

Familial agenesis of the cerebellar vermis

A syndrome of episodic hyperpnea, abnormal eye
movements, ataxia, and retardation

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SOME TWO YEARS AGO we investigated a child with profound psychomotor retardation who had had an occipital meningoencephalocele removed at birth. Contrast studies were carried out which showed a large midline defect in the posterior fossa and absence of the vermis. At the time we disregarded the nurses' comments about the child's abnormal breathing. A year later, Dr. P. P. Demers referred this patient's baby brother to us because he was concerned about his abnormal breathing and retarded development. It was then found that a third and older child in this family was retarded, ataxic, and breathing abnormally. Finally we were able to trace yet another sibling who had died in fancy and who, at autopsy, proved to have agenesis of the vermis. This diagnosis was then confirmed in the two affected living children by contrast studies.

From this investigation there emerged a familial syndrome of episodic hyperpnea, abnormal eye movements, ataxia, and mental retardation associated with a common malformation in the four affected siblings, agenesis of

the vermis. This syndrome has not previously been described in the literature.

The affected children will be presented in the order in which the abnormality was identified, which happens to be in reverse to the birth order (Fig. 1).

CASE REPORTS

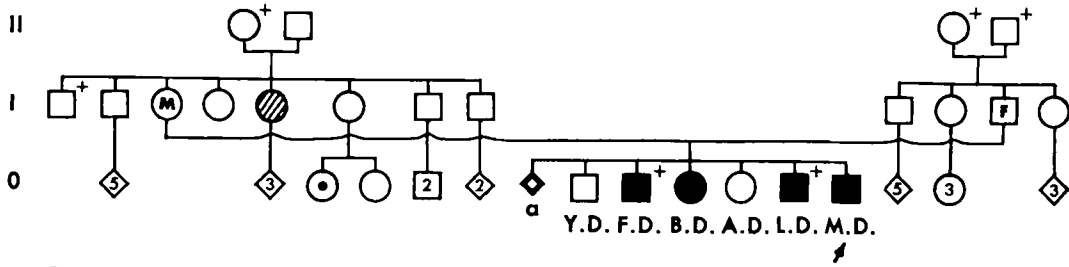
Case 1. M. D., a 6-month-old French Canadian boy, was admitted to the Montreal Children's Hospital on Oct. 9, 1967, for evaluation of abnormal breathing and developmental retardation. He was the last of six children in his sibship, born after a normal pregnancy. Forceps were used during delivery. There was no history of trauma or anoxia at birth; however, his breathing, even at birth, was abnormally rapid. He smiled early. At the age of

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LEGEND:

- Male
- Female
- + Deceased
- ◇ Abortion
- ◇ Sibship of size 3, all normal
- ◐ Absence attacks
- ⊙ Microcephaly
- Dysgenesis of cerebellar vermis

Fig. 1. Pedigree of the D family. M. D. is case 1, L. D. is Case 2, B. D. is Case 3, and F. D. is Case 4.

4 months, he was unable to hold up his head. At 5 months, he showed almost continuous protruding movements of the tongue.

Examination on admission revealed a well-developed boy in no distress. His nutritional status was good. His head circumference was 44 cm. A few telangiectasiae were seen on the cheeks, ears, and eyelids, more on the right side. A few dilated blood vessels were seen on the conjunctivae. His pupils were equal and reacted well to light, and

the fundi were normal. Abnormal, conjugate, irregular, jerky eye movements were frequently seen, and rotatory nystagmus was present. When fixing with his left eye, the right eye deviated upward and laterally. His mouth was usually held open and his tongue protruded rhythmically. His breathing was abnormal, particularly when he was stimulated. Periods of twelve to sixteen seconds of hyperpnea, usually around 120 per minute but increasing up to 168 per minute, alternated with

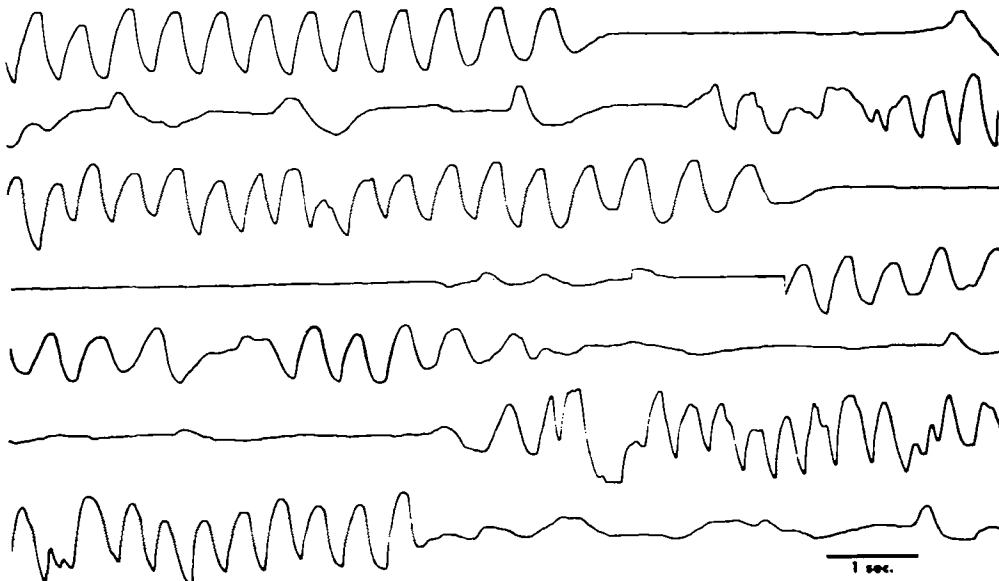


Fig. 2. Case 1. (M. D.) Continuous respirogram tracing recorded with a transducer and a Grass encephalograph at age 9 months. Note hyperpnea and periods of apnea interrupted by single, irregular respiratory excursions. The waxing and waning of amplitude characteristic of Cheyne-Stokes breathing is absent.

periods of apnea lasting five to twelve seconds. Occasional respiratory excursions were noted during the periods of apnea (Fig. 2). During sleep, this respiratory abnormality was absent.

