk. She lacked caution and displayed poor motor planning and poor protective reflexes. She was unable to distinguish hot from cold, and she did not react normally to pinprick or light touch. Visual acuity was very poor consequent to corneal clouding from recurrent traumatic corneal abrasions related to aberrant corneal sensation and defective lacrimation. She had undergone four ophthalmologic surgical procedures. She had not had any seizures. Intellectually, she displayed an excellent memory and vocabulary and spoke in complete sentences. She was not toilet-trained, despite constant parental efforts, and appeared unable to recognize bladder fullness.

Case 2

A 12-year-old right-handed boy was the product of a 37-week gestation that was complicated by placental insufficiency requiring emergency cesarean delivery. Apgars were 9 and 9 at 1 and 5 min. Birth weight was 2240 g (2nd percentile); head circumference measured 32 cm (25th percentile). At birth, the child was noted to be dysmorphic and mildly scoliotic (radiographs reportedly were negative for structural lesions of the spine). Mild metatarsus varus deformity and clinodactyly of the fifth fingers were noted.

Evaluation at 13 months revealed global developmental delay. At 14 months, head circumference was 44 cm (< 1st percentile). Neurologic examination revealed mildly depressed deep tendon reflexes with downgoing plantar reflexes.

The child apparently had both central and obstructive apnea and had two respiratory arrests during the first year of life, one of which was consequent to jugular venipuncture. Surgery during infancy was performed for an unspecified bowel malrotation. Infrequent seizures were noted throughout childhood, many associated with fever. CT at 6.5 years old revealed ventriculomegaly and deficiency of the septum

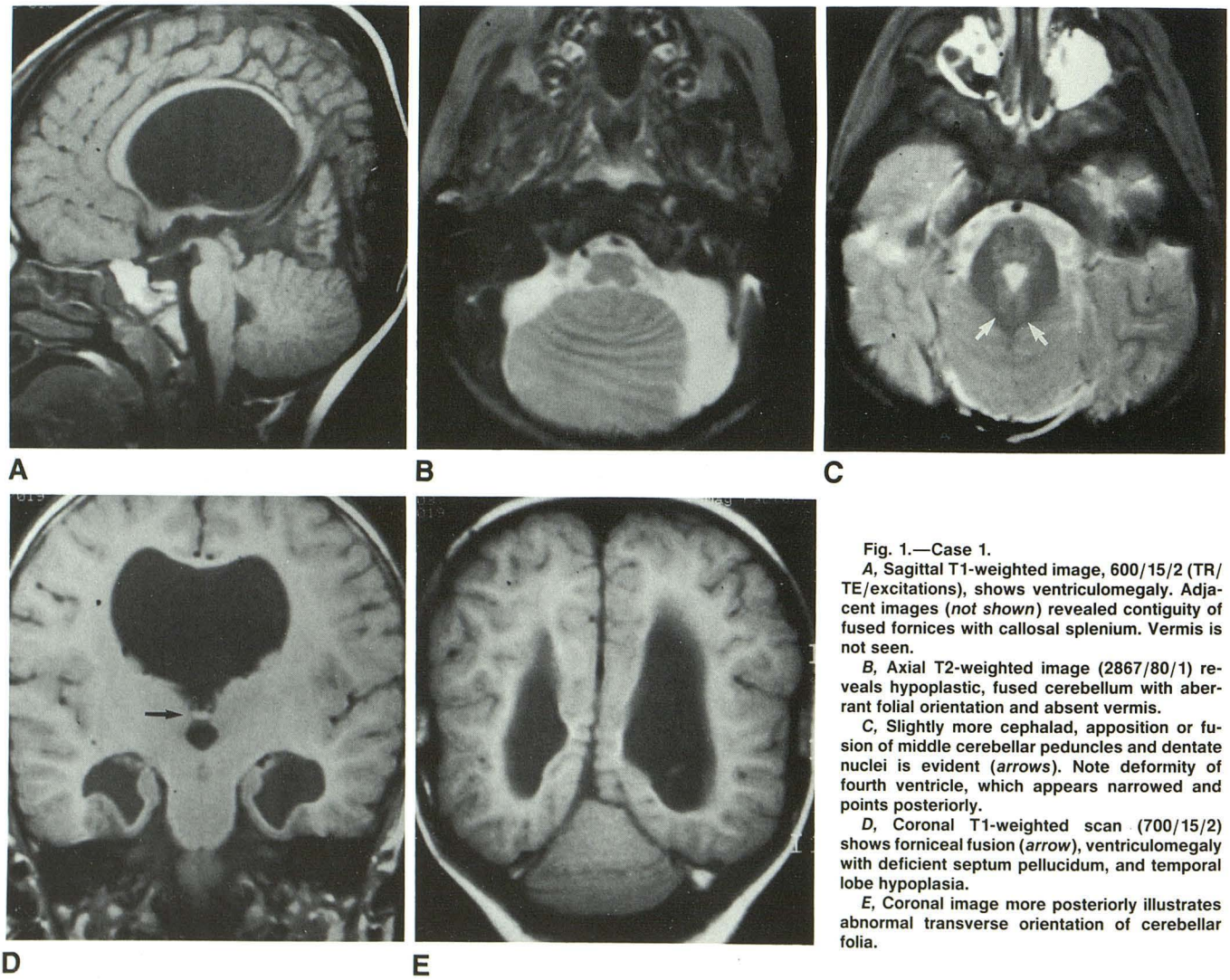


Fig. 1.—Case 1.

