Arch. Psychiat. Nervenkr. 226, 311—318 (1979)

Archiv für Psychiatrie und Nervenkrankheiten
Archives of Psychiatry and Neurological Sciences

Hereditary Cerebellar Atrophy (Holmes Type) With Optic Atrophy

A Clinico-Pathological Study of Four Generations in a Family

Herbert Budka, Demeter Seemann, and Walter Danielczyk

Neurological Institute, University of Vienna, and Neurological Department, Lainz Gerontological Hospital, Vienna, Austria

Summary. A family with a dominantly inherited progressive cerebellar ataxia is described; four members of successive generations were affected. Neuropathological examination of one family member classified this disorder as hereditary cerebellar atrophy of Holmes type. An associated optic atrophy has not been previously reported in this disease.

Key words: Cerebellum – Heredoataxias – Inherited disease – Cerebellar degeneration – Ataxia.

Zusammenfassung. Es wird eine Familie mit dominant vererbter Kleinhirnataxie beschrieben; vier Mitglieder aufeinanderfolgender Generationen waren erkrankt. Durch neuropathologische Untersuchung konnte in einem Fall die Diagnose der erblichen Kleinhirnatrophie vom Holmes-Typ gestellt werden. Eine gleichzeitig bestehende Optikusatrophie wurde bisher bei diesem Krankheitsbild noch nicht beschrieben.

Schlüsselwörter: Kleinhirn – Heredoataxien – Erbkrankheiten – Ataxie – Systematrophien.

Introduction

"The chaotic state of our knowledge of the familial cerebellar disorders is due in large part to the absence of morbid anatomical data in the great majority of instances": this statement seems by no means less valid today than 50 years ago when it was made [9]. According to a recent review [8], there are only 12 families [1, 3, 4, 11, 12, 14, 18—21, 25, 27] on record in which neuropathological examinations confirmed a hereditary progressive degeneration of the cerebellar cortex as first described by Gordon Holmes in 1907 [12]. This paper reports clinical

Send offprint requests to: Dr. Herbert Budka, Neurologisches Institut der Universität Wien, Schwarzspanierstraße 17, A-1090 Wien, Austria

0003-9373/79/0226/0311/$ 01.60

observations on four generations of a family with this disease and detailed autopsy findings from one member. The cerebellar atrophy of Holmes type is associated with optic atrophy; to our knowledge, such an association has not been reported previously.

Clinical Observations

Figure 1 shows the predigree of the family Grö.-Kli.-Li.; affected members are printed in black.

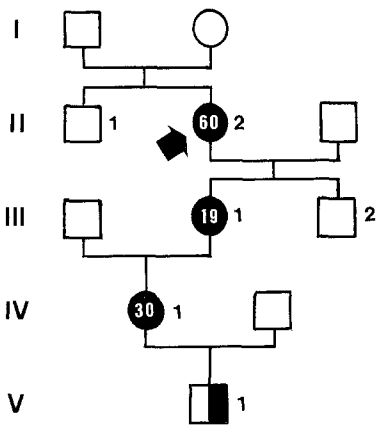

Fig. 1. Family tree. Squares—males; circles—females. Black discs—patients with clinically manifest cerebellar ataxia. Numbers inside black discs designate age of onset of ataxia. Arrow points to patient with neuropathologic examination. Half blackened square —patient with some neurologic abnormalities

The first generation (I in Fig. 1) for which reasonably comprehensive data could be found is represented by the parents of the first affected member (II/2). The father died at age 68 from cardiac failure, the mother succumbed to senile marasmus at age 85. Neither they nor any of their ancestors were known to have been subject to neurologic or psychiatric disorders.

In the second generation (II), an elder brother (II/1) of the first affected member (II/2) emigrated overseas and was lost for follow-up.