The child moved all extremities well. Tone was diminished in the upper extremities. Deep tendon reflexes were brisk and plantar responses were extensor. His head control was poor. A weak grasping reflex was present. He was not able to take objects voluntarily. He was unable to sit without support. Placement reflex was present but he did not place his feet flat on the table when held standing. Held in ventral suspension, his position was characterized by flexion of the head, arms falling in extension, and hips flexed with knees in extension. He was unable to turn from prone to supine or vice versa.

Laboratory investigations, including hemoglobin, hematocrit, serum calcium, phosphorus, alkaline phosphatase, BUN, creatinine, SGOT, T4, ¹³¹I uptake, serum electrophoresis, urinary amino acid chromatography, chromosome studies, vanilylmandelic acid excretion and urinalysis, were normal. Serum lactate was 19 mg. percent (normal, 4 to 26 mg. percent) and serum pyruvate was 0.75 mg. percent (normal, 1.05 to 1.25 mg. percent). Lactate-pyruvate ratio was 24.

Acid-base values were normal on four occasions (Table 1). Immunoelectrophoresis suggested hypogammaglobulinemia. Examination of the spinal fluid showed no white blood cells. Protein was 18 mg. percent, sugar was 60 mg. percent, and the colloidal gold curve was normal. Cerebrospinal fluid electrophoresis was normal. The electroencephalogram was normal and no electrical correlates of the hyperpnea were seen.

A pneumoencephalogram showed normal lateral ventricles and subarachnoid sulci. The fourth ventricle had a globular appearance; it was enlarged posteriorly at the level of the superior and inferior medullary vela. Inferiorly it communicated with a large cisterna magna through a large vallecule. The occipital horns were displaced forward and upward, suggesting high insertion of the tentorium (Fig. 3). This X-ray examination suggested at least partial agenesis of the vermis. On frontal projections, the fourth ventricle, although enlarged, had a grossly normal configuration.

Case 2. L. D. was born at term, weighing 8 lb. He was the fifth of the six children born to this family. The mother's pregnancy was normal.

TABLE 1

	H+	pCO ₂	Base excess	Standard bicarbonate
Case 1	41	33	-4.1	20.8
	43	34	-4.8	20.3
	38	34	-1.3	22.8
	37	36	-0.1	23.8
Case 3	43	33	-5.9	19.2



Fig. 3. Case 1. (M.D.) Pneumoencephalogram. Brow-down view showing the round dilatation of the roof of the fourth ventricle, the large cisterna magna, the wide communication between the cisterna magna and the fourth ventricle, and the narrow brainstem. The position of the posterior horns is abnormally high, indicating high insertion of the tentorium.

Epidural anesthesia and forceps were used. He was found to have an occipital meningoencephalocele. He breathed spontaneously but did not cry at birth. He was limp and had periods of abnormal, rapid respiration. At the age of 1 month, his meningoencephalocele was removed surgically, and the postoperative course was uneventful. The pathological specimen showed only a lining of glial and ependymal tissue underlying the dermis. The child failed to progress in his development. He was admitted to the Montreal Neurological Hospital on Feb. 1, 1967, at the age of 20 months. He was severely retarded and unable to hold up his head or roll over. The child did not show any interest in his environment; he cried and moved continuously but made no attempts to grasp objects. In supine position, lifted by his shoulders, his head hung back and had to be supported. He showed mild spasticity of his adductors. He had an alternating internal strabismus. The optic disks were normal and occasionally he followed light with his eyes. A pulsating skull defect was present in the occipital region.

The nursing staff commented on the child's abnormally rapid and irregular respiration. As we were not aware of the significance of this respiratory abnormality at the time, no further investigations or observations about it are available for this patient.

Hemoglobin, hematocrit, white blood cell count, and X-rays of the chest and spine were normal. Cerebrospinal fluid protein was 14 mg. percent, with no cells and a normal colloidal gold curve. An electroencephalogram showed diffuse increase in slow activity, with no localization and poor

background maturation. A pneumoencephalogram was attempted but the ventricular system did not fill, therefore a ventriculogram was carried out. The brow-up anteroposterior view showed moderate enlargement of the lateral ventricles. The third ventricle was normal in appearance but slightly enlarged. The lateral sinus grooves were high in position, indicating the presence of a high insertion of the tentorium along the lamboid suture. On the lateral brow-down film, there was filling of the fourth ventricle, which appeared as a large midline cavity in the posterior fossa, and of a smaller cavity close to the foramen magnum, probably representing a small cisterna magna filled with air.