***A*, Sagittal T1-weighted image, 600/15/2 (TR/TE/excitations), shows ventriculomegaly. Adjacent images (*not shown*) revealed contiguity of fused fornices with callosal splenium. Vermis is not seen.**

***B*, Axial T2-weighted image (2867/80/1) reveals hypoplastic, fused cerebellum with aberrant folial orientation and absent vermis.**

***C*, Slightly more cephalad, apposition or fusion of middle cerebellar peduncles and dentate nuclei is evident (*arrows*). Note deformity of fourth ventricle, which appears narrowed and points posteriorly.**

***D*, Coronal T1-weighted scan (700/15/2) shows forniceal fusion (*arrow*), ventriculomegaly with deficient septum pellucidum, and temporal lobe hypoplasia.**

***E*, Coronal image more posteriorly illustrates abnormal transverse orientation of cerebellar folia.**

pellucidum. Genetics test at 9 years of age revealed an interstitial deletion of chromosome 2q.

Assessment at 10.5 years revealed head circumference of 51 cm (5th percentile). An exceedingly high arched palate and slight kyphosis were noted. The musculature of the lower extremities appeared to be diminished, and deep tendon reflexes were normal to slightly increased. No definite truncal or appendicular ataxia was detected, although the boy was mildly unsteady on his feet.

