Anterior horn cell disease associated with pontocerebellar hypoplasia in infants

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SUMMARY Three sibs presented with an identical clinical picture of severe mental retardation, cortical blindness, and extensive peripheral paralysis of lower motor neurone type, and died before one year of age. In the one necropsied case, spinal cord lesions, indistinguishable from those of Werdnig-Hoffmann disease, were associated with extreme hypoplasia and atrophy of the cerebellum, and with atrophy of the ventral part of the pons. No prominent abnormalities were found in the nerves sampled despite gross reduction of motor and sensory conduction velocities in two infants. It is proposed that this familial disorder is distinct from Werdnig-Hoffmann disease, and represents a further subtype in the heterogeneous group of the infantile muscular atrophies.

Supraspinal and suprabulbar lesions have long been recognised in Werdnig-Hoffmann disease (Brandt, 1950; Radermecker, 1951, 1953; Thieffry *et al.*, 1955; Miranda-Nieves and Campos-Castello, 1970). In a few cases, gross abnormalities of the cerebellum have been reported in association with the characteristic changes of infantile spinal amyotrophy (Norman, 1961; Norman and Kay, 1965; Weinberg and Kirkpatrick, 1975). These were considered atypical cases of Werdnig-Hoffmann disease, although the clinical picture was quite unusual with mental retardation and spasticity as prominent features. In this paper, we report a familial case of associated cerebellar hypoplasia and spinal anterior horn cell disease, and discuss the nosological situation of this, and of previously reported similar cases, with reference to the more classical spinal amyotrophies of infancy and childhood, and to other forms of cerebellar hypoplasia and atrophy.

Case reports

Case 1, LV, a girl, the third child of healthy unrelated parents, was born at term in breech presentation, weighing 2325 g. The Apgar score at one minute was 2, on account of severe hypotonia and poor respiratory movement. On admission at 10 days, multiple joint contractures were evident. The lower limbs were

fixed in extension and rotated 90° on the truncal axis. The head was turned laterally to the opposite direction (Fig. 1). Hip abduction was limited to 20° on both sides. The thumbs and third fingers were permanently flexed. A severe degree of diffuse muscular atrophy was evident with very little spontaneous movement. Tendon reflexes could not be found. Bilateral Babinski and Rossolimo signs, however, were elicited. Intercostal muscles were paralysed, the diaphragm appearing normal. There was marked retrognathism, and the tongue was atrophic and fasciculating. Suction was weak, and no gag reflex was found. A right facial palsy was evident. The cry was bitonal on account of a partial abductor paralysis as shown by laryngoscopy. Ocular jerks of a large amplitude were noted, and the child did not follow objects. Photomotor responses were preserved. The child had no interest in her surroundings, and mental development remained quite limited until her death, at age 3 months, from respiratory insufficiency. Cranial circumference was 36.5 cm at 6 weeks (–1.8 SD).

SPECIAL INVESTIGATIONS

The CSF, fundi, and electroretinogram were normal. Visual evoked potentials were of an immature type with delayed positive deflection. Pneumoencephalography revealed slight enlargement of the lateral ventricles with large cisterna magna and prepontine cisterna. The brainstem appeared abnormally thin. Electromyography of the quadriceps, deltoids and tibialis anterior muscles displayed intermediate tracings with high amplitude potentials, interpreted

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Fig. 1 Abnormal position of lower limbs, permanent flexion of thumbs, and retrognathism.

as typically neurogenic. Motor nerve conduction velocity (right peroneal nerve) was 8 m/s. Sensory nerve conduction velocity was 15 m/s (median nerve) and 16 m/s (sural nerve).

POSTMORTEM EXAMINATION

Except for terminal bronchopneumonia, significant abnormalities were limited to the nervous system. The material received for examination consisted of the brain, the spinal cord, and a sample of the crural nerve, fixed in formol saline. Paraffin and celloidin-embedded sections of the central nervous system were stained with haematoxylin-eosin, Nissl's tech-

nique for neurones, Loyez's technique for myelin, and Holzer's technique for fibrillary glia. Serial sections of pons and medulla were available. The femoral nerve was stained by haematoxylin-eosin and Masson trichrome. Frozen sections were stained by Oil Red O and Sudan Black.

After fixation, the brain weighed 475 g (mean for age 516 g). The cerebellum and brain stem were extremely small (Fig. 2), weighing together 8 g. The cerebellar hemispheres were tiny and flattened, the vermis being relatively better preserved. Due to the minute size of the cerebellum, however, it was not possible to make out the various parts. The size of the brain stem was about half that of a control of the same age. The spinal cord was grossly normal. The anterior nerve roots, however, were abnormally thin. On coronal section the lateral ventricles were slightly dilated. Horizontal sections through the brain stem showed that the ventral portions of the pons and medulla were more affected than the dorsal parts (Fig. 3).

