Complicated Hereditary Spastic Paraparesis With Cerebral White Matter Lesions

David H. Gutmann, Kenneth H. Fischbeck, and John Kamholz

Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia

A family is described with 5 males in a single generation affected with a previously undescribed complicated form of hereditary spastic paraparesis (HSP). The disease is characterized by speech difficulties, lower limb spasticity and hyper-reflexia, mental retardation, cerebellar ataxia, and tremor. The disease starts in the first decade of life and progresses for 3 to 6 years before stabilizing. Magnetic resonance imaging (MRI) of the brain demonstrates bilateral posterior periventricular white matter lesions. Visual evoked responses are markedly prolonged, but electromyography (EMG) and nerve conduction velocity studies are normal. Three of the 4 living affected members of this pedigree exhibit red-green color vision defects. The presentation of a new complicated hereditary spastic paraparesis syndrome in this pedigree extends our understanding of the variability and heterogeneity of this syndrome and suggests an approach for the evaluation of similar families in future genetic studies.

KEY WORDS: leukodystrophy, hereditary white matter disease, dysmyelination, X-linked recessive

INTRODUCTION

Hereditary neurological disorders which result in spastic paraparesis can be separated into 2 subgroups based on whether the phenotype is "pure" or "complicated." Pure hereditary spastic paraparesis (HSP), or Strümpell disease, is manifested clinically by lower limb spasticity and hyper-reflexia without other neurological findings [Holmes and Shaywitz, 1977]. This form may be an autosomal dominant (McKusick 18260), recessive (McKusick 27080), or X-linked (McKusick 31292) trait with variable onset and clinical severity [McKusick, 1988]. Pathological analysis suggests corticospinal and posterior column tract degeneration and demyelination without involvement of the brain above the level of the medulla. In one X-linked pure HSP pedigree, linkage was demonstrated to a restriction fragment length polymorphism (RFLP) marker in the q21-22 region of the X-chromosome [Keppen et al., 1987].

Complicated HSP pedigrees are clinically variable and genetically heterogeneous. In addition to lower limb spasticity and hyper-reflexia, these kinships may have associated nystagmus, pigmentary abnormalities (McKusick 27075, 27068), mental retardation, sensory neuropathy, optic atrophy (McKusick 18283), cerebellar ataxia (McKusick 27055), movement disorders (McKusick 18280, 31289), motor neuron disease with amyotrophy (McKusick 18270), or sensorineural deafness (McKusick 31291). Complicated HSP can likewise be autosomal dominant (McKusick 18260), autosomal recessive (McKusick 27080), or X-linked (McKusick 31290). In one X-linked complicated HSP kinship (McKusick 31290), linkage was demonstrated to an RFLP marker in the q28 region of the X chromosome [Kenwrick et al., 1986]. Few of these pedigrees have been evaluated biochemically, radiographically, or electrophysiologically to exclude other known metabolic or dysmyelinating diseases.

Here, we report a previously undescribed type of complicated HSP with cerebral white matter lesions in 5 boys. This disorder is distinct from Pelizaeus-Merzbacher disease and other leukodystrophy and HSP syndromes by clinical and biochemical analysis. The relationship of this condition to previously described HSP syndromes is discussed in the context of a suggested approach for the evaluation of similar families for further study.

CLINICAL REPORTS

Five black brothers manifested a type of HSP (Fig. 1). No other relatives were affected, including 2 normal sisters (ages 26 and 28) and 10 normal sibs of the mother. The parents are from Alabama and are not known to be related to previously described kinships with complicated HSP. All patients were the product of normal gestation and delivery and appeared normal in infancy. The manifestations of the affected males in this pedigree are summarized in Table I.

Received for publication August 31, 1989; revision received November 3, 1989.

Address reprint requests to Dr. David H. Gutmann, Neurology Department, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104.

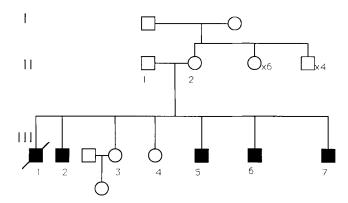


Fig. 1. The pedigree of the affected patients. Males are represented by squares and females are represented by circles. Open squares and circles represent unaffected individuals while closed squares and circles represent affected members.