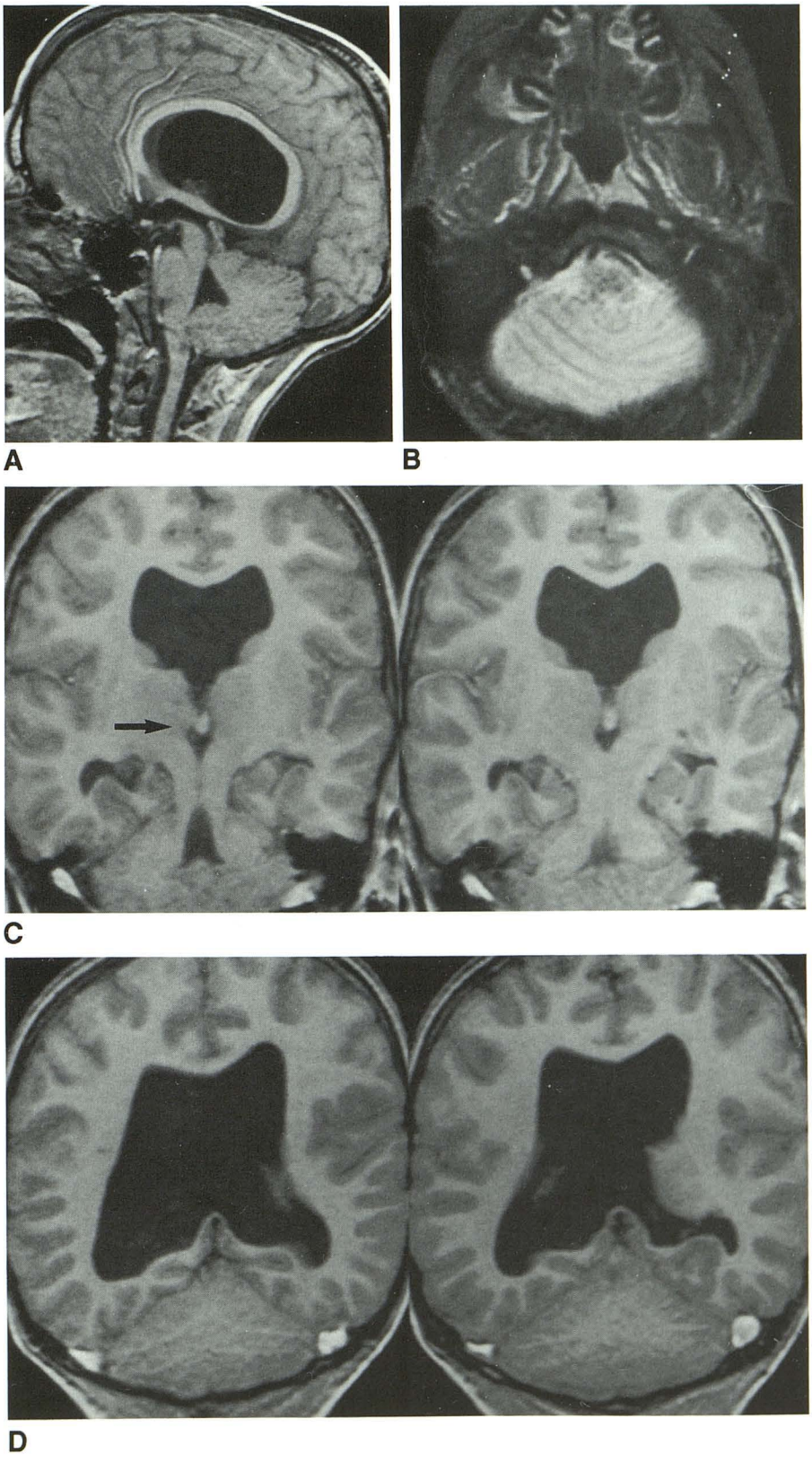


Fig. 2.—Case 2.

***A*, Sagittal spoiled gradient-recalled image (SPGR), 35/5/1/35° (TR/TE/excitations/flip angle), which is heavily T1-weighted, reveals contiguity of fused fornices with callosal splenium. Vermis is not seen. Intravascular signal is characteristic of SPGR images.**

***B*, Axial T2-weighted scan (2870/80/1) reveals small, fused cerebellum with aberrant folial orientation.**

***C* and *D*, Coronal SPGR images (35/5/1/35°) confirm cerebellar fusion, absent vermis, ventriculomegaly with absent septum pellucidum, fused fornices (*arrow*), and hypoplastic temporal lobes.**

MR (Fig. 2) of the brain at ages 10 years 8 months and 12 years 6 months revealed ventriculomegaly, deficiency of the septum pellucidum, fusion of the cerebellar hemispheres, and a hypogenetic vermis. The corpus callosum was present, although stretched; no anomalies of cerebral neuronal migration were apparent. The pituitary gland, infundibulum, and optic chiasm appeared normal. No abnormal signal was detected in the white matter. Ophthalmologic evaluation revealed no optic atrophy.

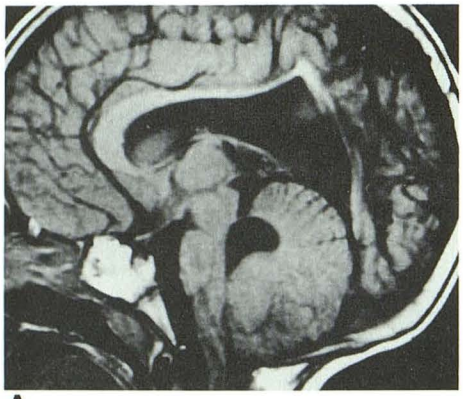
The child was reevaluated at 12 years of age, when he was considered to be at a plateau stage of development with moderate mental retardation. Although still learning new words and having memorized his address and phone number, he could not read or write or be left alone. His speech was extremely dysarthric, and he had a conductive hearing loss, although he could successfully localize sound with bilateral hearing aids. Motor examination revealed extremely diminished muscle bulk and mild diffuse hypertonicity. He was apraxic and demonstrated only minimal dexterity. He had a lurching, broad-based gait, could not hop, and used a complete Gowers maneuver when arising from the floor.

Case 3

A 4-year-old boy was diagnosed in utero as hydrocephalic, and shunting was done 2 days after birth. CT of the brain at birth revealed obstructive hydrocephalus, absence of the septum pellucidum, and a small posterior fossa. His development was slow, and he was entered into an infant stimulation program requiring special schooling. At 4 years, he was unable to speak, although he could vocalize sounds, and he displayed a normal range of emotional responses. He was able to feed himself and walk independently, albeit ataxically, and he could navigate stairs in both directions.

MR at 4 years 3 months revealed a grossly dysmorphic brain (Fig. 3). The ventricles were decompressed such that the frontal horns were nearly coapted and posterior parietal cortical infolding had developed (consequent to the shunt and not representing anomalies of neuronal migration). The septum pellucidum was not apparent, and the corpus callosum, although distorted from the hydrocephalus, appeared fully formed. CSF signal could be seen in the inferior third ventricle, but the superior posterior portion of the third ventricle was eclipsed by fused thalami. The pituitary gland was normal, but the optic chiasm was markedly hypoplastic. The fornices appeared fused, and the temporal lobes were underdeveloped. The tectum appeared fused and posteriorly pointed. The aqueductal flow void was not apparent on any sequence.