The *first affected member* of this family (Grö. F., II/2), a female, was hospitalized from age 65 until her death at age 85. There was no major illness in her history. The neurological disorder began around the age of 60 years when unsteadiness of gait, impairment of writing, tremor, and impairment of movement control were first noticed, followed by vertigo, memory loss, and bladder dysfunction. From the age of 65, short attacks of collapse occasionally occurred, without after effects except transitory left-sided hemiparesis. Neurologic examination on hospital admittance at age 65 revealed bilateral optic atrophy, nystagmus at horizontal deviation bilaterally, dysarthria with scanning speech, generalized hypotonia, exaggerated tendon reflexes especially on the left side, slight weakness on the left side, prominent bilateral intention tremor in the finger-nose test, also marked ataxia in the heel-knee test, irregular swaying in Romberg's test, and an ataxic broad-based gait. Loss of recent memory and impairment of reasoning ability were also noted. In the following two decades, signs and symptoms of cerebellar dysfunction and dementia slowly progressed. Falls to the ground were frequent and on one occasion caused a fracture of the left radius. One year before death, the EEG was diffusely abnormal: there was diffuse slowing (6.5 to 7.5 s) and theta-delta activity and sharp waves were predominantly frontobasal and bilateral and temporally more on the left side; there was loss of reaction to lid opening and closing. The patient died with clinical signs of pneumonia at the age of 85 years. General autopsy revealed liver cirrhosis of little progression, sacral decubitus, and a left-sided inguinal hernia; the thoracic organs were not examined. A detailed account of the neuropathologic examination is given below.

Patient II/2 was married to a male of apparent healthy ancestry who died aged 46 years from bronchial asthma. Their two children represent the third generation (III).

The elder son (III/2), at the moment still living at the age of 71 years, suffers only from bronchial asthma. The daughter (Kli. I., III/1) is the *second affected member* of the family. There was visual impairment since childhood; since age 19, disorder of speech and unsteadiness of gait and upper limb movements were noted. She was hospitalized several times with a diagnosis of multiple sclerosis. At admittance to our department at the age of 27 years, bilateral optic atrophy, convergent paresis of the left eye, nystagmus at horizontal deviation bilaterally, a slurred, scanning, and explosive speech, generalized hypotonia, forearm and finger hypodiadochokinesis, intention tremor in the finger-nose test, exaggeration in the heel-knee test, and falling to the right side and to the rear in Romberg's test were noted. There was also loss of old and recent memories and impairment of reasoning ability and attention. From the permanent hospitalization until now, cerebellar dysfunction has slowly progressed, most prominent symptoms are increase of intention tremor in finger-nose and heel-knee tests, truncal ataxia, and speech dysarthria; she can walk only with assistance. The patient is now 68 years old and still hospitalized. An EEG, performed one year ago, showed moderate diffuse abnormality with loss of alpha reaction, some theta activity in frontal and lateral regions, and occasional sharp waves occipitally. A CAT scan, performed in the Neurological Clinic, University of Vienna, showed moderate enlargement of the fourth and lateral ventricles and also widening of the upper vermial cystern. A recently performed audiographic examination of cochleovestibular functions revealed depression of higher frequencies in accordance with the age and normal vestibular function in the caloric response. The patient was married to a man from an apparent healthy family.

The fourth generation (IV) is represented only by a female (Li. F., IV/1), who is the *third affected family member.* There are no major diseases in her history. Since the age of 30, she noted vertigo and unsteadiness of gait, later also dyscoordination in target movements of the upper limbs with slow progression. Recently, she was examined neurologically as an outpatient: nystagmus at horizontal deviation bilaterally, syllabic speech, prominent ataxia in finger-nose and heel-knee tests, generalized hypotonia, symmetrical exaggeration of tendon reflexes, broad-based staggering gait and irregular swaying in Romberg's test. Fundi and visus were normal. An EEG was at the limits of normalcy with some steep waves frontobasally and temporally, accentuated at the right side. This patient is now 48 years old and still able to work as an office clerk.

Her only (there was one miscarriage) son (Li. M., V/1) represents the fifth generation to be followed. To date, age of 28 years, he shows no definite signs of manifest cerebellar disease, although there are some neurologic abnormalities worth noting. For several years, he has complained of cephalea with occasional vertigo and unsteadiness of gait; his right forearm was recently fractured. When he was seen recently as an outpatient, neurologic examination showed slight left-sided ptosis, convergent paresis of the right eye, horizontal nystagmus at gaze to the right, slight general hypotonia, and some truncal unrest in Romberg's test. A recently performed EEG was slightly abnormal with activation of steep waves temporally and occipitally on the right side in hyperventilation.

