Virchows Arch A (1987) 410:339–345

Virchows Archiv A

Olivo-ponto-cerebellar atrophy with muscular atrophy, joint contractures and pulmonary hypoplasia of prenatal onset

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Summary. The clinical and pathological features of a female neonate with congenital joint contractures and pulmonary hypoplasia are described. Neuropathological examination revealed a widespread neuronal degeneration with a predominantly olivo-ponto-cerebellar distribution and muscle pathology consistent with neurogenic atrophy. This is the first reported case of congenital joint contractures and pulmonary hypoplasia with pathologically documented olivo-ponto-cerebellar degeneration. The observation further illustrates that the so-called fetal akinesia sequence or Pena-Shokeir I syndrome is an aetiologically non-specific symptom complex that can be caused by a number of underlying mechanisms.

Key word: Arthrogryposis multiplex congenita – Neurodegenerative disorder – Olivo-ponto-cerebellar atrophy – Perinatal autopsy

Introduction

Neuromuscular dysfunction of the fetus is an important cause of congenital contractures (arthrogryposis multiplex congenita) (Hageman and Willemse 1983). Spinal anterior horn disease has been described specifically as a cause of congenital muscular atrophy and contractures (Clarren and Hall 1983; Moerman et al. 1983). Disorders that cause spinal anterior horn dysfunction are mostly confined to the spinal cord as in Werdnig-Hoffmann disease, but in other cases may be part of a multisystem neuronal degeneration such as the olivo-ponto-cerebellar atrophies. The present case report shows that prenatal onset of neuronal degeneration in a predominantly olivo-ponto-cerebellar distribution can occur, and may manifest itself clinically in the syndrome of congenital joint contractures and pulmonary hypoplasia.

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Case report

This infant girl was the first-born of young, healthy, non-consanguineous parents. The pregnancy was complicated by polyhydramnios, and the mother experienced very weak fetal movements. The patient was born at term and died few hours after delivery in severe respiratory distress. The body weight was 2,430 g (P_{10} = 2,600 g), the crown-rump length 32.8 cm, and the head circumference 34.5 cm (P_{50-75}). Clinically, (Fig. 1) multiple rigid joint contractures were evident, and the muscle mass of the extremities was markedly reduced. Passive movement of the shoulders was very restricted and the elbows were fixed in flexion. The hands displayed radial deviation, severe campto- and clinodactyly, and absent palmar creases and dermal ridges. The hips were ankylosed in extreme anteflexion and the knees in hyperextension. A severe talipes calcaneovarus deformity was present bilaterally. The face was flattened, and showed ocular hypertelorism, divergent strabismus, and micrognathia. X-ray examination disclosed no additional skeletal malformations. Chromosomal analysis revealed a normal 46XX female karyotype, confirmed by G- and Q-banding.

Pathological examination. On incision of the extremities, the skeletal muscles were extensively replaced by adipose tissue and difficult to identify. The diaphragm was markedly elevated, paper-thin, and almost transparent. The intercostal muscles