Infratentorially, the superior and middle cerebellar peduncles appeared fused around a distorted fourth venticle. The anterior medullary velum was present, but stretched dorsally. The superior vermis appeared mostly intact and was upwardly herniated through the



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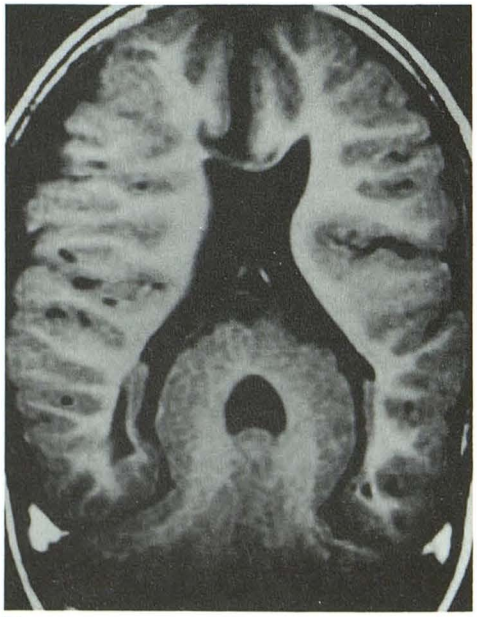

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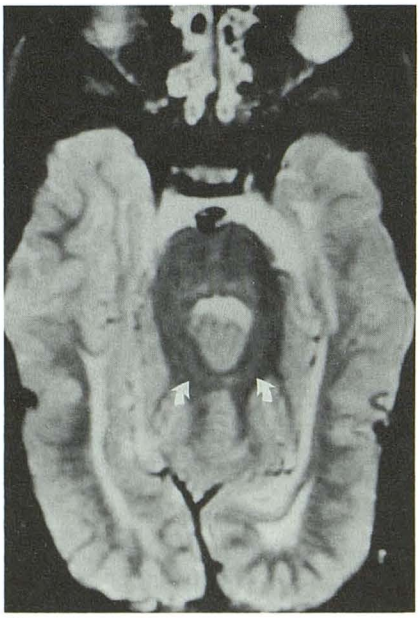

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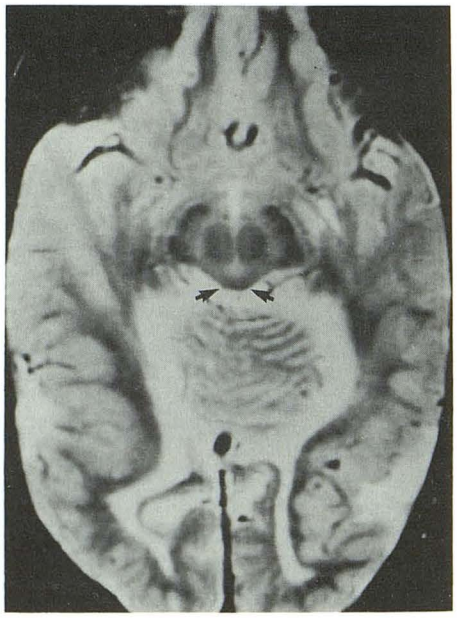

D

Fig. 3.—Case 3.

***A,* Sagittal T1-weighted image, 600/20/2 (TR/TE/excitations), reveals stretched, distorted corpus callosum. Note abnormal superior collicular bulge, enlarged fourth ventricle, and elevated anterior medullary velum. Vermis is not seen clearly.**

***B,* Coronal image (500/20/2) confirms upward transtentorial herniation. Inferomedial cerebellum is swept up with remnant of cerebellum simulating vermis. Septum pellucidum is absent.**

***C,* Axial T2-weighted images (2400/80/1) reveal fusion of middle cerebellar peduncles and horseshoe-shaped (fused/apposed) dentate nuclei (*arrows*) within fused cerebellar white matter.**

***D,* More cephalad, superior colliculi appear fused (*arrows*).**

tentorial incisura, most likely consequent to the hydrocephalic decompression. The inferior vermis was not well identified, and the tonsils were apposed in the midline. Except for the tectal and aqueductal anomalies, the brainstem appeared normal.

Discussion

Despite abundant study, much of human neuroembryology remains poorly understood. Nowhere is this more evident than in the posterior fossa. Although Chiari's original description of hindbrain anomalies took place nearly 100 years ago, academic debate continues over the origin of his type II malformation [9]. Occipital cephalocele is another posterior fossa anomaly whose origin is still unsettled [10, 11]. In addition, at least four distinct malformations of the cerebellar vermis have been described, including the Dandy-Walker malformation (DWM), Joubert syndrome, tectocerebellar dysraphia, and rhombencephalosynapsis [12–19]. The DWM consists of partial or complete vermian agenesis, cystic dilatation of the fourth ventricle, and an enlarged posterior fossa with incomplete descent of the tentorium and venous sinuses. Supratentorial and systemic anomalies frequently accompany the posterior fossa malformation [15–17]. Joubert syndrome (global developmental delay, episodic tachypnea and apnea, retinal dystrophy, and jerky eye movements) also consists of vermian hypoplasia or aplasia; however, neither a posterior fossa cyst nor hydrocephalus is seen, and the clinical presentation is entirely different [13, 18, 19]. Tectocerebellar dysraphia consists of vermian hypoplasia or aplasia, occipital cephalocele, and dorsal traction of the brainstem, such that the hypoplastic cerebellar hemispheres rotate around the brainstem and lie ventrolateral to the brainstem [12]. Finally, rhombencephalosynapsis consists of vermian hypogenesis or agenesis, not associated with the disconnected cerebellar hemispheres of Joubert syndrome, nor with a posterior fossa cyst, nor with abnormal cerebellar hemispheric rotation, but with cerebellar, dentate, peduncular, and collicular fusion.