Microscopically, the most remarkable lesions were found in the cerebellum, pons, medulla oblongata, and spinal cord. Cerebellar hypoplasia was especially

Fig. 2 Extreme hypoplasia of cerebellum and brain stem.

Fig. 3 Pons. Horizontal section. Luxol fast blue. Marked atrophy of pes pontis.

marked in the hemispheres which consisted of only a few broad and simplified folia (Figs. 4 and 5). The granule cell and Purkinje cell layers were extremely thin, having entirely disappeared in some places. The vermis was more easily identifiable; it contained an outer granular layer. The dentate nuclei were hardly distinct. They were poorly convoluted, the neurones forming rounded clusters in several places. The white matter was markedly gliotic, and its myelination was somewhat poor. The pes pontis was severely atrophic. Only a few neurones remained in the pontine nuclei, and gliosis was marked. Gliosis was also severe in the middle cerebellar peduncles with only a few myelin sheaths. In the medulla, the inferior olives were extremely atrophic and poorly convoluted. Only a few neurones were present, some of them with a ballooned cytoplasm and eccentric nucleus. The nucleus ambiguus was not identifiable. Loss of cells was evident

in the XIIth nerve nucleus which contained some swollen and chromatolytic neurones in axonal reaction. In the spinal cord, mostly in its lumbar portion, the number of anterior horn cells was reduced, as compared with a control of the same age (Fig. 6). Several neurones were small and retracted. Others displayed eccentric nuclei and ballooned, chromatolytic cytoplasm (Fig. 7). Myelin sheaths in the anterior nerve roots were sparse and thin, and the number of axons was reduced. No abnormalities were found in the thalami, cerebral peduncles, substantia nigra, red nuclei, and nuclei of the IIIrd, IVth, VIth, and VIIth nerves. The cortex was not affected. Myelination of the cerebral hemispheres, pyramidal tracts, and tracts of the spinal cord appeared normal as did the posterior nerve roots. In the lenticular nuclei, a few chromatolytic cells were seen. In the femoral nerve, the number of myelin sheaths seemed

Fig. 4 Horizontal section through cerebellum. Luxol fast blue. Extreme atrophy of hemispheres with poorly convoluted folia. Less marked involvement of vermis.

Fig. 5 Cerebellar cortex. Nissl ($\times 90$). Alteration of internal granular cells layer which disappears totally in some places.

to be diminished with several empty endoneurial sheaths. This finding was deemed compatible with Wallerian degeneration but the technique used was insufficient for complete assessment.

Case 2, EV, a boy, the older brother of case 1, was the second child of the family. He was born at term weighing 3140 g. From birth, he was hypotonic, breathing movements were poor, and the cry was

weak. Limb mobility was extremely limited. The facies was expressionless with retrognathism, and swallowing was impaired. On admission at age 1 month, there was diffuse muscular atrophy and paralysis involving also the intercostal muscles. His cry was very much like his sister's, and similar joint contractures were noted. Tendon reflexes were brisk. The plantar responses were extensor, and there were definite bilateral Rossolimo signs. Cranial circum-

(a)

(b)

Fig. 6 Spinal cord: anterior horn. Nissl ($\times 35$) (a) neuronal rarefaction as compared to (b) spinal cord: anterior horn. Nissl ($\times 35$) control of same age.

ference was 35.5 cm (-1.2 SD). When admitted again at 4 months of age, limb paralysis was complete, with severe muscular atrophy predominating proximally. Tendon jerks were no longer obtainable in the lower limbs but still present in the arms. Pain sensitivity was grossly preserved. Mental retardation was now evident as were coarse ocular jerks. There was facial diplegia. Cranial circumference was 39.3 cm (-1.9 SD). He died at 7½ months. There was no necropsy examination.

SPECIAL INVESTIGATIONS

CSF protein concentration was 0.72 g/l at 1 month, and 0.56 g/l at 5 months. Pneumoencephalography showed normal sized ventricles with a very large

cisterna magna and large prepontine cisternae. Electromyography of the tibialis anterior disclosed fibrillation activity, and polyphasic motor unit potentials. Motor nerve conduction velocity (median nerve) was 13 m/s, and sensory nerve conduction velocity (right median nerve) 17 m/s at 1 month. At 4 months motor nerve conduction velocity could no longer be estimated as stimulation produced no muscle response. Muscle biopsy of the vastus lateralis at 6 weeks of age was interpreted as normal. Biopsy of the sural nerve revealed no abnormality on histological and ultramicroscopic examination. A histogram of nerve fibre diameter was normal for the age. Teasing showed no major anomalies of the nerve fibres. Internodal distances were, however, excessively

Fig. 7 Spinal cord: anterior horn. Nissl ($\times 220$). One neurone with ballooned cytoplasm and eccentric nucleus.

variable for fibres of similar diameters, especially so in the smallest ones. The significance of this is uncertain.