Neuropathologic Findings in Patient II/2 (arrow in Fig. 1)

The brain (N.I., No. 18–66) of the first affected member who died at the age of 85 years was severely atrophic, weighting only 925 g. Cerebral atrophy was moderate while there was severe cerebellar atrophy, most prominent in the vermis and dorsal paramedian areas although ventral parts were also involved. On histologic slides, myelination of brain stem and cerebellum appeared largely normal; however, there was severe fibrillary gliosis of cerebellar white matter mainly in the vermis and dorsal hemispheric parts. In addition, there was gliosis of medial vestibular nuclei and prominent gliosis with nerve cell loss in the inferior olives (Fig. 2). The cerebellar cortex showed a total to subtotal loss of

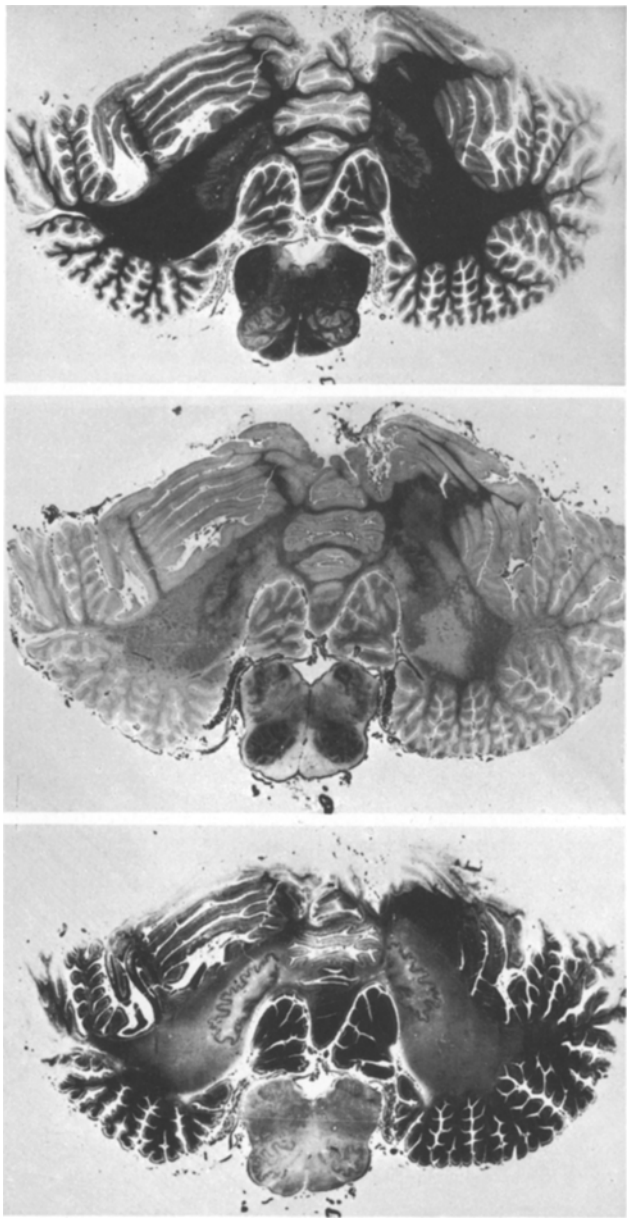

Fig. 2. Sections through cerebellum and medulla in myelin (Klüver-Barrera, above), glial fiber (Kanzler, middle), and cell (Cresylviolet, below) stains, showing severe foliar atrophy and gliosis most prominent in the vermis and dorsal paravermial parts of the cerebellar hemispheres, relatively spared myelination, and intense gliosis of inferior olivary nuclei, and, to a lesser degree, of medial vestibular nuclei

Purkinje cells with moderate Bergmann glia proliferation, slight gliosis of the molecular layer (Fig. 3A), numerous 'empty baskets' (Fig. 3C), and occasional degenerating Purkinje cells with cytoplasmic vacuoles (Fig. 3D). The dentate nuclei showed only slight nerve cell reduction; the basis pontis was entirely normal. The optic chiasm showed prominent ill-defined axon and myelin loss with unilateral accentuation (Fig. 3B); the bulbi were not examined. The basal ganglia showed only age-related changes. Marked senile cortical atrophy with