The original description of rhombencephalosynapsis dates to 1914, when Obersteiner [1] reported the postmortem findings in an apparently normal 28-year-old man who committed suicide by drowning [1]. In this seminal case, Obersteiner described the incidental finding of a single, horseshoe-shaped, fused dentate nucleus, fused superior cerebellar peduncles, deficient vermis, and abnormal cerebellum. Since then, 13 additional cases have been described [2–7], including seven by Gross et al. [2–4] (although it is unclear from the two articles and one abstract published by Gross et al. whether these three reports truly reflect seven distinct cases). These cases are summarized in Table 1. Although the autopsy findings differ somewhat, a pattern of dentate fusion, cerebellar peduncular fusion, cerebellar hemispheric hypoplasia and fusion, and vermian agenesis/hypogenesis is apparent. De Morsier [20] named the disorder *rhombocephalosynapsis*, which was subsequently amended by Gross [3] to *rhombencephalosynapsis*.

Development of the posterior fossa differs significantly from that of the supratentorial brain. Whereas the telencephalon undergoes a normal cleavage process known as diverticulation (whereby two hemispheres are created), the cerebellum arises from two distinct embryonic primordia known as the rhombic lips [21]. The vermis arises superiorly, between these two embryonic cerebelli. Under normal conditions, the vermis represents the only cerebellar interhemispheric connection, whereas the peduncles afford cerebellar communication with the brainstem and the remainder of the neural axis.

The cerebellum arises from the alar plate of the rhombencephalon (Fig. 4). At Carnegie stage 15 (approximately 33 days gestation), the cerebellum is composed of rostral and caudal parts [22]. The rostral portion arises from the rhombic lips, which start to develop along the lateral aspect of the alar plate of the isthmic segment (between the developing mesencephalon and the metencephalon) during stages 13 and 14. From these parts will form the superior medullary velum as well as part of the cerebellar hemispheres. The caudal portion arises from rhombomere 1, the embryologic segment immediately caudal to the isthmic segment. At this stage, all cranial nerves can be identified, with the exception of the olfactory and optic nerves. Concurrently, supratentorial development includes longitudinal zoning of the diencephalon and the amygdaloid body and hippocampal thickening [22].

At stage 16, approximately 37 days gestation, while further cellular proliferation occurs, no new structural changes to the future cerebellum are noted. Supratentorial development, however, involves the earliest recognition of the future interhemispheric sulcus as dorsal and rostral telencephalic growth is observed while the midline seam remains tethered by the commissural plate and lamina terminalis. The neurohypophysis is not yet consistently observed; the commissure of the superior colliculi is recognized [23].

During stage 17 (41 days), cerebellar development includes the earliest recognition of the external cerebellar bulge (future flocculonodular lobe) and the internal cerebellar bulge, which will become the vermis and part of the cerebellar hemispheres. Prosencephalic development at this stage is notable for the forebrain septum and the first septal nucleus. They represent the earliest link between the olfactory area and the amygdaloid/hippocampal region. Within the diencephalon, fibers can be detected crossing the chiasmatic plate [24].

Stages 18 and 19 (44 and 48 days, respectively) feature elaboration of the future flocculi, superior cerebellar peduncles, and dentate and olivary nuclei, as well as the first recognition of distinguishable choroid plexus within the fourth ventricle. Also noted are further developments of the prosencephalic septum and optic chiasm [25].

In light of this embryologic chronology, it is possible to speculate about the neuroembryology of posterior fossa malformations, including occipital cephalocele, the DWM, Joubert syndrome, tectocerebellar dysraphia, and rhombencephalosynapsis. Given that the rostral neuropore closes during stage 11, and that occipital cephalocele may represent a defect of herniation rather than one of incomplete neural tube closure [10, 11], it would seem that occipital cephalocele, tectocerebellar dysraphia, and rhombencephalosynapsis are likely to be early developmental expressions, probably occurring during stages 14–17. One key feature of these malformations is tectal fusion, which is a common finding in occipital cephalocele and tectocerebellar dysraphia [10–12]. As noted in Table