Through various maneuvers, passage of gas from the fourth ventricle to the basal cisterns was obtained. This indicated that there was some degree of communication between the ventricular system and the subarachnoid space, in spite of the nonfilling of the ventricular system at the time of lumbar pneumoencephalography attempted under general anesthesia. The radiological examination suggested complete agenesis of the vermis. The brainstem was fully outlined and appeared underdeveloped. The child made no further progress in development in the following eight months. He died shortly after admission to a custodial institution at the age of 30 months, following an

illness with repeated vomiting. Postmortem examination was not performed.

Case 3. B. D., the next oldest affected, was the third child of the family. She was born at term in 1959, after normal delivery. On the second day of life, she was irritable and noted to have abnormal breathing. Her milestones were markedly delayed. At the age of 6 she was able to stand, and at 8 years of age she was walking without aid but would occasionally stagger.

She was admitted to the Montreal Children's Hospital on Dec. 11, 1967, at the age of 8 years. Her head circumference was 52.5 cm. Her palate was high and vaulted, and her tongue was large and often protruded. The ears were large but not abnormally placed. She had no telangiectasiae. Eye movements were full but incoordinate, with fine, irregular, usually horizontal but occasionally rotatory nystagmus, and spontaneous nystagmus on forward gaze was sometimes seen.

Abnormal involuntary movements were present. These consisted of irregular, mainly unilateral jerks involving the shoulder girdle, accompanied by rotation of the head to the opposite side, blinking, and facial movements. Such myoclonic-like movements were particularly obvious when she was upset. Tone was diminished. Deep tendon reflexes were normal. Plantar responses were in flexion. Her hand movements were incoordinate

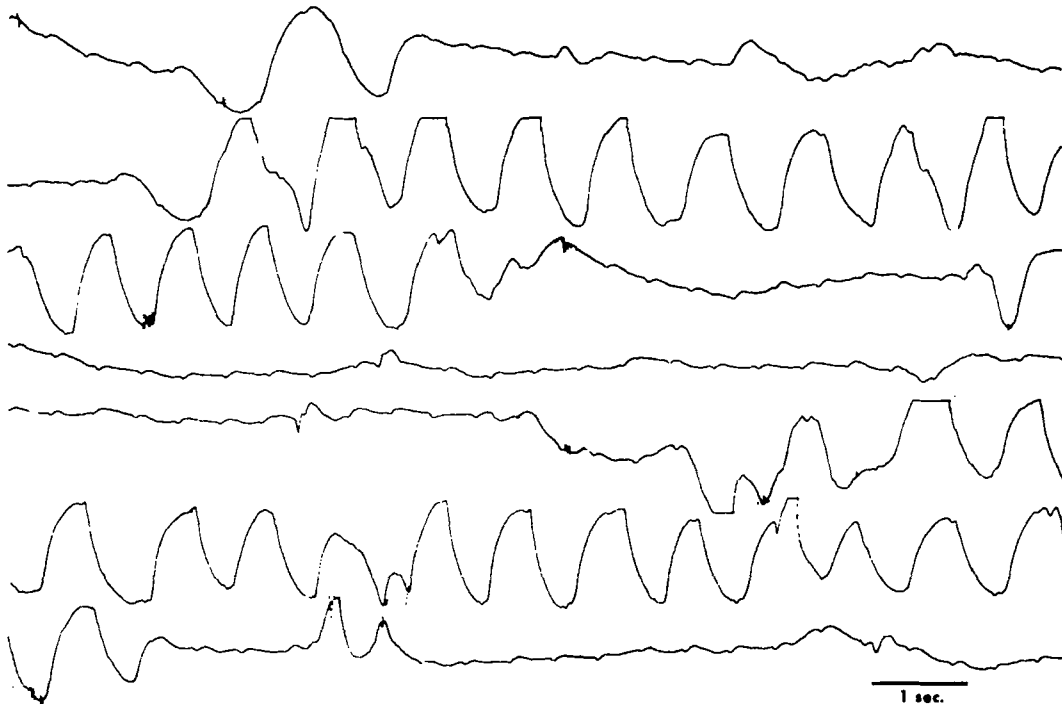


Fig. 4. Case 3. (B. D.) Continuous respirogram tracing recorded with a transducer and a Grass encephalograph at age 8 years. Periods of hyperpnea and apnea with occasional isolated respirations. In comparison with M. D., the respiratory rate is slower but duration of the bursts is similar.

and her gait was ataxic, broad based, and puppet-like.

She showed periods of hyperpnea lasting six to ten seconds, followed by periods of apnea; this was noticeable when she was excited but not when she was crying (Fig. 4). She said single words but did not enunciate clearly, particularly consonants. Tongue movements were sluggish and awkward. She did not appear to use elevation of the tongue for speech. She was unable to control her breathing span or to coordinate her breathing and her voice. When she started a word, either her voice or breathing or both faded out before she was able to complete it. Occasionally, when breathing and voice were coordinated, a loud clear word could be heard.

She was easily frightened but responded well to reassurance. She had a tendency to perseveration. She imitated well and had a good memory for persons and objects.