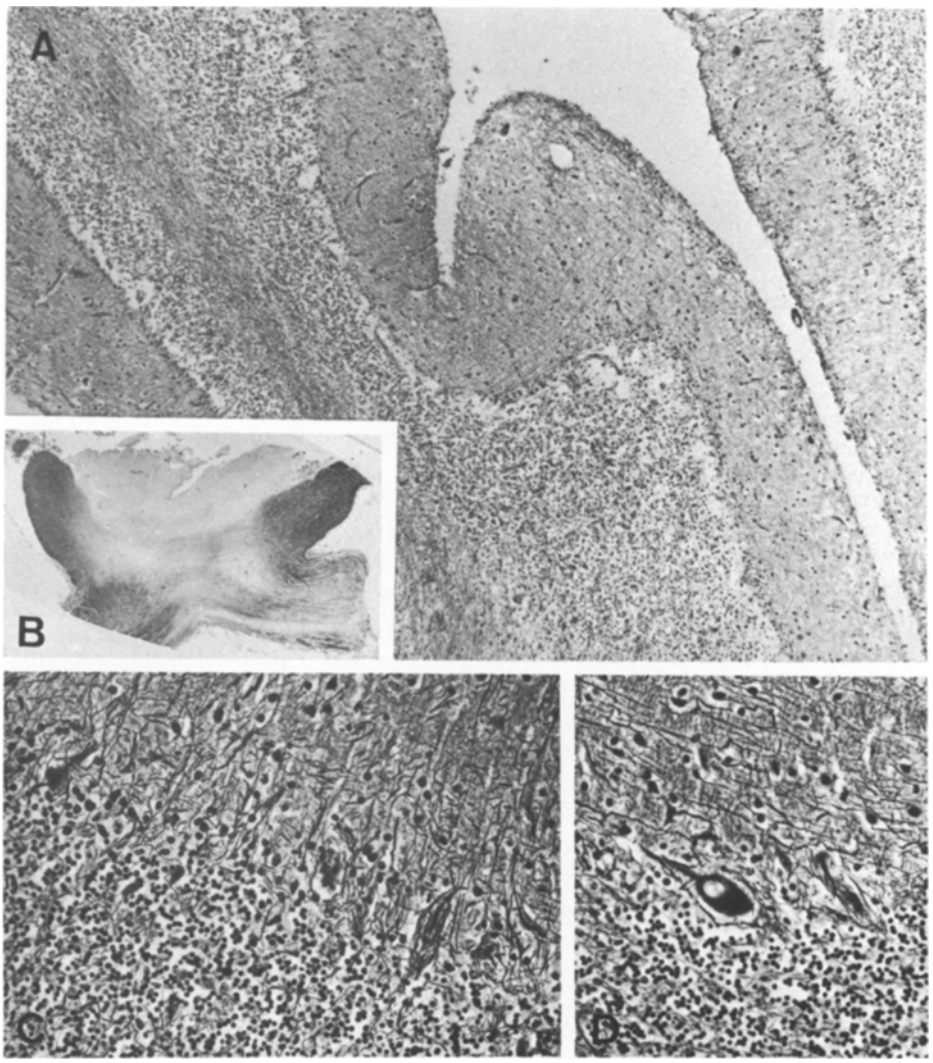

Fig. 3. **A** Cerebellar folia with complete loss of Purkinje cells, moderate Bergmann glia proliferation, moderate thinning of granule layer, and slight gliosis of molecular layer. Bodian × 63. **B** Optic chiasm with severe myelin loss. Klüver-Barrera × 4. **C** Numerous 'empty baskets' in the cerebellar cortex. Bodian × 180. **D** Large vacuole in degenerating Purkinje cell of cerebellar cortex. Bodian × 180

numerous plaques (only in the cerebrum), neuronal tangles, and granulovacuolar degeneration, and a moderate metabolic astrocytosis (secondary to hepatic cirrhosis) were found. Moderate sclerosis of basal vessels was accompanied by some small old vascular scars in the mesencephalon. The oblongata-cervical junction was normal, without evidence for tract degenerations; unfortunately, the spinal cord, nerves, and muscle could not be examined.

Discussion

Neuropathological examination of one family member revealed a severe cerebellar cortical atrophy mainly of the Purkinje cell type, accentuated orally and dorsally with secondary degeneration of inferior olives, thus classifying this ataxia as further example of pure cerebellar or so-called cerebello-olivary atrophy [12]. This pathologically defined disorder [26] should not be confused [29] with Pierre Marie's 'hereditary cerebellar ataxia' [17], an exclusively clinical syndrome which has been shown already by Holmes [13] to comprise a wide variety of pathologically heterogeneous conditions. Thus, Marie's attempt to define a clinical grouping [17] is probably responsible for the endless confusion which has arisen over various forms of the heredoataxias [8, 9, 13, 26, 29]. In the absence of sufficient knowledge to form a more satisfactory basis of classification, differentiation of various forms of hereditary ataxias must be based on pathological examination of the nervous system [8, 10, 26].