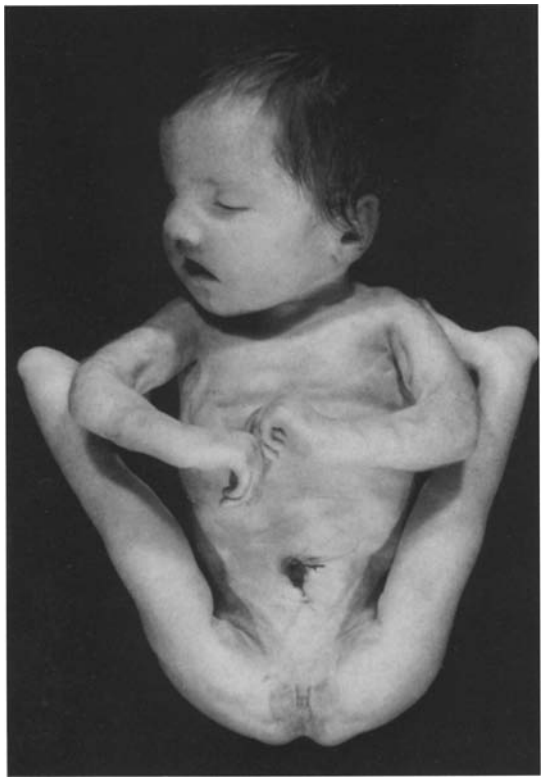

Fig. 1. The patient. For description see text

were also atrophic. The lungs were hypoplastic (combined weight 13,8 g, lung weight/body weight ratio 0.0059). There were no cardiovascular anomalies. The abdominal viscera showed no abnormalities.

The brain weighed 305 g after fixation. The cerebral hemispheres were symmetrical but exhibited an abnormal convolutional pattern with an increased number of narrower than normal gyri. The olfactory bulbs and tracts were present. The optic nerves, other cranial nerves and blood vessels of the circle of Willis were normal. There was atrophy of the cerebral peduncles. The ventral part of the pons was unduly small and wedge-shaped. The cerebellar hemispheres and the inferior olives appeared shrunken. The spinal cord was normal macroscopically.

Coronal sections through the cerebrum revealed dilated ventricles I–III, and a reduced amount of central white matter. The cortical gray matter had an apparently normal thickness. The corpus callosum, fornix, septum pellucidum and basal ganglia were grossly normal. Transverse sections through the brain stem demonstrated a patent aqueduct and a dilated fourth ventricle. The white matter of the cerebellar hemispheres was atrophic and the dentate nuclei could not be identi-

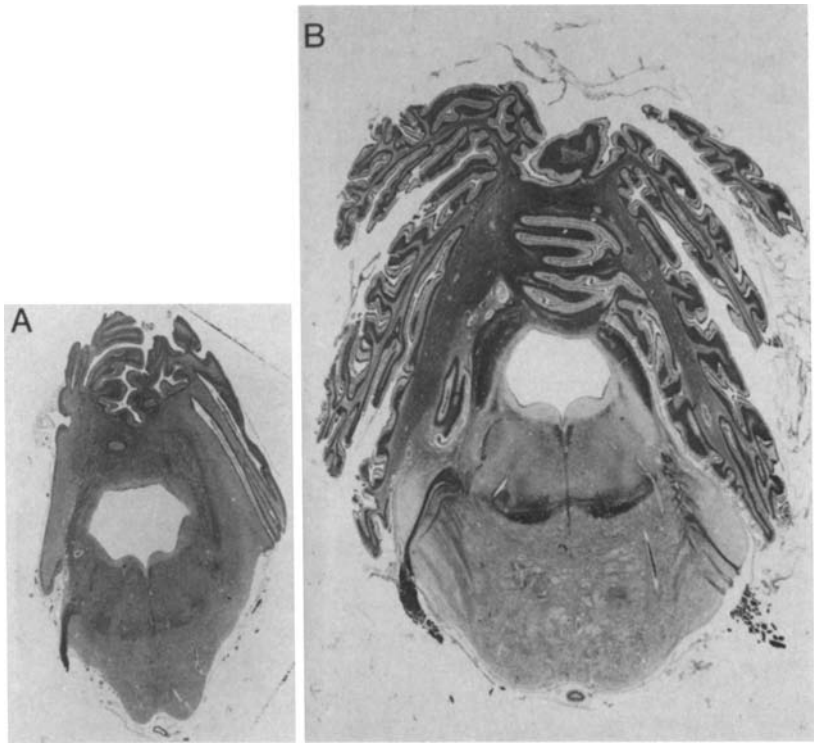

Fig. 2. A. Transverse section through cerebellum and brainstem at the level of the trigeminal nerve. Slightly asymmetrical section, showing the neocerebellar hypoplasia as contrasted to the development of the vermal folia. The ventral part of the pons is wedge-shaped and hypoplastic with invisible longitudinal fascicles. LFB-stain, ×2.6. **B.** Control section from a full term neonate showing well developed neocerebellar folia and well developed ventral pons with longitudinal fascicles clearly visible. LFB-stain, ×2.6