Patient 1

Case II-1. The father is clinically unaffected at age 65 with normal neurological status. He has been chronically hospitalized for alcoholism and psychiatric problems. MRI of his brain was normal.

Patient 2

Case II-2. The mother has no symptoms at age 53, with normal neurological status, normal chromosomes, and normal red-green color vision. MRI of her brain demonstrated bilateral periventicular white matter lesions (Fig. 2). Visual evoked potentials were normal.

Patient 3

Case III-1. This patient walked at age one year and was normal until age 8, when he developed slurred speech and difficulty climbing stairs, and was noted to be mentally retarded. The speech and walking difficulties progressively worsened until age 11. His examination was remarkable for lower limb spasticity without weakness, generalized hyper-reflexia, and bilateral extensor responses to plantar stimulation. He wore glasses for myopia but had no auditory deficits or cerebellar-type ataxia. He developed rheumatic fever and died in 1976 at age 20 after 2 heart valve replacements. No autopsy was performed.

Patient 4

Case III-2. This 31-year-old right-handed man walked at age 9 months and developed normally until age 8, when he developed difficulty climbing stairs and slurred speech, and mild mental retardation became apparent. The speech and walking difficulties worsened progressively until age 12. On examination he had slight scissoring when walking, spastic lower limbs without weakness, a brisk jaw jerk reflex, generalized hyper-reflexia, and bilateral extensor responses to plantar stimulation with nonsustained clonus at the ankles. Funduscopic examination, red-green color vision, and visual acuity were normal. He developed seizures at age 29 which were managed successfully with phenytoin. An electroencephalogram was normal. Visual evoked

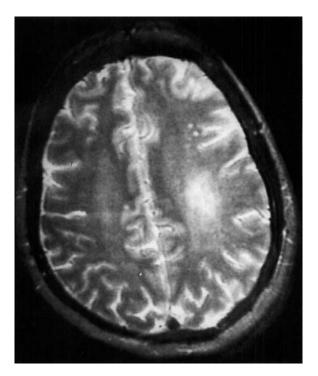


Fig. 2. Magnetic resonance imaging of II-2 demonstrating bilateral periventricular white matter disease ($T_E = 80$, $T_R = 3,000$). Images were generated on a 1.5 Tesla General Electric Signa Unit.

potentials were significant for prolongation of P100 to 115 sec bilaterally. MRI of the brain demonstrated bilateral posterior periventricular white matter lesions (Fig. 3).

Patient 5

Case III-4. This 27-year-old right-handed woman walked at age one year, developed normally, attained average grades in high school, and participated in junior high school track. On examination she was unremarkable, with normal visual acuity, red-green color vision, and fundi. MRI of the brain demonstrated periventricular white matter lesions. Visual evoked potentials were normal.

Patient 6

Case III-5. This 25-year-old right-handed man walked at age 2 years and was noted to be slower than the other children. At age 12 he developed difficulty walking and was noted to be mentally retarded. His walking difficulties continued to progress until age 15, when he intermittently required a wheelchair. On examination he had a wide-based ataxic gait, a coarse postural tremor, titubation, ataxic speech, dysmetria, spastic lower limbs without weakness, a brisk jaw jerk reflex, generalized hyper-reflexia, and bilateral extensor responses to plantar stimulation with sustained clonus at the ankles. Fundi were normal; however, he was noted to have defective red-green color vision on Ishihara color plate testing, with normal visual acuity. Farnsworth-Munsell 100-Hue color vision testing at the

Patient	Age of onset (years of pro- gres- sion)	Clinical manifesta- tions	Clinical 	Color vision	Radiology	Nd	EMG, NCV	VEP, EEG	Karyo- type	VLCFA
III-1	8 (3)	Difficulty walking, slurred speech, learning disability	Spasticity, hyper- reflexia, dysarthria	Nd	Nd	Nd	Nd	Nd	Nd	Nd
III-2	8 (4)	Difficulty walking, slurred speech, learning disability seizures	Spasticity, hyper- reflexia clonus, jaw jerk	Nl	Abnl MRI	Nd	Nd	Nl EEG, Abnl VEP	Nd	Nd
III-5	12 (3)	Difficulty walking, tremors, slurred speech, learning disability	Ataxia, spasticity tremor, clonus, jaw jerk, hyper- reflexia	Abnl	Abnl MRI	Nd	Nl	Abnl VEP	Nd	NI
III-6	6 (3)	Difficulty walking, slurred speech, learning disability tremors	Tremor, ataxia, spasticity, hyper- reflexia	Abnl	Abnl CT	NI	NI	Nd	NÌ	Nl
III-7	6 (6)	Difficulty walking, slurred speech, learning disability tremors	Tremor, ataxia, spasticity, hyper- reflexia	Abnl	Nd	Nd	Nd	Nd	Nd	Nd