The mode of inheritance in our family strongly suggests a dominantly inherited disorder, as in the majority of cerebello-olivary atrophy families [28]. Although the mean age of onset of ataxia is said to range from 34 [24] to 45 [10] or 46 years [8], our first patient did not show neurologic symptoms before the age of 60, almost as late as Richter's case with an onset at 70 years [21]. Earlier onset of ataxia in the following generations might suggest anteposition, as in a recently described family [15]; however, this may be statistically biased.

The clinical picture of all three patients with manifest ataxia is in full accordance with a progressive cerebellar disturbance typical for the Holmes type of cerebellar atrophy [8]. Dementia was prominent in the first two generations, already appearing in patient III/1 rather early, as in the Akelaitis' family [1]; later development of dementia [3, 4, 20, 25, 27] is most probable due to age-related changes as demonstrated by typical senile tissue changes in our first patient. However, in this context it should be remembered that a peculiar form of middle-age heredoataxia with dementia has been described in an Austrian family, characterized morphologically by systemic atrophies and widespread amyloid plaques also in the cerebellar cortex, strikingly similar to the 'slow virus' Kuru disease of New Guinea [23]. The exaggerated tendon reflexes of our first patient are more likely to be due to the pathologically verified vascular scars than to extension of the atrophic process to the cerebrospinal tracts, which might suggest a link to the clinical description of hereditary spastic ataxia with retinal and vestibular degeneration [2]. As happened with our second patient, several such cases were initially misdiagnosed as multiple sclerosis [8, 9, 15].

Optic atrophy, observed in two family members and verified pathologically in the first, has not been previously reported in autoptically proven cerebello-olivary atrophy of Holmes type, although it is frequently mentioned in clinical series of 'cerebellar ataxia' [9, 24] which might comprise many examples of the Friedreich category where optic and cochleovestibular degeneration is common [5]. Although not present yet in the younger members of the last two generations of our family, optic atrophy may develop in the future in these patients.

EEG changes were found in three of our four patients, two of which showed loss of alpha reaction. Diffuse slowing and theta-delta activity are likely to

represent only unspecific concomitant changes found also in various clinically diagnosed forms of heredoataxias [16, 22].

Reports of two families [6, 7] suggested that not only clinical but also pathological features of heredoataxias may vary; in these families, some members showed unequivocal morphological lesions of olivopontocerebellar atrophy, whereas others presented only cerebellar cortical changes. Does this mean that one single autopsy performed in a family with heredoataxia fails to define sufficiently the pathologic type of the disease? In some rare, both clinically and pathologically atypical cases with very early onset, as in the two families mentioned above, the answer might be yes; there are still too few autopsy reports of more than one member in a sibship to settle this question definitely. However, in our family the clinical picture is so constant over three generations (the youngest member, V/1, now 28 years old, may still develop the full syndrome) and accords so well with previous reports [see 8] that also consistency of the pathological classification seems warranted.