Case 3, CV, the oldest brother of cases 1 and 2, was born at term weighing 2200 g. The parents stated that hypotonia, respiratory paralysis, and joint contractures were noticed from birth. Tendon reflexes were not found. The cry was weak and swallowing was impaired. He seemed mentally retarded and died at 6 weeks of age from respiratory complications. No investigations were done, and no necropsy was performed.

Comments

The unusual picture of central and lower motor neurone involvement in three sibs, with almost identical clinical features and course, leaves little doubt that all three infants were affected with the same illness. In the one pathologically verified case, an extreme degree of cerebellar hypoplasia was associated with degenerative changes in the spinal anterior horn cells and brain stem nuclei, indistinguishable from those recorded in Werdnig-Hoffmann's disease.

The same—or a closely similar—association of cerebellar hypoplasia and atrophy with anterior horn cell abiotrophy, has been reported previously in two patients (Norman, 1961; Weinberg and Kirkpatrick, 1975). In all three necropsied patients (Table), there was a conspicuous loss of large anterior horn cells with several greatly inflated chromatolytic perikarya. Several brain stem nuclei were similarly affected, and the thalami were involved in one patient (Norman, 1961). In every case, the cerebellum was very much

reduced in size, the hemispheres being even more compromised than the vermis. The cerebellar lesions were mixed in type, with both atrophy of apparently previously normally formed structures and hypoplasia of a malformative type, with reduction in the number of convolutions and abnormal disposition of the cellular layers. The dentate nuclei were atrophic and malformed with rounded groups of cells present in two cases. The pons, especially in its ventral part, was severely affected, the nuclei pontis and transverse fibres being greatly reduced in number, in association with a severe gliosis. The inferior olive also had minor malformations in Norman's case and in our case 1.

The clinical picture was one of severe, and perhaps progressive, mental retardation, spasticity and contractures, and diffuse peripheral paralysis of the trunk and limbs with hypotonia. In at least two cases the pharyngolaryngeal musculature was affected and, in all patients, respiratory failure was evident. All infants died before the end of their first year. In addition to these general features, several interesting points emerged in our patients in whom far more clinical data are available than the scanty information existing on the two previous infants. Thus, we have been able to document the peripheral character of the paralysis, with loss of deep tendon reflexes and electrical signs of denervation. Additional features, not previously recorded, include microcephaly, cortical blindness with abnormal eye movements, laryngeal involvement with a peculiar cry, pyramidal tract signs, intercostal muscles paralysis, and definite lowering of motor and sensory nerve conduction velocity. The progressive course of the disorder was illustrated in case 2, where tendon reflexes, initially present, were no longer found at 4 months of

Table Summary of findings in six reported cases

Case	Sex	Age at onset	Clinical findings	Family	Age at death	Neuropathological findings
Norman (1961)	M	birth	Hypotonia. Adductor spasms. Mental deterioration. Respiratory failure. Impairment of swallowing.	0	6 mo.	<i>Spinal cord</i> : WH* changes. <i>Medulla</i> : neuronal loss in inferior olives and cranial nuclei. <i>Pons</i> : atrophy and gliosis of the pes. <i>Cerebellum</i> : poorly developed folia, loss of granular and Purkinje cells, atrophy of nucleus dentatus. Normal vermis. <i>Thalamus</i> : neuronal loss.
Weinberg and Kirkpatrick (1975)	M	birth	Hypotonia. Absent tendon jerks. Respiratory failure. Impairment of swallowing. Muscle biopsy: neurogenic atrophy.	1 normal half-sibling	4 d	<i>Spinal cord</i> : WH changes. <i>Medulla</i> : neuronal loss in inferior olives. Gliosis. <i>Pons</i> : severe reduction of pontine nuclei. <i>Cerebellum</i> : poorly developed folia mostly in hemispheres. Atrophy of deep nuclei
Present cases 1	F	birth	Hypotonia; muscular atrophy; paralysis of limbs and respiratory muscles. Absent tendon jerks; pyramidal tract signs; cranial nerve involvement. Mental retardation. Low conduction velocity.	+ sister of cases 2 and 3	3 mo	<i>Spinal cord</i> : WH changes. <i>Medulla</i> : atrophy of inferior olives and cranial nuclei. <i>Pons</i> : gliosis of pes; neuronal loss of intrinsic nuclei. <i>Cerebellum</i> : poorly developed folia; loss of granules and Purkinje cells; severe atrophy of nucleus dentatus; vermis partially spared.
2	M	birth	Hypotonia; muscular atrophy; disappearance of tendon jerks; paralysis of limbs and intercostal muscles; pyramidal tract signs; cranial nerve involvement; mental retardation; low conduction velocity of nerves.	+ brother of cases 1 and 3	7½ mo	NE†
3	M	birth	Hypotonia; absent tendon jerks; limb contractures; cranial nerve involvement; mental retardation.	+ brother of cases 1 and 2	1½ mo	NE
Norman and Kay (1965)	F	? first seen at 11 mo	Hypertonic lower limbs; increased tendon reflexes left Babinski; mental retardation.	+ 1 brother similarly affected died at 11 mo	22 mo	<i>Spinal cord</i> : WH changes; poor myelination of posterior and lateral fasciculi; gliosis. <i>Medulla</i> : neuronal loss of cranial nuclei. <i>Pons</i> : normal. <i>Cerebellum</i> : loss of granular and Purkinje cells in hemispheres and vermis; gliosis; atrophic changes of cells of dentate nucleus. <i>Thalamus</i> : extreme atrophy and gliosis.