TABLE I. Characteristics of Complicated HSP Syndrome*

* For details, refer to the case summaries; Nd = not done, NI = normal, Abnl = abnormal.

Wills Eye Hospital (Philadelphia, PA) demonstrated a pattern of color blindness most consistent with an acquired color vision deficit [Farnsworth, 1943]. Plasma very long chain fatty acids (VLCFA) were normal on 2 separate occasions, as were plasma and urine organic acid quantification, aryl-sulfatase A levels, and ceramide β -galactosidase levels. Visual evoked potentials were remarkable for significant prolongation of P100 to 180 msec bilaterally. Results of electromyography (EMG) and nerve conduction testing were normal. Magnetic resonance imaging of the brain demonstrated bilateral periventricular white matter lesions (Fig. 4) that failed to enhance with gadolinium (data not shown).

Patient 7

Case III-6. This 22-year-old left-handed man walked at 10 months and developed normally until age 6 when he presented with difficulty walking, mild dysarthria, and tremor. His symptoms progressed, and he required a wheelchair intermittently by age 9. A computerized tomogram of the brain at age 11 demonstrated periventricular white matter hypodensities. His performance at school continued to deteriorate, and his tremor began to interfere with his ability to feed himself. Cerebrospinal fluid was normal. VLCFA and an ACTH stimulation test for adrenoleukodystrophy (ALD) were normal. Hexosaminidase A and B levels were normal. EMG and nerve conduction velocity testing were normal. Chromosomes were normal. Examination showed mild titubation, coarse postural tremor, a scissoring spastic gait, spastic lower limbs without weakness, generalized hyper-reflexia, and bilateral extensor responses to plantar stimulation. Fundi were normal; however, he was noted to have defective red-green color vision on Ishihara color plate testing, with 20/20 visual acuity.

Patient 8

Case III-7. This 18-year-old right-handed man walked at age one year and developed normally until age 6, when he developed a tremor and difficulty walking, and he was noted to be mildly retarded. His tremor and difficulty walking continued to progress until age 12.

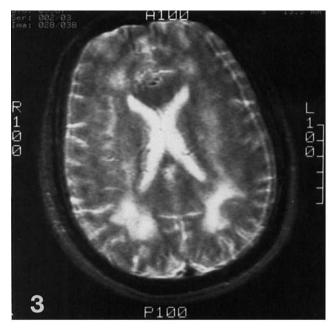


Fig. 3. Magnetic resonance imaging of III-2 demonstrating periventricular white matter disease ($T_E = 80, T_R = 3,000$).

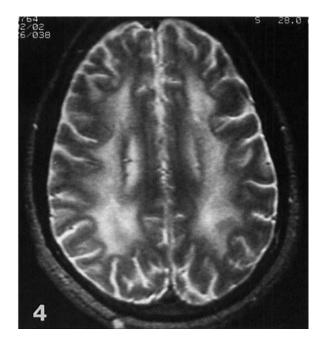


Fig. 4.Magnetic resonance imaging of III-5 demonstrating the posterior periventricular white matter disease ($T_E = 80$, $T_R = 3,000$).

His examination is remarkable for mild truncal ataxia, slight dysarthria, clumsy movement of both hands, spastic lower limbs without weakness, generalized hyper-reflexia, and bilateral extensor responses to plantar stimulation. Funduscopic examination was normal; however, he was noted to have defective red-green color vision on Ishihara color plate testing, with 20/20 visual acuity. Farnsworth-Munsell 100-Hue color vision testing performed at the Wills Eye Hospital demonstrated a pattern of color blindness most consistent with an acquired color vision deficit.

