# DEVELOPMENTAL ARREST OF THE CEREBELLUM

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## SYNOPSIS

**a case of developmental arrest of the cerebellum associated with multiple congenital anomalies in a female neonate has been described. The absence of fissures in the dorsolateral aspects of the rudimentary cerebellum and the consistent lack of an external granular layer in the cerebellar cortex suggest that the arrested development occurred prior to the 10th week of gestation. Accompanying the cerebellar malformation were severe changes in or a complete absence of the brain stem nuclei that are known to be connected with the cerebellum.**

## INTRODUCTION

Failure of development of extensive regions of the cerebellum is a relatively rare condition, although ever since Combettes (1831) described a case of complete absence of the cerebellum in an adolescent imbecile, a number of other studies has been made (see Dow and Moruzzi, 1958). The interest that these cases hold is not so much their rarity as the light that they may throw on early cerebellar development and on the correlated changes in the brain stem nuclei that are known to be structurally connected with the cerebellum. Since no such cases appear to have been reported in the local literature (Gwee and Ransome, 1973) it was thought of interest to make a study of an available specimen of cerebellar malformation in which the cerebellum formed a mere knob located astride the fourth ventricle.

## CASE REPORT

This Chinese female neonate was delivered at 41 weeks gestation and survived 28 minutes. Post-mortem showed a small baby weighing 1.2 kg with a crown-heel length of 40 cm and a crown-rump length of 27 cm. The head and chest circumference was 23 cm. There were multiple congenital malformations that included endocardial fibroelastosis of the left

atrium, bilateral congenital cystic adenomatoid malformation of the lung, microphthalmia, displasic double uterus, talipes equinovarus and bilateral tubular ectasia of the kidney.

The brain was small and weighed 93 g. The cerebal hemispheres showed the relatively simple convolutional pattern of 24 weeks gestation (Fig. 1). There was no hydrocephalus. Except for the trigeminal nerve (Fig. 2) none of the external attachments of the other cranial nerves appeared to have been preserved. In the midbrain the tectum was represented by two pairs of shallow mounds. The hindbrain was remarkable for the smallness of the cerebellum which bore no fissures on its dorsal and lateral aspects (Fig. 2). There were no recognizable cerebellar lobes. There was no trace, grossly, of the cerebellar peduncles. On the ventral aspect, the pons and inferior olivary tubercles were entirely absent. The external configuration of the spinal cord was relatively normal with recognizable cervical and lumbar enlargements.

## MATERIALS AND METHODS

For histological study the brain and spinal cord were fixed in 10 per cent aqueous formalin. The brainstem with the cerebellum was detached from the forebrain and divided into two blocks, one consisting of midbrain and the other of hindbrain and cerebellum. These together with portions of the cervical and thoracic cord were embedded in celloidin and sectioned in the coronal plane at 30 um thickness. Every 10th section was stained by Nissl's method with cresylfast violet and the adjacent section by Woelcke's method for myelinated axons (Luna, 1968). An age-matched control specimen, stained in similar ways, was available for comparison. The inferior olivary nuclei in the Nissl stained medulla oblongata of the malformed brain were drawn serially with a precision micro-projector.

## RESULTS

### Medulla oblongata

In Nissl stained sections the main inferior olivary nuclei appeared as unconvoluted and interrupted dorsal and ventral laminae that were open at their lateral ends (Fig. 3). The nuclei extended rostrally from the level of the lateral reticular nucleus to the point caudally where the hypoglossal nucleus terminated (Fig. 4). The medial accessory olivary nuclei were evident at the mid-olivary levels. The neurons were of the multipolar type with prominent nuclei and nucleoli and their cytoplasm contained moderately stained medium sized Nissl granules. The arcuate nuclei normally associated with the medullary pyramids were entirely absent. The dorsal column nuclei were relatively undifferentiated but the nuclei of the trigeminal and hypoglossal nerves were readily identified.

In Woelcke preparations no myelinated axons were observed in the inferior olivary nuclei but neuroglia stained deeply. The medullary pyramids were unmyelinated and unstained. On the other hand, the gracile and cuneate tracts, though unmyelinated, stained deeply for neuroglia. The inferior cerebellar peduncles were markedly reduced and were unmyelinated and unstained.

### Pons

The basis pontis was attenuated and in Nissl preparations the pontine nuclei were seen as small scattered groups of immature neurons containing scanty and pale staining cytoplasm situated mostly in the lateral portions of the pons (Fig. 7). In contrast, the vestibular, the facial and the trigeminal nuclei and the nucleus locus coeruleus were readily identified (Figs. 7, 8). In Woelcke preparations the base of the pons was unmyelinated and unstained. On the other hand, in the tegmentum the trapezoid body was myelinated and readily identified. There was some staining of neuroglia in the reduced middle cerebellar peduncles.