*WH=changes of Werdnig-Hoffmann disease.

†NE=not examined.

age. In none of the patients were cerebellar signs recorded.

Although some of the clinical symptoms and signs are readily explainable in view of the pathological lesions—for example, peripheral paralysis, absent reflexes, and cranial nerve palsies—no satisfactory account can be given in any of the cases for the mental defect, blindness, spasticity, and lack of cerebellar signs. The latter, however, is quite common in congenital malformations of the cerebellum (Greenfield, 1954), and the young age at death might have pre-

vented their appearance. The slow nerve conduction velocity repeatedly found in two of our infants is puzzling, since no major myelin sheath abnormalities were found in the nerves sampled, and since the slowing was much more marked than that occasionally mentioned in lower motor neurone disease (Gamstorp, 1967; Raimbault and Laget, 1972). In the face of the pathological findings, however, we do not think that a diagnosis of primary nerve disorder is warranted, unless the normal aspect resulted from a sampling error.

The clinicopathological picture present in the three completely documented cases and, in all probability, in our two other patients, is probably to be regarded as a specific morbid entity, distinct from Werdnig-Hoffmann disease. Although the two previously reported patients were considered as cases of Werdnig-Hoffmann disease with unusually extensive supraspinal involvement, the chance association of two uncommon central nervous system anomalies in several infants is highly unlikely, and the occurrence of this symptom complex in three sibs makes this hypothesis even less tenable. The most likely hypothesis is that of a genetic, probably recessive, disorder, resulting from the action of a single mutant gene.

The infantile spinal atrophies have recently been shown to encompass several disorders with distinct clinical and genetic features (Zellweger *et al.*, 1969; White and Blaw, 1971; Van Wijngaarden and Bethlem, 1973; Bunday and Lovelace, 1975), and it is conceivable that the cases here described constitute one further rare subtype within this group. Other hypotheses, such as a viral disorder resembling that which occurs in cats infected with feline panleukopenia virus and other viral agents (Kilham *et al.*, 1971; Brown *et al.*, 1973; Monjan *et al.*, 1973), seem less likely in view of the degenerative type of the cord lesions, and the lack of inflammatory changes in the cord despite the postnatal progression of the disorder.

The relationship of our cases and those of Norman (1961), and Weinberg and Kirkpatrick (1975), with a few other related cases deserves some comment. Norman and Kay (1965) have reported the cases of two siblings affected with a disorder which they considered to be an unusual variant of Werdnig-Hoffmann disease, featuring cerebellar degeneration in addition to spinal, brain stem, and thalamic involvement. In the one pathologically documented case (Table) cerebellar lesions were of a purely degenerative character without evidence of malformation, and the degree of atrophy was far less severe. The pes pontis was normal as were the inferior olives. The clinical picture was predominantly one of spasticity with brisk reflexes and mental retardation leading to death at 22 months of age. Whether these patients were affected with a milder form of the disease here reported is impossible to state, in spite of clinical and pathological resemblances. There were no malformations of the cerebellum or brain stem, suggesting that the noxious agent had been active later than in the present patients, and the authors considered these cases distinct from the case of cerebello-spinal disorder they had reported previously.

On the other hand, the cases of cerebello-pontine hypoplasia described by Norman and Ulrich (1958) as hypoplasia pontoneocerebellaris, are certainly

different from the present cases since, in spite of the similarity of the cerebellar and olivo-pontine lesions, the spinal cord was not involved.

Addendum

Since submission of this paper we have been informed by Dr P. Procopis (Sydney, NSW, Australia) that he has observed a family in which siblings had been affected with the same disorder. Pathological findings in two of these children were identical to those in our case 1.

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