DISCUSSION

In this report we describe 5 brothers with a "complicated" form of HSP. In this family hyper-reflexia and spasticity were accompanied by ataxia, tremor, and learning disabilities with the onset in the first decade of life. Radiographic abnormalities were seen in the posterior periventricular white matter on MRI scan in both the affected men and their asymptomatic mother and sister. There is no peripheral nervous system impairment detectable by physical exam, EMG, and nerve conduction studies. Three of the 4 living men exhibit red-green color vision deficits by Ishihara color plate testing, but without optic atrophy. Visual evoked potential latencies were prolonged in the 2 individuals with color vision deficits who were tested. However, 100-Hue testing indicated that the color vision deficits were the result of an acquired process related to significant visual pathway white matter disease rather than a congenital disorder. Results of assays for aryl-sulfatase A (metachromatic leukodystrophy, MLD), galactosylceramide β -galactosidase (Krabbe disease), urinary N-aspartic glutamate (Canavan disease), hexosaminidase A and B,

and VLCFA (ALD) were all normal [Kolodny and Raghavan, 1983; Matalon et al., 1988; Moser et al., 1984; O'Neill et al., 1985; Suzuki and Suzuki, 1970; Norman et al., 1960].

Complicated HSP syndromes can be autosomal dominant, autosomal recessive, or X-linked traits, and thus represent a heterogeneous group of disorders. Only a few of these patients have been examined postmortem. and most were investigated before the development of advanced imaging studies or the delineation of biochemical markers for the leukodystrophies. Pathological analysis in 2 kinships with autosomal dominant complicated HSP demonstrated white matter destruction, demyelination, and gliosis in the periventricular areas, centrum semiovale, cerebellum, and spinal cord [Poser et al., 1957; Eldridge et al., 1984]. These areas of white matter destruction were similar to the location of the MRI findings in our patients. However, the clinical presentation among the various families with complicated HSP is quite variable (Table II), and it is likely that complicated HSP represents a number of distinct disease entities.

Other hereditary disorders can also present with spastic paraparesis and may overlap clinically with complicated HSP. These include several of the leukodystrophy syndromes, such as ALD, MLD, Krabbe disease, Canavan disease, and Pelizaeus-Merzbacher disease. The family described here has clinical manifestations similar to those found in these leukodystrophies but lacks the characteristic biochemical and radiographic abnormalities [Penner et al., 1987; Barkovich and Jackson, 1989]. Other diseases, such as hereditary spinocerebellar degeneration, Alexander disease, and hexosaminidase A and B deficiencies can

Age of onset	Clinical manifestations ^a	Pathology	Inheritance ^b	Reference
6 years	Depigmentation, foot drop, sensory neuropathy	Axonal degeneration on sural nerve biopsy	?	Abdallat et al. [1980]
0-5 years	Sensory polyneuropathy	Loss of myelinated fibers in peripheral nerve, nl CNS	?	Cavanagh et al. [1979]
1–3 years	Ataxia, cerebellar signs, nystagmus, incontinence, foot deformities, vibration and position sensation dimunition		AR	Bouchard et al. [1978]
50–60 years	Ataxia, pseudobulbar palsy, incontinence, ophthal- moparesis	—	?	Ferguson and Critchley [1929]
5–20 years 5–20 years	Ataxia, optic atrophy Central retinal degenera- tion, amyotrophy, mental retardation (+/- ophthal- moplegia)		? ?	Henkes et al. [1972] Kjellin [1959]
Variable	Mental retardation, ich- thyosis	Demyelination in frontal lobes, basal ganglia atro- phy	AR	Baar and Galindo [1965]
1–2 years	Dysarthria, amyotrophy, foot deformities, nystagmus, mental retar- dation		AR	Holmes [1905], Cross and McKusick [1967a]
5 years	Crural hypopigmentation, peroneal neuropathy, dys- arthria	_	AD	Stewart et al. [1981]
14–16 years	Pseudobulbar palsy, amyo- trophy, mental retarda- tion, nystagmus, dystonia, incontinence	Muscle motor unit atrophy	?	Gilman and Horenstein [1964]
1 year	Sensory neuropathy, mental retardation, incontinence	—	AD	Koenig and Spiro [1970]
14-18 years	Dementia, dysarthria, tremor, athetosis		AR	Cross and McKusick [1967b]
10-20 years	Distal amyotrophy	_	AR,AD	Silver [1966], Garland and Astley [1950]
5–10 years	Foot deformities, peroneal muscle atrophy, sensory neuropathy	_	?	Dyck and Lambert [1968]
1–5 years	Foot deformities, muscle at- rophy, cerebellar speech, postural dystonia	Cerebral, cerebellar and spi- nal cord white matter de- struction, basal ganglia atrophy	AD	Poser et al. [1957]
35–45 years	Cerebellar tremor, ataxia, incontinence	Decreased white matter in periventricular areas and cerebellum	AD	Eldridge et al. [1984]
5-20 years	Lead-pipe rigidity, tremor, athetosis	—	?	Dick and Stevenson [1953]
6-12 years	Learning disabilities, dys- arthria, cerebellar tremor and ataxia	Periventricular white mat- ter lesions	?	This paper
1-15 years	Movement disorder, optic atrophy, ataxia		AR	Costeff et al. [1989]
5–9 years	Athetosis, tremor, sensory loss, optic atrophy	—	XL	Bruyn and Went [1964]; Went [1964]
Birth	"Cerebral palsy", nystagmus, athetosis, cer- ebellar ataxia and tremor	_	XL	Baar and Gabriel [1966]
Birth	"Cerebral palsy", nystagmus, cerebellar ataxia and tremor	_	XL	Blumel et al. [1957]
Childhood	Nystagmus, optic atrophy, absent vibration/position sensation	_	XL	Thurman et al [1971]