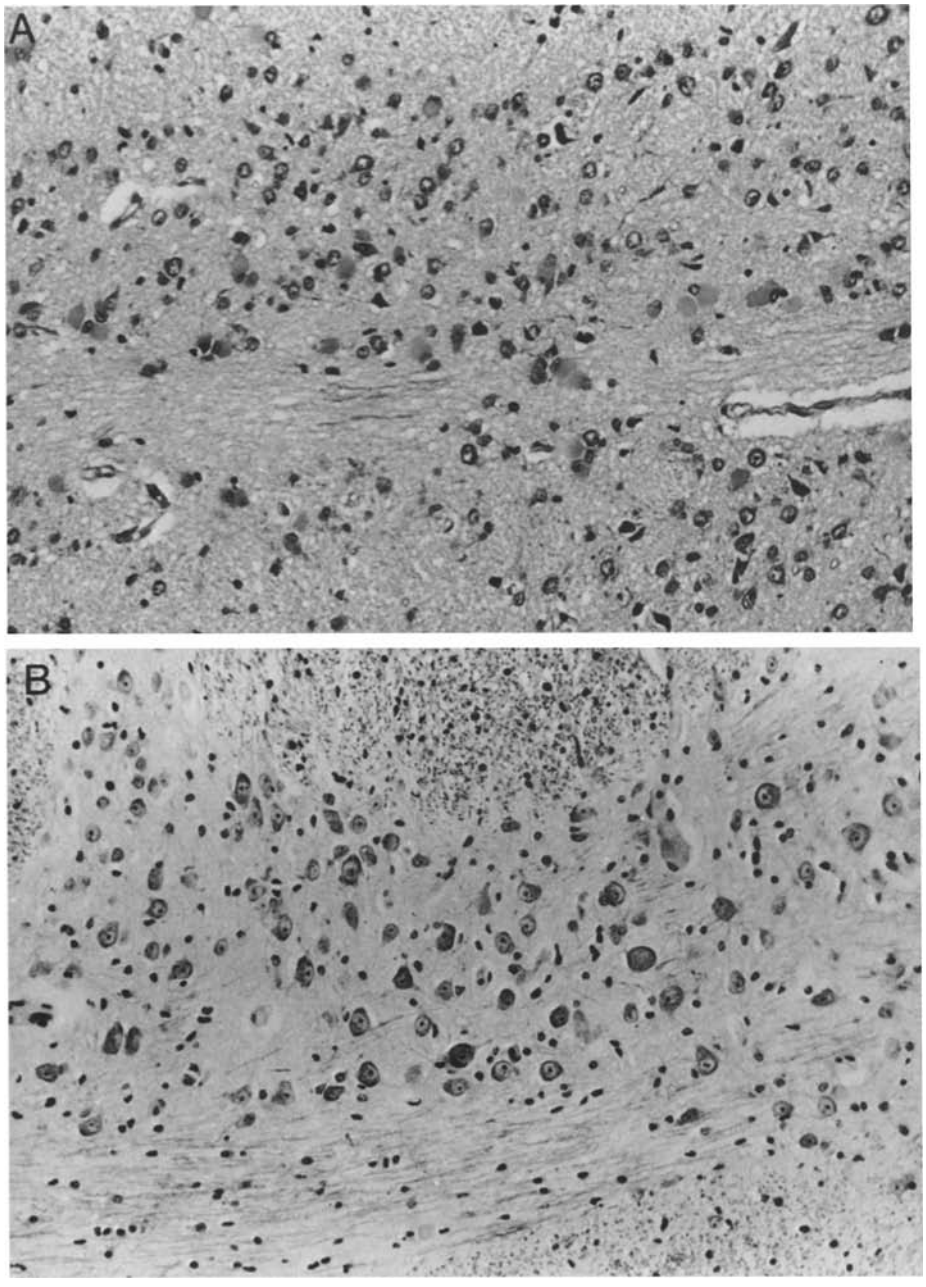

Fig. 3. A. Ventral pons. Paucity of neurons, astrocytic proliferation and reactive large astrocytes shown. LFB-stain, ×208. **B.** Control section of ventral pons (case shown in Fig. 2B) showing well developed pontine neurons in normal numbers. LFB stain ×208

fied macroscopically. The size of the vermis was within the normal neonatal range.