Laboratory investigations, including hemoglobin, hematocrit, urinalysis, total serum protein, blood sugar, urinary amino acid chromatography, and chromosomal studies, were normal. Examination of the spinal fluid revealed no cells, protein of 11 mg. percent, and sugar of 70 mg. percent. An electroencephalogram showed mild diffuse increase in slow activity without localization or lateralization, and background activity was poorly developed for the age. Acid-base studies showed normal hydrogen ion concentration and moderate hypobasemia combined with mild hypocapnia (Table 1). A lumbar pneumoencephalogram showed moderately enlarged lateral ventricles. There was globular enlargement of the upper fourth ventricle. The cisterna magna and the vallecula appeared large, without any outline of the cerebellar tonsils. High insertion of the tentorium was noted (Fig. 5). This examination suggested partial agenesis of the vermis. Both the upper and the lower portions of the vermis appeared involved; however, some tissue in the middle part seemed to have been preserved.

Case 4. F. D., the second child of this family, was born in July 1957. He was delivered at term, weighing 8 lb. There was no physician in attendance at the time of delivery. He did not breathe for about four minutes after birth. His respiration was then described as very rapid, interrupted by periods of apnea without cyanosis. The impression of the attending physician was that the child was dyspneic. Temperature oscillations between 97° and 101° F. and intermittent diarrhea were noted. The child died in hospital at 3 months of age. An autopsy was performed.

There was no external gross malformation of the cerebral or cerebellar hemispheres, but a moderate degree of dilatation of the ventricular system was observed. The cerebellar vermis was absent. The fourth ventricle, slightly dilated and covered over by a thin membrane, was seen between the cerebellar hemispheres.

Sections of the cerebellar hemisphere, the brain-



Fig. 5. Case 3. (B.D.) Pneumoencephalogram. A midline tomogram shows the round dilatation of the posterior and superior aspect of the fourth ventricle and the presence of gas in the subarachnoid spaces on top of the vermis. The space between this gas and the lumen of the fourth ventricle is much smaller than normal, indicating atrophy of the vermis. Note also the presence of a large cisterna magna, narrow pons, and a high insertion of the tentorium, as indicated by the unusually high position of the occipital horns.

stem at the levels of the inferior medullary olive, the facial nucleus, and the cingulate gyrus and insula were available for review. All were 20 μ thick, paraffin-embedded, and stained with hematoxylin and eosin. Over the cerebellum, the leptomeninges were thin and free of inflammatory infiltrate. The external granular layer was present but of irregular thickness. The molecular layer showed mild astrocytic glial proliferation. Purkinje cells were present in normal number. In the internal granular layer, Golgi cells appeared in normal density, but the granules seemed to be less numerous than usual. At the junction between the internal granular layer and the white matter, there were a few groups of neurons resembling Purkinje cells. These were pale and lacked Nissl substance in their cytoplasm. There was almost no glial proliferation around these heterotopias (Fig. 6). The dentate nucleus showed neuronal loss. The characteristic band-like structure of this nucleus was not always preserved, and the neurons were sometimes grouped in clusters. They were pale and sometimes acidophilic, and the cell borders were often difficult to visualize. Near the dentate in the

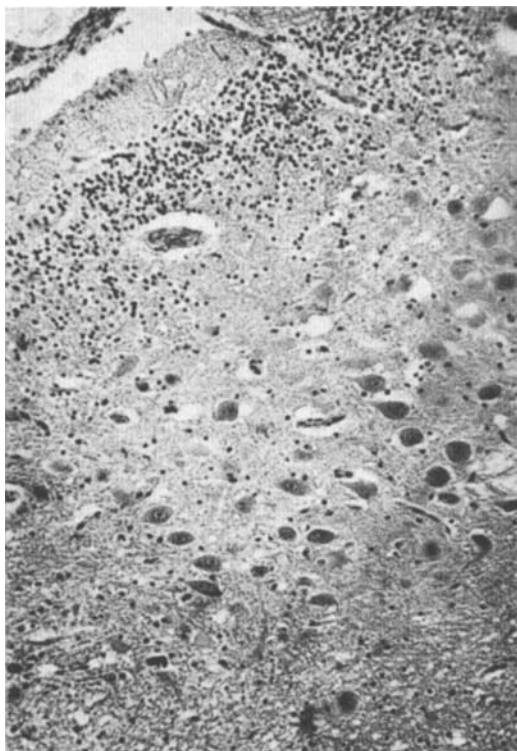


Fig. 6. Case 4. (F.D.) Cerebellar cortex. Note subcortical neuronal heterotopia and diminished density of granular cells. Hematoxylin and eosin, $\times 115$.

axis of the hemispheric white matter, there were clusters of cells with round nuclei, rich in chromatin resembling granular cells. They were usually grouped around a capillary. Between these clusters, large pale neurons, disseminated in an irregular fashion and resembling the neurons described in the subcortical heterotopias, were found. The cortical and subcortical vessels were of normal caliber, their walls were unremarkable, and there was no perivascular infiltrate. Myelination of the white matter appeared normal throughout.

At the level of the inferior olive, the neurons were normal in number. They were pale and distended, with hazy outlines. There was no demyelination of the pyramidal, olivo-cerebellar, or cerebello-olivary tracts. The lateral reticular nucleus, as well as the nuclei of the floor of the fourth ventricle, where seen, appeared normal.

The pons appeared narrowed in its anteroposterior diameter. The ependymal layer of the fourth ventricle was partially destroyed, but this seemed to be artifactual. The facial nuclei and the pontocerebellar, corticospinal, and corticopontine tracts were normal. The cerebral cortex at the level of the cingulate gyrus and the insula showed no anomaly in the architecture of the layers. The neurons showed signs of ischemic necrosis. No in-

flammatory infiltration and no abnormality of the subcortical white matter was seen.