### Cerebellum

The dorsolateral surfaces of the cerebellum were relatively smooth (Figs. 5 and 7) but in the caudal portion of the ventral vermis some degree of fissuration was evident. Where it could be recognized the cerebellar cortex in Nissl preparations consisted uniformly of the following zones: deep to the pia and external limiting membrane was a marginal zone devoid of neurons; deep to the marginal zone was a zone of fusiform neurons of several cell thickness in which the long axes of the neurons were orientated perpendicular to the cortical surface; deep to the zone of fusiform neurons was a zone of small neurons of variable thickness and density with long axes of the neurons orientated randomly (Fig. 8). Elsewhere, particularly in the dorsal "vermis" the cortical pattern was bizarre (Fig. 5). In such regions cell nests with embryonic matrix were commonly found. Cell nests with embryonic matrix were also a feature of the roof nuclei which contained multipolar neurons of variable sizes with deeply

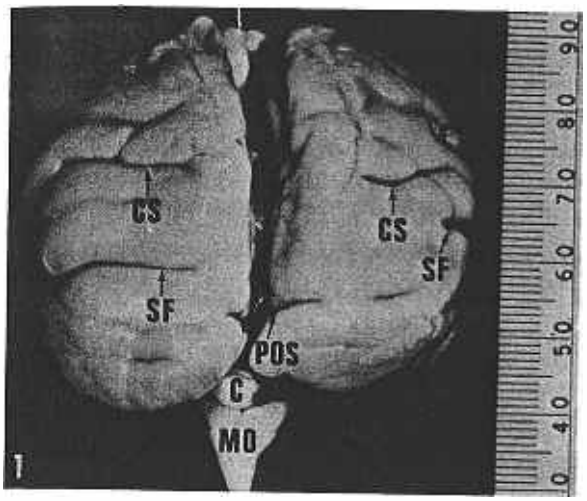


Fig. 1. Dorsal view of the whole brain. Observe the relatively simple configuration of the cerebral hemispheres and the positions of the major fissures. The dorsal tip of the cerebellum can just be made out. C = cerebellum; CS = central sulcus; MO = medulla oblongata; POS = parieto-occipital sulcus; SF = Sylvian fissure. Scale in mm.

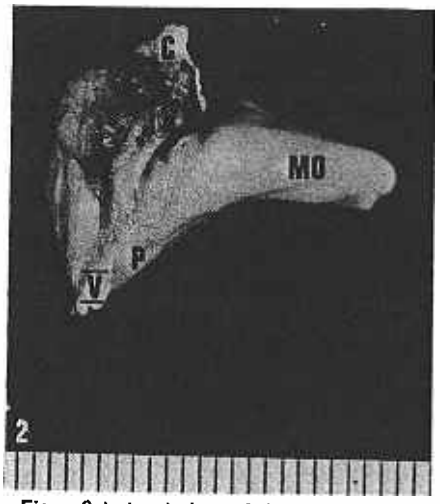


Fig. 2. Lateral view of the pons, medulla and cerebellum. The attenuated basis pontis as well as the small dimensions of the cerebellum can easily be appreciated. C = cerebellum; MO = medulla oblongata; P = pons; V = root of trigeminal nerve. Scale in mm.

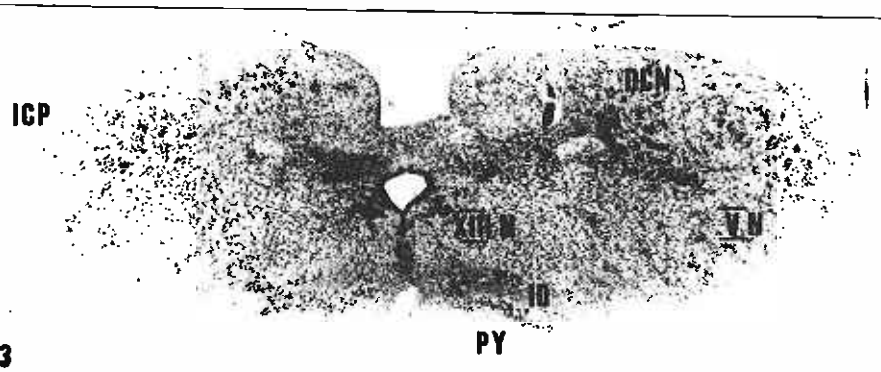


Fig. 3. Transverse section through the medulla oblongata at the mid-inferior olivary level. Note the absence of the arcuate nuclei in the region of the pyramids, and the attenuated inferior cerebellar peduncles. DCN = dorsal column nuclei; ICP = inferior cerebellar peduncle; IO = inferior olivary nucleus; PY = pyramid; XII N = hypoglossal nucleus. Nissl technique, x 15.