TABLE II. Reported Kinships With Complicated Hereditary Spastic Paraparesis

(Continued)

256 Gutmann et al.

TABLE II. Reported Kinships With Complicated Hereditary Spastic Paraparesis (continued)

Age of onset	Clinical manifestations ^a	Pathology	Inheritance ^b	Reference	
Childhood	Mental retardation, nystagmus, optic atrophy, absent vibration/position sensation	_	XL	Johnston and McKusick [1962]	
10 years	Diminished vibration/posi- tion sensation, cerebellar ataxia/tremor, deafness, learning disabilities, nystagmus		XL	Wells and Jankovic [1986]	
Childhood	Optic atrophy, mental retar- dation	_	XL	Kenwrick et al. [1986]	

^a Clinical manifestations in addition to spasticity and hyper-reflexia.

^b Inheritance pattern (AD = autosomal dominant; AR = autosomal recessive; XL = X-linked).

also be excluded on clinical, genetic, or biochemical grounds [Adachi et al., 1973; Barrett and Becker, 1985; Konishi and Kamoshita, 1975; Konigsmark and Weiner, 1970]. The clinical presentation in this family is also different from other reports of complicated HSP in the literature (Table II), suggesting that our patients have a distinct, previously undescribed neurologic disorder.

The inheritance pattern in this pedigree is most likely X-linked recessive, since all the affected individuals are males. However, autosomal inheritance cannot be ruled out at this time. An X-linked recessive pattern of inheritance is also suggested by the abnormalities seen on MRI scans of both the mother and her asymptomatic daughter. Comparable MRI findings are also found in 10-15% of unaffected carriers of ALD, a clinically similar X-linked disorder. In one pedigree with X-linked HSP, optic atrophy, and mental retardation, linkage with the St14 (DXS52) marker at Xq28 near the ALD locus was demonstrated [Kenwrick et al., 1986; Auborg et al., 1987]. However, no MRI or VLCFA analysis was reported for these individuals.

Although the genes for "pure" and "complicated" X-linked HSP have been localized to different regions of the X chromosome, the location of the gene in our family still remains open. Preliminary RFLP analysis demonstrated no linkage to St14 (DXS52) in this pedigree. The lack of linkage to St14 suggests that the gene in this complicated HSP syndrome is not closely linked to either Xq28 or the ALD locus [Gutmann et al., 1989]. A similar result was previously reported in two other complicated HSP pedigrees [Fischbeck et al., 1987]. Linkage studies using PGK, DXS287, and proteolipid protein cDNA and genomic probes generously provided by Dr. Lynn Hudson (National Institutes of Health) were uninformative in the present family. Further molecular analysis will be necessary to define the chromosome location of the disease gene in this syndrome.