The D family. In addition to the four affected children, there are two other siblings. The oldest boy, now age 11, is entirely normal. The fourth child was diagnosed to have congenital stridor in infancy but has developed normally and, in particular, has never shown periodic hyperpnea.

The father is a dentist who carries out radiological work in his current practice. He has a portwine hemangioma over the right side of his nose and the right upper lid. The mother has a few telangiectasiae on her cheeks, ear lobes, and eyelids.

The family is of French origin and the parents have common ancestors who married in Quebec City in 1656, nine generations ago (Fig. 7). Because of other ancestors with a common name on both sides of the family, some consanguinity may also have occurred five generations ago, at the beginning of the nineteenth century. Because of its remote occurrence, the consanguinity in this family does not appear to be significant in producing the abnormality affecting the siblings described above. Nevertheless, in this instance, dysgenesis of the vermis appears to be inherited as an autosomal recessive.

REVIEW OF THE LITERATURE

Since the first description by Rossi¹ in 1891, agenesis of the vermis has been reported in some 14 publications²⁻¹⁵ which are summarized in Table 2. Single cases have been described and pathological findings have been available in each case. A further sporadic case from our hospital is included in this review.¹⁶ Cases where the diagnosis was based on radiological findings alone (e.g., Vogt and Astwazaturow¹⁷), and where pathological confirmation was missing, have not been included.

Agenesis of the vermis was complete in 4 cases and partial in 12. In the latter, the postero-inferior vermis was missing, whereas the anterosuperior portion was preserved. The reverse was never described, and this is in keeping with current understanding of the embryogenesis of this structure.

Survival after birth varied from two days to seventy-one years, and its duration was probably related to the presence of other associated malformations or disorders such as, for instance, profound retardation. From a review of these cases, there is no reason to believe that the absence of the vermis itself in any way affects the life span of the individual. Some of the patients were of normal intelligence and had no neurological signs. Two of them lived

to the ages of 70 and 71 years, respectively, and one committed suicide at the age of 28. These three patients had no associated malformations. Psychomotor retardation was, however, commonly found in other patients of this group. Hypotonia and incoordination have also been mentioned. The periodic hyperpnea described in our patients has not been noted in any of the reports reviewed.

Familial incidence was suggested by de Haene.¹⁴ Two brothers of his patient had a similar clinical picture and died in childhood. In these two siblings of the proband, the malformation was not confirmed radiologically and autopsy was not performed. Lhermitte's patient also had a sibling who was similarly affected clinically.¹⁰ The parents were consanguineous.

In some cases, maldevelopment of the cerebellar hemispheres and nuclei was found; in others, the olivary nuclei were involved. Disturbed cytoarchitecture of the cerebellar cortex was sometimes found and, in some cases, neuronal heterotopias were present in the

white matter. In some cases, however, agenesis of the vermis was the only malformation of the cerebellum. Associated midline malformations of the central nervous system were found in at least half of the cases described. These included cranioschisis, myelomeningocele, agenesis of the corpus callosum, arhinencephalia, diastematobulbia, and others.

In addition to these cases, agenesis of the vermis may occur in association with considerable dilatation or enlargement of the fourth ventricle. In this second group of cases, one is inclined to suspect that internal hydrocephalus may have been a factor in the fourth ventricle enlargement and may have led to the abnormality of the vermis. In the case of Ostertag,¹⁸ agenesis of the vermis was associated with a bulging cyst-like dilatation of the fourth ventricle communicating with hydromyelia extending to T-6.

In Castrillon's case¹⁹ the inferior vermis was absent, the roof of the fourth ventricle was reduced to a membrane, and the cavity communicated directly with the cisterna magna.

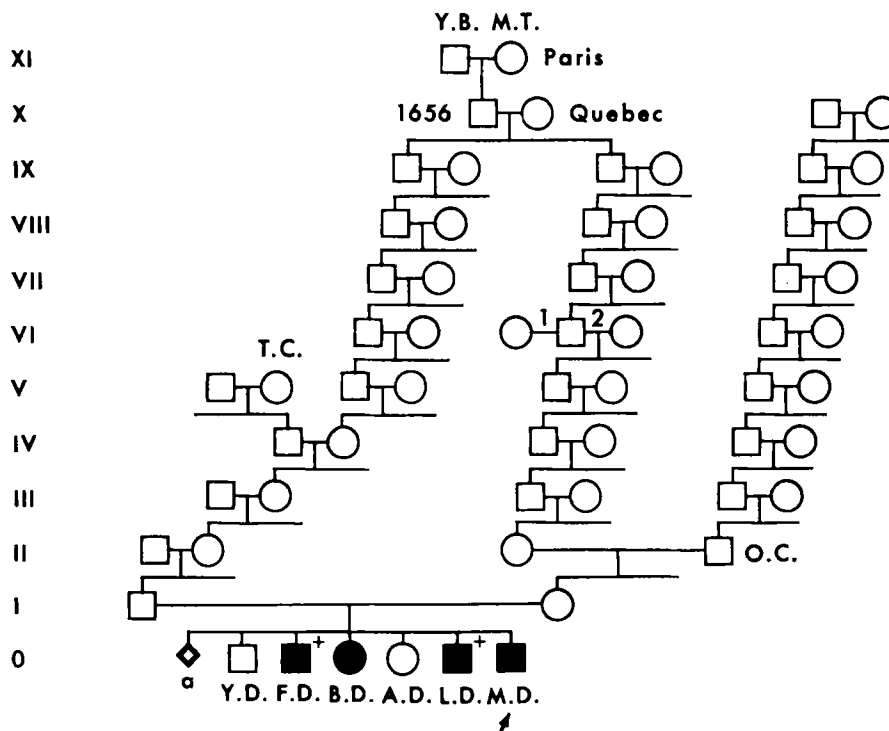


Fig. 7. Family tree of the D family showing common ancestors of parents nine generations ago. The surname C also appears in both the father's and mother's family, suggesting the possibility of additional consanguinity.