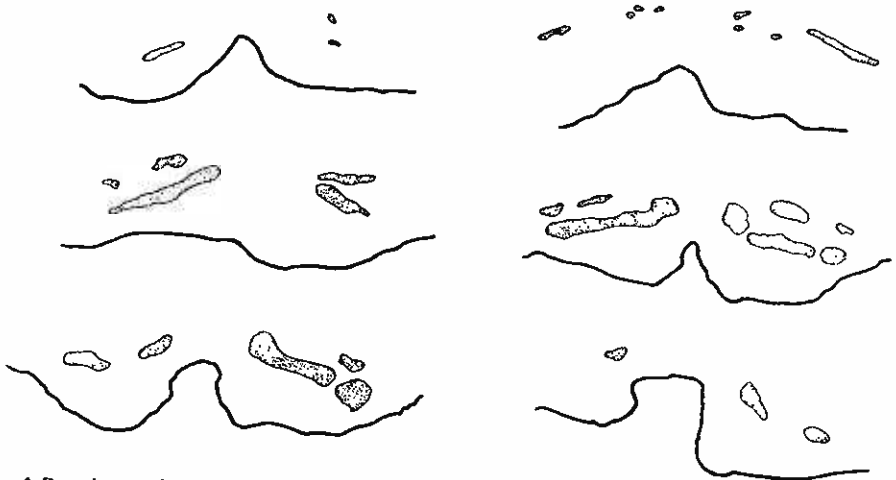


Fig. 4. Drawings of representative sequential transverse sections of the inferior olivary nuclear complex, proceeding horizontally and vertically from the most rostral level in the upper left to the most caudal level in the lower right. Left olive lies on viewer's right.

stained coarse Nissl granules (Figs. 5, 6). The dentate nuclei were absent. Woelcke preparations of the cerebelum revealed no myelinated axons but neuroglia stained throughout and markedly so in the caudal part of the ventral vermis.

### Midbrain

In Nissl preparations, the colliculi, the nuclei of the trochlear and oculomotor nerves and the substantia nigra were readily identified (Fig. 10). In contrast, the red nuclei were conspicuous by their absence at the superior collicular level. Myelinated axons were well demonstrated in the medial and lateral lemnisci in the Woelcke material (Fig. 9). There was moderate staining of neuroglia in the inferior colliculi but the superior cerebellar peduncles were absent.

### Spinal cord

The Nissl preparations of the spinal cord demonstrated the cell groups in the grey matter well and in the thoracic segments Clarke's column was readily identified. In the Woelcke material, none of the longitudinal nerve tracts showed any myelinated axons although the dorsal columns stained markedly for neuroglia. On the other hand, the dorsal and ventral roots were heavily myelinated.

## DISCUSSION

Several features of the present case deserve comment. The external configuration of the malformed cerebellum was of the simplest. The dorsal and lateral aspects lacked fissures. Only in the caudal part of ventral vermis was fissuration observed. During normal development, by the 10th-12th week, fissuration has occurred in the vermis and the process then extends to the cerebellar hemispheres (Langelaan, 1919). One this basis it may be construed that the arrested development in the malformed cerebellum would have occurred prior to this period.

In most previous accounts of agenesis of the cerebellum where remnants of the cerebellar cortex could be identified, these had the expected histological structure of the mature brain (e.g. Anton and Zingerle, 1914; Rubinstein and Freeman, 1940; Stewart, 1956). However, Warrington and Monsarrat (1902) described an extremely rudimentary cerebellum in a 6 week infant in which there was absence of histological development except in the lateral parts where in a few areas a cerebellar cortex with granular, molecular and Purkinje cell layers could be recognized. Unfortunately in this case which bears a close resemblance with the presently described one, the cerebellar cortex was not illustrated histologically and it is not clear if the granular layer described was the external or internal granular layer of the infantile cerebellar cortex (Raaf and Kernohan, 1944). Prior to the 10th week the foetal cerebellar cortex consists of a ventricular zone, an intermediate zone and a nuclear free marginal zone next to the pia and the external limiting membrane (Ravic and Sidman, 1970). The external granular layer first appears at about the 11th week as a thin layer of cells deep to the external surface of the cerebellum but outside the marginal zone. At about the same time a broad irregular condensation of cells forms between the inner limit of the marginal zone and the outer part of the intermediate zone. It is from this irregular band of cells that the Purkinje neurons are derived (Ravic and Sidman, 1970). In the cerebellar cortex of the malformed brain described presently, there was no evidence of any external granular layer. However, at the inner boundary of the marginal zone was a band of neurons that was distinctly separated and different from the neurons situated deep to them. The histological structure suggests that the developmental arrest occurred prior to the migration of neurons to form the external granular layer, i.e. between 9-11 weeks. The band of neurons along the inner border of the marginal zone would correspond in position to the Purkinje zone of the normal developing cortex.