References

1. Akelaitis, A. J.: Hereditary form of parenchymatous atrophy of the cerebellar cortex associated with mental deterioration. Am. J. Psychiat. **94**, 1115—1137 (1938)
2. Bergstedt, M.: Hereditary spastic ataxia with central retinal degeneration and vestibular impairment. In: Handbook of Clinical Neurology, P. J. Vinken, G. W. Bruyn, eds., Vol. 21, 383—388. Amsterdam-Oxford-New York: North Holland & American Elsevier 1975
3. Bielschowsky, M., Bouman, L., Sillevis Smitt, W. G.: Über eine ungewöhnliche Form von cerebellarer Heredo-Ataxie. Jb. Psychiat. Neurol. **51**, 1—15 (1934)
4. Bogaert, L. van: Sur une atrophie cérébelleuse tardive du type Marie-Foix-Alajouanine héréditaire et familiale avec une atrophie pallidale partielle cliniquement muette. J. belge Neurol. Psychiat. **47**, 268—286 (1947)
5. Bogaert, L. van, Martin, L.: Optic and cochleovestibular degenerations in the hereditary ataxias. I. Clinico-pathological and genetic aspects. Brain **97**, 15—40 (1974)
6. Carpenter, S., Schumacher, G. A.: Familial infantile cerebellar atrophy associated with retinal degeneration. Arch. Neurol. **14**, 82—94 (1966)
7. Carter, H. R., Sukavajana, C.: Familial cerebello-olivary degeneration with late development of rigidity and dementia. Neurology (Minn.) **6**, 876—884 (1956)
8. Eadie, M. J.: Cerebello-olivary atrophy (Holmes type). In: Handbook of Clinical Neurology, P. J. Vinken, G. W. Bruyn, eds., Vol. 21, 403—414. Amsterdam-Oxford-New York: North Holland & American Elsevier 1975
9. Ferguson, F. R., Critchley, M.: A clinical study of a heredo-familial disease resembling disseminated sclerosis. Brain **52**, 203—225 (1929)
10. Greenfield, J. G.: The spino-cerebellar degenerations. Oxford: Blackwell 1954
11. Hall, B., Noad, K. B., Latham, O.: Familial cortical cerebellar atrophy. Brain **64**, 178—194 (1941)
12. Holmes, G.: A form of familial degeneration of the cerebellum. Brain **30**, 466—489 (1907a)
13. Holmes, G.: An attempt to classify cerebellar disease, with a note on Marie's hereditary cerebellar ataxia. Brain **30**, 545—567 (1907b)
14. Kato, Y., Takayama, K., Tsujiyama, Y., Kaga, T., Satowa, H.: Two autopsy cases of the spino-cerebellar degeneration with the combination of the cerebral atrophy. Brain Nerve (Tokyo) **22**, 1201—1208 (1970)
15. Lenz, H., Pürgyi, P.: Zerebellare Ataxie in 3 Generationen mit anscheinend dominantem Erbgang. Wien. klin. Wschr. **88**, 762—764 (1976)
16. Liversedge, L. A., Emery, C.: Electroencephalographic changes in cerebellar degenerative lesions. J. Neurol. Neurosurg. Psychiat. **24**, 326—330 (1961)

17. Marie, P.: Sur l'hérédo-ataxie cérébelleuse. Sem. méd. Paris **13**, 444—447 (1893)
18. Mathieu, P., Bertrand, I.: Etudes anatomocliniques sur les atrophies cérébelleuses. Rev. Neurol. (Paris) **51**, 721—765 (1929)
19. Miyoshi, I., Sato, T., Takagi, S.: A case report of hereditary cerebellar ataxia. Folia Psychiat. Neurol. Japon. **15**, 281—287 (1961)
20. Richter, R. B.: A clinico-pathologic study of parenchymatous cortical cerebellar atrophy. Report of a familial case. J. Nerv. Ment. Dis. **91**, 37—46 (1940)
21. Richter, R. B.: Late cortical cerebellar atrophy. A form of hereditary cerebellar ataxia. Am. J. Hum. Genet. **2**, 1—29 (1950)
22. Sack, G., Gruss, B., Lössner, J., Bachmann, H.: EEG-Untersuchungen bei spinozerebellaren Ataxien. Psychiat. Neurol. med. Psychol. (Leipzig) **29**, 521—528 (1977)
23. Seitelberger, F.: Eigenartige familiär-hereditäre Krankheit des Zentralnervensystems in einer niederösterreichischen Sippe. Wien. klin. Wschr. **74**, 687—691 (1962)
24. Sjögren, T.: Klinische und erbbiologische Untersuchungen über die Heredoataxien. Copenhagen: Munksgaard 1943
25. Thorpe, F. T.: Familial degeneration of the cerebellum in association with epilepsy. A report of two cases, one with pathological findings. Brain **58**, 97—114 (1935)
26. Ule, G.: Die systematischen Atrophien des Kleinhirns. In: Handb. spez. path. Anat. Histol., O. Lubarsch, F. Henke, R. Rössle, Hrsg., Bd. XIII/1 A, 934—988. Berlin-Göttingen-Heidelberg: Springer 1957
27. Weber, F. P., Greenfield, J. G.: Cerebello-olivary degeneration: an example of heredofamilial incidence. Brain **65**, 220—231 (1942)
28. Weiner, L. P., Konigsmark, B. W.: Hereditary diseases of the cerebellar parenchyma. Birth defects: Original Article Series **7**, 192—196 (1971)
29. Zülch, K. J.: Über die anatomische Stellung der Kleinhirnrindenatrophie und ihre Beziehung zur Nonne-Marieschen Krankheit. Dtsch. Z. Nervenheilk. **159**, 501—513 (1948)

Received October 13, 1978