TABLE 2
AGENESIS OF THE VERMIS

Authors	Age at death	Clinical data	Cerebellar pathology	Associated CNS malformations
Rossi ¹ 1891	Complete 31 years	Mental defect	Abnormal cytoarchitecture of cerebellar cortex	
Rossi ² 1892	Complete 2 days			Cranioschisis
Gredig ³ 1905	Partial 10 days		Anterosuperior vermis normal	Myelomeningocele
Obersteiner ⁴ 1916	Partial 28 years	Normal intelligence; no neurological signs	Heterotopias in cerebellar white matter; cerebellar hemispheres contiguous; abnormal cytoarchitecture of cerebellar nuclei and superior vermis	
Guttman ⁵ 1929	Partial 5 years	Epilepsy and hemiparesis secondary to postvaccination encephalopathy	Anterosuperior vermis normal	Agenesis of the corpus and septum pellucidum; gyrus in the parieto-occipital region
Lyssenkow ⁶ 1931	Complete 25 years	Unable to walk	Hypoplasia of cerebellar hemispheres; malformation of dentate nuclei; atrophy of the olivary system	
Pines et al. ⁷ 1932	Partial 24 years	Mental defect	Hypoplasia of dentate nuclei with partial atrophy of the left inferior olivary nucleus; upper vermis normal	
Rubin ⁸ et al. ⁹ 1940	Partial 71 years	Normal intelligence, no neurological abnormality until two years before death following stroke	Anterosuperior vermis normal; extreme hypoplasia of cerebellar hemispheres	Arhinencephalia
Sahs ⁹ 1941	Partial 16 years	Head- and body-turning attacks since age 6; nystagmus	Anterosuperior vermis well developed	
Lhermitte et al. ¹⁰ 1944	Partial 20 months	Turricephaly, high-arched palate, mental retardation; one sister showed similar clinical picture; parental consanguinity; possible familial case	Anterosuperior vermis normal	Atrophy of the occipital lobe; numerous large cysts in cerebral hemispheres; absence of posterior part of the cerebellum

Brodal ¹¹ 1945	Partial	11 years	Psychomotor retardation; incoordination of leg movements; hydrocephalus	Anterosuperior vermis normal; abnormal cytoarchitecture of dentate nuclei	Frontal meningocele; absence of the olfactory bulbs and tracts; agenesis of corpus callosum; spina bifida
de Morsier ¹² 1954 Case 1	Partial	2 months		Anterosuperior vermis normal; hypoplasia of the medial and dorsal accessory olivary nuclei	
de Morsier ¹³ 1955	Complete	2 months		Hypoplastic spinocerebellar tracts in spinal cord	
de Haene ¹⁴ 1955	Partial	4½ years	Flaccid, unable to walk; two brothers with identical symptomatology; familial case	Anterosuperior vermis normal; hypoplasia of cerebellar nuclei	
de Morsier et al. ¹⁵ 1962	Partial	70 years	Normal intelligence; no neurological abnormality	Anterosuperior vermis normal; malformation of the cortical structures of the cerebellar hemispheres and dentate nuclei	Absence of septum pellucidum and fornix; hypoplasia of corpus callosum
Eisenring et al. ¹⁶ 1968	Partial	2 months	Klippel-Feil syndrome; cleft palate	Anterosuperior vermis normal	Diastematomal bulbia

Eisenring et al.¹⁶ studied yet another patient with absence of the vermis, who also showed a cyst-like dilatation of the fourth ventricle. In addition, there was aqueduct occlusion leading to considerable proximal hydrocephalus. This case, and the case referred to in Table 2, will be reported in detail later.

Absence of the vermis is also a significant feature of the Dandy-Walker syndrome. In 1914, Dandy and Blackfan²⁰ described a 13-month-old child with congenital aplasia of the vermis associated with a midline cyst and obstruction of the foramen of Magendie. They considered atresia of the foramen of Magendie to be the primary malformation. In 1921, Dandy²¹ discussed this problem further and considered the dilatation of the fourth ventricle and absence of the vermis to be secondary to the internal hydrocephalus.

In 1954 Benda²² reviewed the literature and presented six additional cases. He showed that there is noninvolution of the posterior medullary velum of the fourth ventricle which persists as a thick membrane. There is some permeability of the foramen of Magendie or of the velum, and thus the obstruction is usually not complete. The features of this syndrome are dolichocephaly with thinning of the occipital squama, high insertion of the tentorium and lateral sinuses, internal hydrocephalus with cyst-like dilatation of the fourth ventricle, lateral displacement of the cerebellar hemispheres, and partial or complete aplasia of the vermis.²³ In some cases, however, there is rostral displacement and atrophy of the vermis, as described by d'Agostino and associates²⁴ and by Gibson.²⁵ Such changes seem related to the internal hydrocephalus, in particular to the fourth ventricle enlargement.