The primordia of the cerebellar roof nuclei are clearly recognizable by the 13th week (Ravic and Sidman, 1970). The presence of cell nests and embryonic matrix in these nuclei is characteristic of foetal and neonatal cerebellar cortices (Friede, 1973). The preservation of the roof nuclei in the malformed cerebellum suggests a viable reciprocal relationship between them.

The bilateral defect in the inferior olivary nuclei and the severe depletion of neurons in the nuclei pontis in the present case are remarkable in view of the early arrest of the development of the cerebellar cortex (before the 10th week) based on morphological and histological grounds. It has been suggested that if the process that gave rise to a cerebellar malformation occurred early and prior to the differentiation of the inferior olivary nuclei, then there was a constant sparing of this structure (Brodal, 1946). The anlagèn of the inferior olivary and the pontine nuclei are recognizable as early as the 8th week (Essick, 1912) although their differentiation is effected at 20 weeks and later (Dodgson, 1962).

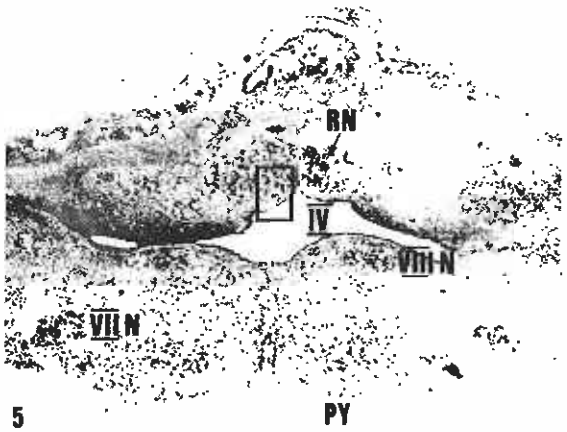


Fig. 5. Transverse section of cerebellum and medulla at the level of the roof nuclei. PY = pyramid; RN = roof nucleus; IV = fourth ventricle; VII N = facial nucleus; VIII N = medial vestibular nucleus. Nissl technique, x 10.5.

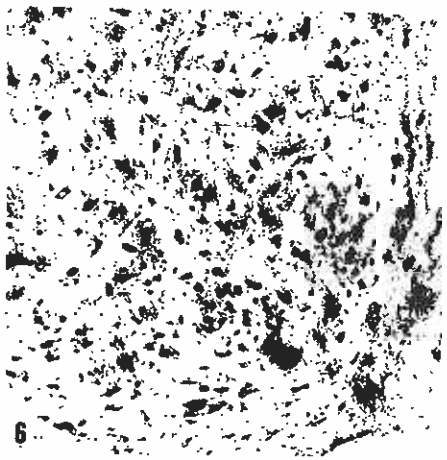


Fig. 6. Higher power photograph of the enclosed area in Fig. 5 to show the multipolar character of the neurons in the roof nuclei. Nissal technique, x 95.

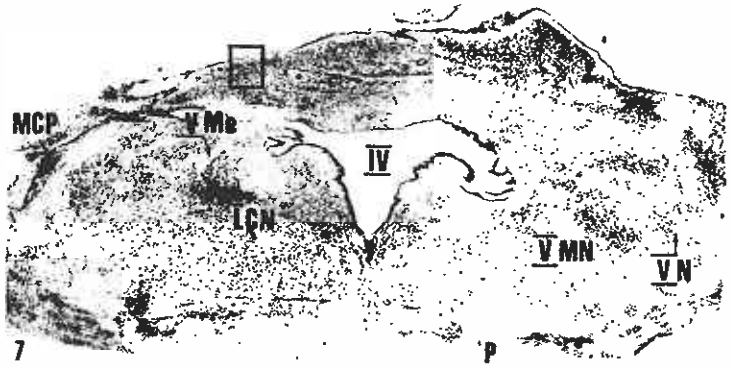


Fig. 7. Transverse section of cerebellum and pons at the level of the motor nucleus of the trigeminal nerve. LCN = Nucleus locus caeruleus; MCP = middle cerebellar peduncle; P = pons; IV = fourth ventricle; V Me = Mesencephalic nucleus of the trigeminal tract; V MN = Motor nucleus of the trigeminal nerve; VN = Main sensory nucleus of trigeminal nerve. Nissl technique, x 10.