TABLE 1: Summary of Reported Cases of Rhombencephalosynapsis

Variable	Reference								
	Obersteiner [1] (1914)	Gross and Hoff [2] (1959)	Gross [3] (1959) (two cases)	Kepes et al. [5] (1969)	Gross et al. [4] (1978) (five cases)	Schachenmayr and Friede [6] (1982)	Michaud et al. [7] (1982)	Isaac and Best [8] (1987) (two cases)	Truwit et al. (1991) (three cases)
Age[a]	28 yr	2 mo	(1) 6 wk; (2) 2½ yr	6 mo	2 mo–26 yr	4 wk	7 hr	(1) 11 yr; (2) 35 yr	(1) 3½ yr; (2) 12 yr; (3) 4 yr
Sex	M	F	(1) F; (2) M	M	–	M	F	(1) M; (2) F	(1) F; (2) M; (3) M
Dentate nucleus	Fused	Fused	(1) Fused; (2) partially fused	Fused	Fused (all cases)	Fused	Apposed	Fused in both	Fused/apposed in all three
Cerebellum	Tonsils normal but separated	Hypoplastic, spherical	(1) Hypoplastic, fused; (2) hypoplastic, fused, tonsils present	Hypoplastic	Fused (all cases)	–	Hypoplastic, spherical	–	(1) Hypoplastic, spherical, tonsils fused; (2) hypoplastic, spherical, tonsils fused; (3) supratentorial herniation
Sup. vermis	Fused culmen & declive; absent linguia	Absent	Absent, not definable (both cases)	–	Absent	Absent	Absent	Absent (both cases)	(1) Very rudimentary; (2) hypoplastic; (3) present
Inf. vermis	Large uvula & nodulus, absent tuber & pyramis	–	(1) Deficient; (2) deficient; gliotic pyramis	–	Absent	Absent except for a few remnants of nodulus	Absent	Absent (both cases)	(1) Absent; (2) absent; (3) not definable
Olivae	Inf. hypoplastic	Inf. present	Inf. hypoplastic (both cases)	–	Inf. hypoplastic (all cases)	Inf. normal, sup. absent	Inf. normal, sup. absent	–	–
Inf. cerebellar peduncle	–	Fused	Fused (both cases)	–	–	–	–	(2) Normal	(1) Fused/apposed; (2) fused/apposed; (3) normal
Mid. cerebellar peduncle	–	–	(1) Ovoid, deficient; (2) ovoid	–	–	Fused	–	(2) Normal	Fused/apposed (all cases)
Sup. cerebellar peduncle	Fused	Fused	Fused (both cases)	–	Abnormal course	Fused	–	(2) Normal	Fused/apposed (all cases)
Ant. medullary velum	Absent	–	(1) Hypoplastic; (2) absent	–	Absent (all cases)	Absent	–	–	(1) Present; (2) not seen definitely; (3) present, stretched
Medullary pyramids	–	–	–	Poorly developed	–	–	Normal	–	Present (all cases)
Flocculi	Present	Rudimentary	(1) Well developed; (2) present	–	–	Present	Absent	(2) Absent	(1) Present; (2) probably present; (3) probably present
Gray matter heterotopia in posterior fossa	Yes	Yes	Yes (both cases)	–	–	–	–	(2) No	–
Fourth ventricle	–	–	(1) Enlarged	Small cephalad	–	Narrow roof	Large	–	(1) Small inverted teardrop; (2) small inverted teardrop; (3) large cephalad
Colliculi	–	Fused	(1) Abnormal inf.	Fused	–	Fused inf.	–	–	(1) Not fused; (2) not fused; (3) fused

Aqueduct	–	–	(2) Patent	Atretic	–	Narrow gliotic slit	Patent	(1) Narrow gliotic bridges; (2) gliotic	(1) Grossly patent; (2) grossly patent; (3) not visible
Corpus callosum	–	Diffusely thinned	(1) Narrow; (2) hypoplastic rostrum	–	Deficient (one case); dysgenetic (one case)	–	Thinned	–	(1) Thinned; (2) thinned; (3) distorted
Septum pellucidum	–	–	(1) Absent	–	Absent (one case)	Absent	Absent; septooptic dysplasia	–	(1) Absent; (2) deficient; (3) absent
Ant. commissure	–	–	Hypoplasia (both cases)	–	Hypoplasia (one case)	Normal	Hypoplasia	–	(1) Not identified definitely; (2) present; (3) present
Hydrocephalus	No	–	Yes (both cases)	Yes	–	Yes	Yes	Yes (both cases)	(1) Yes; (2) ventriculomegaly; (3) yes
Other CNS anomalies	–	Abnormal gyri, diminished white matter	(1) Hypoplastic pons; (2) fused thalami, thinned fornix, prominent sulci & fissures	Fused thalami, atresia of third ventricle	Temporal lobe hypoplasia (two cases); parietal cephalocele, hydromyelia (one case)	L parietal cephalocele, hypoplastic falx, bifid C1–C4; absent olfactory tracts/bulbs, mamillary bodies, pineal gland	Post. pituitary absent; hypoplastic optic nerves, tracts, chiasm	–	(1) Fused fornices contiguous with splenium; hypoplastic chiasm, hippocampi; (2) fused fornices contiguous with splenium, hypoplastic hippocampi; (3) fused fornices & thalami, hypoplastic temporal lobes & optic chiasm
Hypertelorism	–	Yes	Yes (both cases)	–	–	–	–	–	No (all cases)
Anomalies outside CNS	–	Yes	(1) Low-set ears, deformed occipital bone; (2) undescended testes	–	–	–	Cardiovascular respiratory, genitourinary, musculoskeletal anomalies	–	(1) Arched palate, low-set ears; (2) high arched palate; (3) strabismus, "asthma"
Clinical findings	Normal	–	(1) Death from cachexia, penetrating keratomalacia; (2) mental retardation, strabismus, oxycephaly, pes cavus, death from pneumonia	Spastic quadriparesis, bilateral optic atrophy, convergent strabismus	–	Nonidentical twin, hypotonia, death from pneumonia	Normal 46,XY	(1) Slight developmental delay in school; sudden death; (2) behavioral disorder, psychomotor epilepsy, death from status epilepticus	(1) Balance problems, impaired sensation, delayed motor development, normal intellect; (2) balance problems, mild spasticity, intellectual impairment, dysarthria, apraxia; (3) balance problems, ataxia, intellectual impairment