In many patients with the Dandy-Walker syndrome, additional midline malformations, such as agenesis of the corpus callosum, have also been described. This would suggest that factors other than internal hydrocephalus developing in utero may be significant in the etiology of this malformation.

Occurrence of the Dandy-Walker syndrome in three siblings was described by Benda²² and in another family by d'Agostino and associates,²⁴ suggesting a recessive mode of inheritance in some cases. Agenesis of the vermis has also been described in animals. Complete

agenesis occurs in the dog²⁶ and, in the goat, it has been reported in association with cyst-like dilatation of the fourth ventricle, suggesting internal hydrocephalus.²⁷ Familial partial agenesis involving the postero-inferior vermis was described in the dog by Dow²⁸ and in "hymutated hydrocephalous" mice by Brodal et al.²⁹ Sporadic occurrence of this malformation in a calf was reported by Lesbre and Forgeot.³⁰ Congenital tremor in pigs is related to cerebellar hypoplasia involving mainly the vermis. This condition was investigated by Done and Harding,³¹ who considered it to be due to viral infection in utero.

DISCUSSION

Two types of vermis defect may be encountered—complete or partial agenesis. In the latter, the defect is in the postero-inferior part, whereas the anterosuperior part may be relatively well developed. These findings may be accounted for by the embryogenesis of the cerebellar vermis. The cerebellum in man develops through bilateral cell proliferation in the dorsal plate of the rhombencephalon. In the early stages, for instance, in the 12-mm. fetus (Hochstetter^{32,33}), the median part of the cerebellar plate is very thin, and, at the 42-mm. stage, the more massive lateral parts meet in the midline. At first they seem to be only contiguous at their ependyma-lined medial surfaces, then the ependyma disappears and there is a fusion of these lateral anlagen. The fusion of the cerebellar crests begins rostrally and the anterior part of the vermis is formed before its posterior part. One may conclude that, in cases of complete agenesis of the vermis, the agent responsible for the malformation intervenes earlier than in cases with partial agenesis. For this reason, also, partial agenesis of the anterosuperior part of the vermis does not appear to occur.

Other midline malformations are often found in association. Indeed, in the four children reported here, the degree of abnormality ranged from partial agenesis in Cases 1 and 3 to complete agenesis in Case 4 and complete agenesis with myelomeningocele formation in Case 2. The findings in this family parallel the range of malformations described in individual cases in the literature.

De Morsier¹³ considered that the defect in

the closure of the posterior lip of the rhombencephalon represents a true rhomboschisis. This explanation would certainly account for the cases where there is no evidence of hydrocephalus or increase in intracranial pressure, but where true agenesis of the vermis occurs. It is, however, possible that a transient increase in ventricular pressure may occur in utero and lead to the closure defect. This could also account for the high insertion of the tentorium and the lateral sinuses in cases such as the ones reported here. In cases with internal hydrocephalus of the Dandy-Walker syndrome, the increase in intraventricular pressure leading to the cyst-like dilatation of the fourth ventricle appears to be a significant factor which may cause atrophy and dysplasia of the vermis.

The neuronal heterotopias found in one of our patients, as well as in other cases, are not specific and may be observed whenever there is interference with the normal migration of neurons, as shown by Brun³⁴ in 1916. Such heterotopias have also been described by Norman³⁵ to occur around the dentate nuclei and in subcortical white matter in Trisomy 13-15.

From the review of the literature, it appears that agenesis of the vermis in itself is not necessarily associated with gross neurological abnormality and that it is compatible with normal intelligence and survival. In our cases, it is associated with mental retardation, hypotonia, or ataxia. Furthermore, the retardation, periodic hyperpnea, abnormality of eye movements, and ataxia may also be related to diffuse cerebral involvement, in addition to the cerebellar and brainstem dysfunction. Radiologically, however, the agenesis of the vermis is the most striking finding common to our cases. This is also true when the brain is examined macroscopically. The brainstem appeared underdeveloped as well, judging by the contrast studies, but the few brainstem sections which were available to us showed no abnormality. The material was not adequate for complete study of this area.

The respiratory abnormality consists of periods of hyperpnea alternating with periods of apnea, interrupted by occasional single inspirations. The disorder of respiration was apparent shortly after birth, intensified when the child was stimulated, and tended to improve with age. In Case 3, it was still present



Fig. 8. H. E., age 9 months, demonstrating low-set ears, flat nose bridge, pectus excavatum, flexion contracture of the wrists, and polydactyly.

when the child was 8 years old, but only when she was upset or had been crying. The rate of hyperpnea was slower and the duration of the periods of overbreathing was shorter in comparison with the respiratory pattern of Case 1 at age 6 months.

This type of respiration resembles what has been described by Plum and Posner³⁶ as cluster breathing, with occasional apneustic breaths. A lesion high in the medulla or low in the pons produces this type of respiratory abnormality, according to these authors. The respiration also resembles Biot's breathing, as

reproduced by Hoff and Breckenridge³⁷ by section of the pons in animals, a pattern very similar to the cluster breathing described by Plum and Posner.³⁶ The waxing and waning of Cheyne-Stokes respiration was not observed. The serum lactate level and lactate:pyruvate ratios were normal. There was thus no evidence for a metabolic origin of the respiratory disorder. It is likely that the obvious malformation of the roof of the fourth ventricle, e.g., agenesis of the vermis, is associated with further abnormality of the structures of the floor of the fourth ventricle at pontine and medullary levels.