On microscopy there were patches of microgyria in many areas showing poorly differentiated, festoons of neocortex with fusion of the first layer overlying the abnormal gyri. The subcortical and central cerebral white matter, though reduced in volume, appeared normal. The thalamus was affected by neuronal degeneration and mild reactive astrocytosis with the ventral nuclei relatively preserved and the medial, intralaminar and dorsal nuclei severely depleted with small residual islets of intact neurons. The striatum and pallidum were preserved. Neurons in the hippocampal gyrus were abnormally oriented. The cerebral peduncles were atrophic with abundant reactive astrocytosis. Pontine nuclei were affected by extensive neuronal loss with large reactive astrocytes (Fig. 3). The posterior longitudinal fascicles were intact as were the lemnisci. Within the medulla oblongata the inferior olivary nuclei were subtotally depleted of neurons, only a remnant of the medial portion remaining on both sides (Fig. 5). The olivo-cerebellar and the cerebello-olivary tracts were poorly developed. The

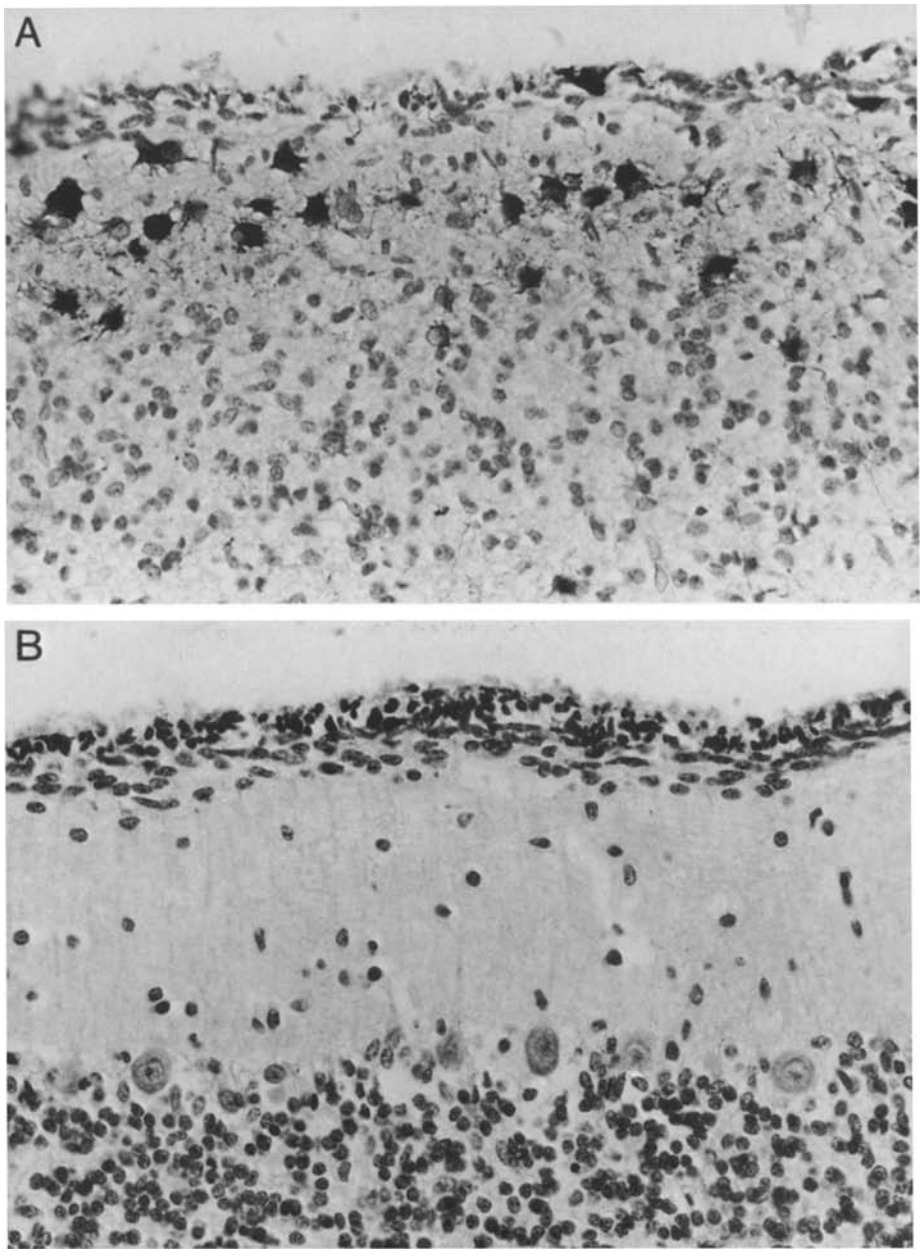

Fig. 4. A. Neocerebellar cortex. Sub-total loss of Purkinje-cells, diminished width of molecular layer, astrocytic proliferation and loss loss of granule cells in the internal granule layer, presence of external granular layer. Large reactive astrocytes are present within and adjacent to the depleted Purkinje-cell layer. GFAP-stain for astrocytes with haematoxylin counterstain, ×330. **B.** Control section of neocerebellar cortex (case shown in **Fig. 2B)** showing normal development. GFAP-stain for astrocytes with haematoxylin counterstain, ×330

superior cerebellar peduncle was absent and the middle and inferior peduncles severely reduced in size.

The cerebellum was grossly undersized. Folial development of the hemispheres was rudimentary (Fig. 2A) when compared with normal neonates (Fig. 2B), with absent myelination of the lateral folia, paucity of internal granule cells and almost total lack of Purkinje-cells and decreased width of the molecular layer (Fig. 4). Large reactive astrocytes took the place of the Purkinje-cell layer and a diminished external granular layer was seen. The dentate nuclei were degenerate with few neurons remaining. The vermis was abnormally formed with aberrantly oriented fissures, but its microscopical structure was normal. The flocculus was also normally developed.

In the spinal cord the long tracts were normally developed for the gestational age with exception of the dorsal and ventral spinocerebellar tracts which were not myelinated. The motor neurons of the spinal cord were generally small, with partial loss especially occurring in the lateral anterior horn column. Degeneration patterns here (as elsewhere) were non-specific. Chromatolysis with eosinophilic swelling and neuronophagia, a familiar feature in