Note.—yr = years; mo = months; wk = weeks; L = left; sup. = superior; inf. = inferior(ly); mid. = middle; ant. = anterior; post. = posterior.

[a] At death or MR imaging (this study only).

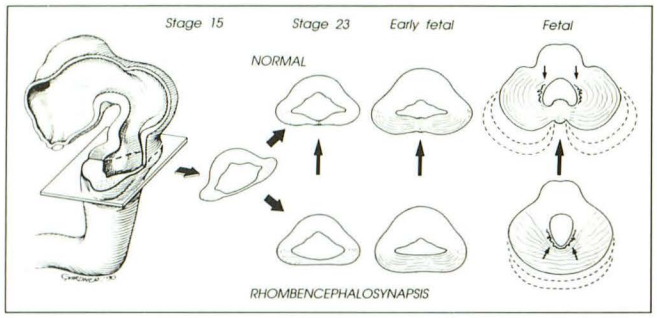

Fig. 4.—Schematic of cerebellar embryology, normal and in rhombencephalosynapsis. At left is three-dimensional conceptualization of embryo at approximately Carnegie stage 15. Section illustrated is near junction of isthmic segment and rhombomere 1, as described in text.

***Top,* Note normal vermian (*long arrows*), cerebellar, and fourth-ventricular development in late embryologic, early fetal, and fetal stages. Also note normally developing dentate nuclei (*small arrows*).**

***Bottom,* Absent vermis results in abnormal cerebellar hemispheric fusion, malorientation of folia, and horseshoe-shaped dentate nucleus (*small arrows*) around teardrop-shaped fourth ventricle.**

***Broken lines* dorsally represent cerebellar growth.**

1, collicular fusion was also observed in four (possibly five) cases of rhombencephalosynapsis, including one of our cases. Further support for the hypothesis that these disorders bear temporal proximity is given by the cases reported by Gross et al. [4] and Schachenmayr and Friede [6], in which parietal cephaloceles were noted, and by cases reported by Gross [3], Kepes et al. [5], and us (case 3), in which diencephalic (thalamic) fusion was observed. Anomalies of diencephalic fusion were also reported in three of four cases of tectocerebellar dysraphia [12].

The DWM and Joubert syndrome, conversely, may represent the sequelae of slightly later gestational insults or genetic expressions. A localized failure of vermian development might spare the remainder of the alar plate, resulting in a normal fourth ventricle and normal cerebellar hemispheres, as seen in Joubert syndrome. Most cases of Joubert syndrome are believed to be genetically determined by autosomal-recessive expression. The DWM, on the other hand, is not genetically determined in most cases; rather, it probably represents a sporadic event. In the DWM, a broad insult to the alar plate involving the dorsal fourth ventricle and rhombic lips may take place [15]. Such an insult could account for fourth-ventricular herniation (cyst) as well as vermian and cerebellar hemispheric hypoplasia. Not all DWMs, however, can be explained by this hypothesis. As is well known, the DWM can occur in association with occipital cephalocele. It is possible that underlying genetic abnormalities are involved and predispose an occipital mesodermal weakness that is exacerbated by the DWM.

The proposed embryologic schema also accounts for the various specific anomalies of rhombencephalosynapsis, including the peculiar transverse orientation of the cerebellar folia, dentate nuclear and varying cerebellar peduncular fusions, absence of the olivary nuclei, the presence of gray matter heterotopias, and the coincident deficient septum pellucidum. In the DWM, the developing cyst may further impede normal cerebellar hemispheric and vermian development. In rhombencephalosynapsis, however, no such interhemispheric impediment is present. As a result, without the normal folial structure imposed by the developing vermis, the cerebellar hemispheres are free to reach interhemispherically and align themselves transversely. In such a case, folial orientation would be abnormal, as seen in Figure 1B. Moreover, as one primitive cerebellar hemisphere might be more or less affected than its counterpart, the folia might slightly rotate with the unequal growth of the hemispheres, resulting in asymmetry of the transverse folial orientation. Such asymmetry was observed in two of our cases, although not specifically reported in the previous cases.