The abnormality of eye movements noted in two of our patients is probably also related to pontine or cerebellar dysfunction, as are the hypotonia and ataxia. The mental retardation suggests additional dysfunction of the cerebral hemispheres. Episodic hyperpnea, abnormal eye movements, psychomotor retardation, and ataxia associated with agenesis of the vermis, which may be demonstrated radiologically, represent a characteristic syndrome which may be recognized clinically. Some months after the study of this family, we had the opportunity to investigate, through the courtesy of Dr. George Karpati, a 9-month-old Jewish infant (H.E.) admitted to the Montreal

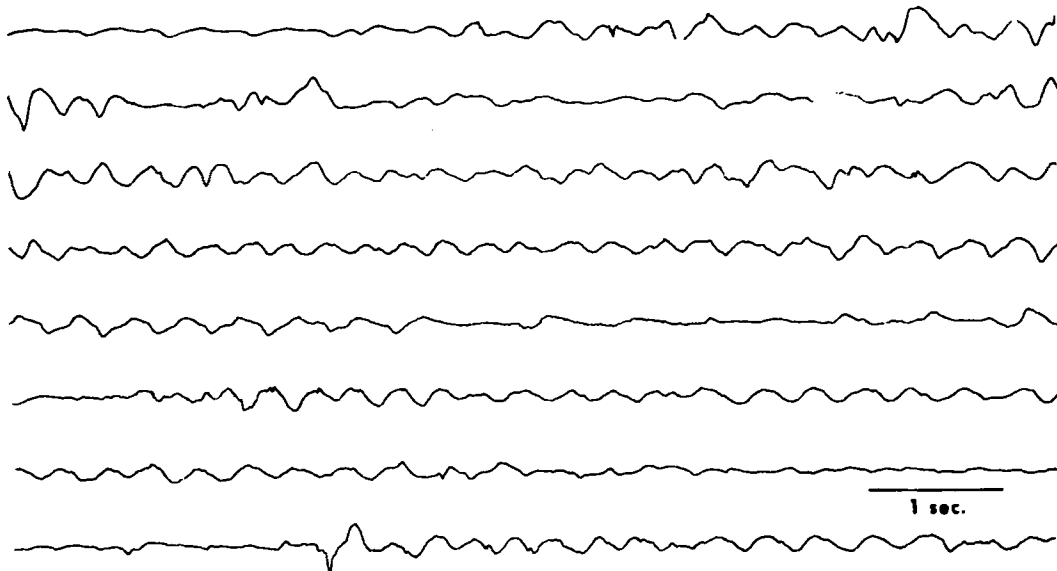


Fig. 9. (H.E.) Continuous respirogram tracing recorded with a transducer and a Grass encephalograph at age 9 months, showing periods of hyperpnea and apnea. During the latter, occasional isolated or slow, shallow respirations were demonstrated.



Fig. 10. (H. E.) Pneumoencephalogram showing an unusually large fourth ventricle and cisterna magna. The fourth ventricle posteriorly shows a round dilatation and communicates widely with the cisterna magna. It is very long, due partly to the high insertion of the tentorium. Note the high position of the posterior horns of the lateral ventricles. On the brow-up view, the gas within the fourth ventricle and pontine cistern outlines a rather narrow pons and medulla oblongata.

Neurological Hospital because of psychomotor retardation and hypotonia. The child had several congenital malformations including low-set ears, high-arched palate, laryngomalacia, polydactylia, micrognathia, micrencephaly, and flexion contractions of the wrists (Fig. 8). Because he also exhibited episodic hyperpnea (Fig. 9), agenesis of the vermis was suspected and proved by pneumoencephalography (Fig. 10). Like the affected members of the D family, this child had a high insertion of the tentorium and the lateral sinuses, as well as upward displacement of the posterior horns of the lateral ventricle. This patient appears to represent yet another sporadic example of the familial syndrome discussed here.

From the genetic standpoint, agenesis of the vermis may be due to an autosomal recessive

gene with pleotropic manifestations or variable expressivity.

SUMMARY

Four siblings in a family with remote consanguinity presented with episodic hyperpnea alternating with apnea, abnormal eye movements, ataxia, and psychomotor retardation. Two of these children had agenesis of the postero-inferior vermis, one had complete agenesis of the vermis, demonstrated at post-mortem, and one had complete agenesis of the vermis with an occipital meningocele.

Awareness of this characteristic syndrome, particularly of the respiratory pattern, led to diagnosis of another sporadic case with the same cerebellar malformation. Review of the literature on agenesis of the vermis led to a comprehensive classification of the malformation based on the embryogenesis. It is related to other midline malformations, which frequently coexist, and to the Dandy-Walker syndrome. Agenesis of the vermis may be asymptomatic in itself. In the syndrome described here, it is probably associated with malformation of pontine and medullary structures, leading to the respiratory abnormality resembling Biot's respiration or Plum's cluster breathing. More widespread cerebral involvement is also suggested by the clinical symptomatology.

The syndrome seems to be inherited as an autosomal recessive with variable expressivity. Its recognition may lead to identification of yet another group of congenital birth defects associated with mental retardation.

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