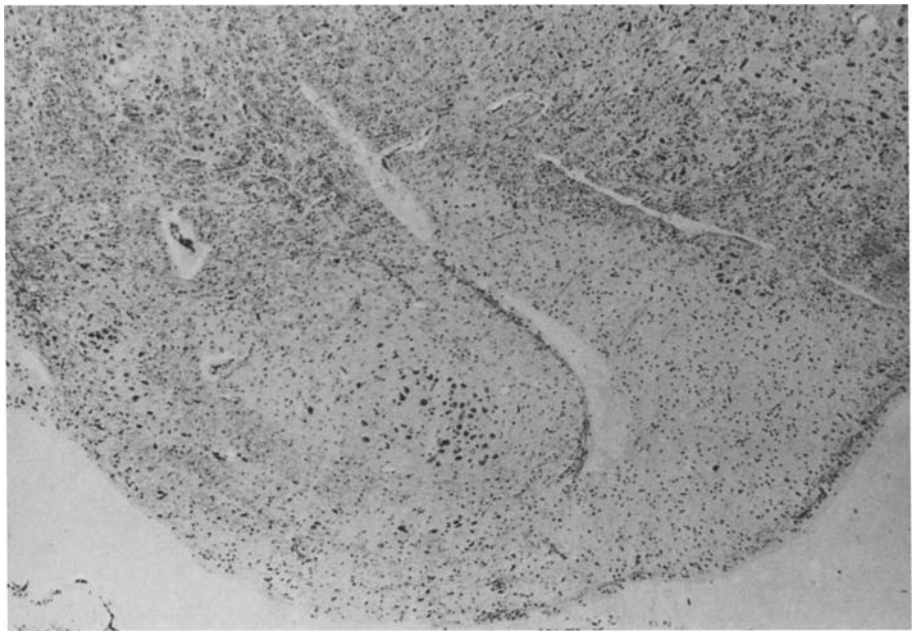

Fig. 5. Site of inferior olivary nucleus at the level of exit of hypoglossal nerve. Severe depletion of olivary neurons. Residual neurons grouped in basomedial part. Absent pyramidal tract. LFB-stain, ×40

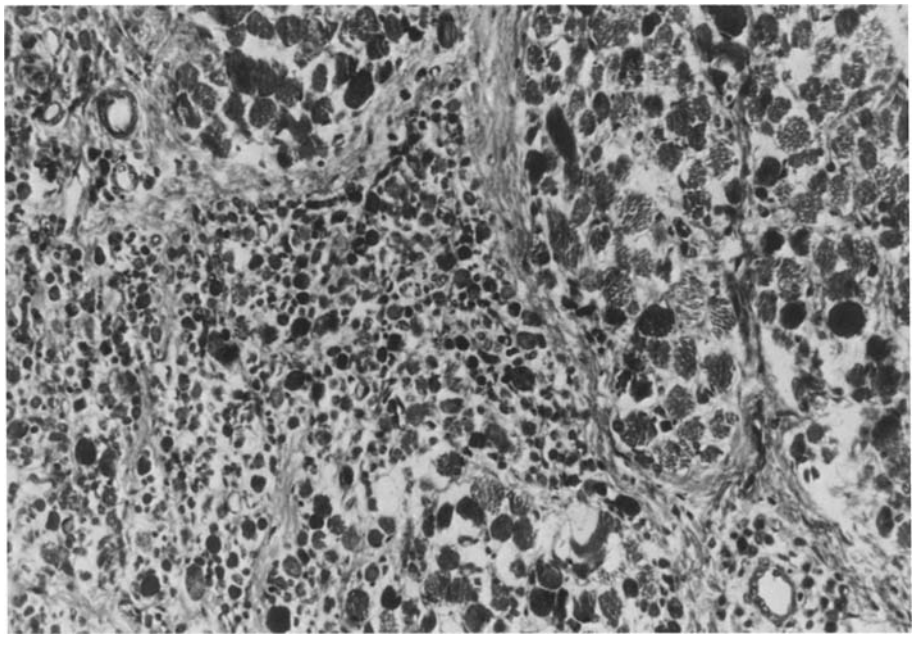

Fig. 6. Quadricepas femoris muscle. Grouped atrophy and endomysial fibrosis. Masson trichrome, ×208

infantile spinal muscle atrophy, was not encountered. Skeletal muscle samples from intercostal muscles, quadriceps femoris muscle and diaphragm showed grouped atrophy of the type that is seen in neurogenic atrophy (Fig. 6).