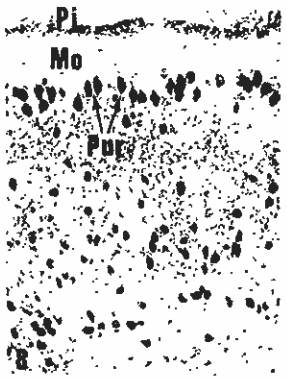


Fig. 8. Higher power photograph of the enclosed area in Fig. 7 to show the histological structure of the cerebellar cortex. Note the absence of an external granular layer. Mo = Marginal zone; Pi = Pia mater and external limiting membrane; Pur = Presumptive Purkinje neurons. Nissl technique, x 95.


Fig. 10. Transverse section of the midbrain at the superior colliculus level. Note the absence of the red nuclei (arrows). Aq = Cerebral aqueduct; BP = Basis peduncle; SC = superior colliculus; SN = Substantia nigra; III N = Oculomotor motor nuclear complex. Nissl technique, x 9.5.

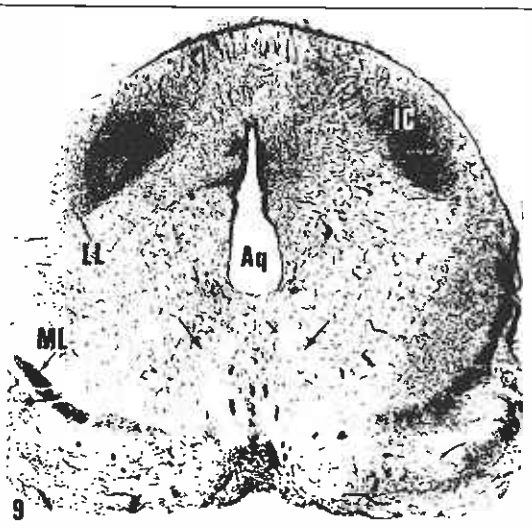


Fig. 9. Transverse section of the midbrain at the inferior colliculus level. Note the absence of the superior cerebellar peduncles (arrows). Aq = Cerebral aqueduct; IC = Inferior colliculus; LL = Lateral lemniscus; ML = Medial lemniscus. Woelcke technique, x 9.

The nature of the change of the neurons in these nuclei could conceivably be of a retrograde neuronal degeneration variety in the case of an extensive cerebellar maldevelopment due to pressure from a ventriculocoele that had arisen after the 20th week (Evard and Caviness, Jr., 1974) or in lesions in the fully formed cerebellum (Holmes and Stewart, 1908). A more likely explanation for the nuclear changes in the present case would be that the factors that were responsible for the arrested development of the cerebellum were also operative in them. The absence of the dentate, the red and arcuate nuclei may also be interpreted in this wise. The preservation of the vestibular nuclei and Clarke's column suggest that these structures formed a viable relationship with the malformed cerebellum.

The degree of myelination of the developing central nervous system has been taken as a measure of its maturity. The process begins in the upper cervical region of the spinal cord and proceeds from there in a cranial and caudal direction. Prior to the laying down of myelin there is a pre-myelin stage of proliferation of undifferentiated glial cells preceding the differentiation of oligodendroglia (Poser, 1968). On the basis of the reported accounts of the time of appearance of myelinated axons in the central nervous system (e.g. Keene and Hewer, 1931; Dodgson, 1962; Minckler and Boyd, 1968), the brain stem and spinal cord of the present case displayed many features of retarded myelination. To cite one example, the gracile and cuneate tracts which in normal development begin to be myelinated at 24 weeks showed only gliosis in the specimen studied.

The study of a solitary case, such as the present one, can hardly hope to throw any light on the aetiology. Malformation of the developing central nervous system may be genetically determined or they may be due to environmental causes. In the latter, three factors have to be taken into account. Firstly, the time of its occurrence or the temporal specificity. Secondly, the nature of the noxious agent. Thirdly, the genetic background of the organism (Dodgson, 1962; Towbin, 1971).

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