As the dentate and olivary nuclei, the peduncles, and the flocculi do not normally first appear until stages 18 and 19, variable closely located genetic defects could be reflected in variable development of the cellular primordia destined to form these structures. Depending on the extent and location of the decrement, these structures either could fail to develop or could develop hypoplastically. Thus, in some cases, the superior cerebellar peduncles would be affected, while in others with slightly different defects, the middle or inferior peduncles would be abnormal. Similarly, the olivary nuclei and flocculi could be affected inconsistently. In fact, as shown in Table 1, although considerable overlap exists, slightly different associated anomalies were present in the various reported cases.

The suggested gestational timing of rhombencephalosynapsis is also consistent with the associated supratentorial anomalies. As noted, structures developing during the period from stages 15 through 17 include the first septal nucleus, the olfactory system, the earliest fibers of the optic tract, the hippocampal/amygdaloid complex, and the thalamus. These structures might be variably developed in the same manner as the infratentorial structures. It is not difficult to speculate that occasional septal deficiency might be observed. Similarly, septal deficiency could be associated with abnormal development of the closely related anterior commissure and fornices.

During this period, the thalamus is undergoing normal longitudinal zoning whereby its future structure is determined [22]. While most cases of rhombencephalosynapsis are not associated with thalamic anomalies, the presence of thalamic fusion, reported in two previous cases and one of our present cases, is not unreasonable given its embryologic activity during this period. The exact mechanism of such a fusion, however, remains unclear.

As seen in Table 1, deficiency or absence of the septum pellucidum was observed in seven cases, including our three cases. Associated in these specific cases are abnormalities of the anterior commissure and thalami. Unfortunately, information regarding the temporal lobes and fornices is available in only two of the previously reported cases. In those cases, temporal lobe hypoplasia was seen with hydrocephalus and absence of the septum pellucidum. In our cases, hypoplasia of the hippocampi and incomplete developmental rotation of the entire complex were observed in all three cases. In addition, forniceal fusion and contiguity with the splenium was

demonstrated in two patients. These latter findings have been reported previously in association with deficiency of the septum pellucidum [20, 26] and were noted by de Morsier [20] in his original description of septooptic dysplasia.

The occurrence of supratentorial anomalies, including deficiencies of the septum pellucidum and anterior commissure, raises the question of a neuroembryonic link between rhombencephalosynapsis and the holoprosencephalies. In fact, Schachenmayr and Friede [6] described absence of the olfactory tracts and bulbs and septum pellucidum in concert with the posterior fossa malformation. Moreover, in reports by Gross [3] and Kepes et al. [5], rhombencephalosynapsis was associated with thalamic fusion and consequent third-ventricular deficiency. In one case, the posterior pituitary lobe was absent; the septum pellucidum was absent; and the optic nerves, chiasm, and tracts were markedly hypoplastic, fulfilling the pathologic diagnosis of septooptic dysplasia [7]. Nevertheless, of all reported cases, in only two was the corpus callosum described as hypoplastic or dysgenetic (see Table 1). Thus, were rhombencephalosynapsis indeed part of the spectrum of holoprosencephaly, it would be unique by its relative sparing of the dominant midline cerebral commissure. Moreover, in no cases of rhombencephalosynapsis has fusion of the cerebral white matter been reported. It is also notable that hypotelorism and facial anomalies—typical of more severe forms of holoprosencephaly—have not been described in any cases of rhombencephalosynapsis, and in fact, hypertelorism was noted in three cases. (Hypertelorism is incompatible with holoprosencephaly because the premaxillary segment of the face is smaller than normal.) Finally, in holoprosencephaly, the cerebellum is usually normal. Rhombencephalosynapsis thus appears to represent a unique malformation of the posterior fossa with occasional supratentorial, midline anomalies, most likely related to the gestational age at the time of insult to the developing rhombencephalon.

The dominant clinical findings in our patients were balance problems and delayed motor development. Motor problems were also reported by Kepes et al. [5] and Schachenmayr and Friede [6]. Nevertheless, no single clinical syndrome can be discerned. Intellectual impairment appears to be variable, as do prognosis and life expectancy. Finally, chromosomal analyses were performed in two of our patients and in the case of Michaud et al. [7]. In one of our cases, an interstitial deletion of chromosome 2q was detected. No chromosomal abnormalities were detected in the other two cases.

To summarize, three cases of rhombencephalosynapsis are reported. This account represents the first such cases to be diagnosed during life. In addition to the neuroradiologic findings, detailed clinical histories are recounted. With additional accounts, a more complete clinical and neuropathologic picture of this unusual posterior fossa malformation can be offered.

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