Discussion

Congenital contractures and lethal pulmonary hypoplasia and weakness were found in a neonate, the affection being due to a rare neurodegenerative disorder with prenatal onset. Cellular degeneration and death characteristically affected neurons of the neocerebellum (Purkinje cells, internal granule cells as well as dentate cells), the ventral pons and the olivary complexes. Severe damage was also seen in some thalamic nuclei. The degenerative nature of the disorder is born out by the presence of a ghost structure at the site of the inferior olivary nucleus and the presence of reactive astrocytes in the main affected areas. The arrested folial development in the neocerebellum (hypoplasia rather than atrophy) marks the early onset of the disorder during cerebellar development. The presence of

neocortical microgyria also indicates that the process started at an early stage of development, in this case probably not later than the fifth month (Friede 1975). The affection of the anterior spinal horns was apparent from the reduction of large neurons, especially those in the lateral columns and the presence of grouped muscle atrophy in various muscles sampled. Widespread neuronal degeneration of a nonspecific nature in sibs exhibiting congenital contractures has been described by Kaarsoo Herrick et al. (1983). Their cases exhibited extreme neocerebellar hypoplasia as well as severe cerebral atrophy but the spinal anterior horn cells were stated to be normal. A pattern of prenatal onset degeneration more closely reminescent of the present case and mainly affecting the pontine nuclei, olivary nuclei and neocerebellar cortex has been described by Norman and Urich (1958), Gross and Kaltenbäck (1959) and Friede (1975). None of these cases were reported to have spinal anterior horn degeneration. The cases of Norman (1961) and Weinberg and Kirkpatrick (1975) had spinal anterior horn degeneration with associated involvement of inferior olives, neocerebellum and pes pontis. Their clinical symptoms were neonatal hypotonia and weakness without contractures. Anterior horn cell disease associated with pontocerebellar hypoplasia and congenital contractures in sibs was described by Goutières et al. (1977). Three sibs died between 6 weeks and 7 months with similar symptoms. Their contractures were mainly distal and dyspneoa was less severe than in the present case. The distribution of neuronal degeneration and gliosis was: in the neocerebellar cortex, which was both underdeveloped with simplified folial pattern, and atrophic, in the pes pontis, the olivary nuclei and the anterior horn cells in the spinal cord. Pulmonary hypoplasia was not mentioned.

The sibs studied by Goutières et al. (1977) resemble our case the most closely. Some differences are obvious, such as death from asphyxia within hours, pulmonary hypoplasia, absence of chromatolysis in the anterior horns of the type seen in Werdnig-Hoffmann disease, thalamic degeneration and neocortical microgyria were all present in our case and absent in the autopsied case of Goutières et al. (1977). The severe contractures as well as the pulmonary hypoplasia in our case can be explained by the neurodegenerative process. The grouped atrophy found in various muscles sampled points to neurogenic atrophy causing weakness and ensuing contractures. Pulmonary hypoplasia may have its origin in lack of innervation to the respiratory muscles. Congenital contractures, pulmonary hypoplasia and the other components of the so-called fetal akinesia sequence or Pena-Shokeir syndrome type I (Pena and Shokeir 1974), have been reproduced experimentally in animals by early denervation (Moessinger 1983). The combined affection of the neocerebellum pons and olivary nuclei by neuronal degeneration puts this disorder in the group of neuronal degenerations called olivo-ponto-cerebellar atrophies (OPCA), a otherwise heterogenous group with documented autosomal dominant and autosomal recessive inheritance, wide variability in age at onset, juvenile and infantile cases occurring, and a variable admixture of other neural systems affected, such as the retina, neocortex, basal ganglia and spinal anterior horn cells (Kongismark and Weiner 1970; Colan et al. 1981; Berciano 1982). Anterior horn affection is not uncommon in OPCA, which includes cases with early juvenile onset (Colan et al. 1981; Berciano 1982).

Though cataloging of multisystem neuronal degenerations in this way puts the emphasis only on those parts most obviously affected, it may be helpful in providing morphological classification pending biochemical elucidation as an inborn error of metabolism. We therefore propose to classify this case as OPCA with associated neurogenic muscle atrophy, thalamic and neocortical changes, with prenatal onset. The neuromuscular affection is believed to have caused the congenital contractures as well as the pulmonary hypoplasia. This case further illustrates that the Pena-Shokeir syndrome type I is etiologically heterogeneous.

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Accepted August 8, 1986