The report of this pedigree with complicated HSP

represents the most comprehensive description in the literature to date with respect to genetic, clinical, radiologic, and biochemical evaluation. Although no pathologic findings are available on our patients to demonstrate unequivocally a leukodystrophy, the clinical, radiographic, and evoked potential studies all suggest white matter disease. It is also clear that these patients are unlike any of the previously reported cases (Table II). However, the relationship of those kinships to the one reported in this communication cannot be assessed until other pedigrees are characterized more completely to eliminate defined hereditary disorders which clinically overlap with "idiopathic" complicated HSP. We conclude that these patients have a complicated X-linked or autosomal HSP syndrome and recommend that all available HSP kinships be evaluated by MRI, Farnsworth Munsell Hue-100 color vision testing, blood and urine analysis to exclude known white matter diseases, and RFLP linkage studies. Once a homogeneous group of "idiopathic" complicated HSP pedigrees is collected, genetic analysis will become more meaningful. Further characterization of these complicated spastic paraparesis syndromes may improve our understanding of myelin formation and repair in the central nervous system.

ACKNOWLEDGMENTS

We thank Dr. Hugo Moser (Johns Hopkins, Baltimore) for VLCFA analysis and helpful discussion, Drs. Paige Kaplan, Elaine Zackai, and John Sladky (Children's Hospital, Philadelphia) for insightful critique of this project, and Dr. Laura Keppen (University of Arkansas, Little Rock) and Dr. Lynn Hudson (National Institutes of Health, Bethesda) for unpublished communications.

We appreciate the help of Mrs. Sylvia Bostic and Ms. Denise Lalli in the preparation of this manuscript.

REFERENCES

- Abdallat A, Davis SM, Farrage T, McDonald WI (1980): Disordered pigmentation, spastic paraparesis and peripheral neuropathy in three siblings: A new neurocutaneous syndrome. J Neurol Neurosurg Psychiatry 43:962-966.
- Adachi M, Schneck L, Cara J, Volk BW (1973): Spongy degeneration of the central nervous system. Hum Pathol 4:331-347.
- Auborg PR, Sack GH, Myers DA, Lease JJ, Moser HW (1987): Linkage of adrenoleukodystrophy to a polymorphic DNA probe. Ann Neurol 21:349–352.
- Baar HS, Gabriel AM (1966): Sex-linked spastic paraplegia. Am J Ment Defic 71:13–18.
- Baar HS, Galindo J (1965): Pathology of Sjögren-Larsson syndrome. J Maine Med Assoc 56:223-226.
- Barkovich AJ, Jackson DE (1989): MRI assessment of normal and abnormal brain myelinization. MRI Decis 3:17-25.
- Barrett D, Becker LE (1985): Alexander's disease: A disease of astrocytes. Brain 108:367-385.
- Blumel J, Evan EB, Eggers GWN (1957): Hereditary cerebral palsy. A preliminary report. J Pediatr 50:454-458.
- Bouchard JP, Barbeau A, Bouchard R, Bouchard RW (1978): Autosomal recessive spastic ataxia of Charlevoix-Saguenay. Can J Neurol Sci 5:61-69.
- Bruyn GW, Went LN (1964): A sex-linked heredo-degenerative neurological disorder associated with Leber's optic atrophy. Part I. Clinical studies. J Neurol Sci 1:59–80.
- Cavanagh NPC, Eames RA, Gaalvin RJ, Brett EM, Kelly RE (1979): Hereditary sensory neuropathy with spastic paraplegia. Brain 102:79-94.
- Costeff H, Gadoth N, Apter N, Prialnic M, Savir H (1989): A familial syndrome of infantile optic atrophy, movement disorder and spastic paraplegia. Neurology 89:595-597.
- Cross HE, McKusick VA (1967a): The Troyer syndrome—A recessive form of spastic paraplegia with distal muscle wasting. Arch Neurol 16:473-485.
- Cross HE, McKusick VA (1967b): The Mast syndrome. Arch Neurol 16:1-13.
- Dick AP, Stevenson CJ (1953): Hereditary spastic paraplegia: Report of a family with associated extrapyramidal signs. Lancet 1:921-923.
- Dyck PJ, Lambert EH (1968): Lower motor and primary sensory neuron diseases with peroneal muscular atrophy. Arch Neurol 18:619-625.
- Eldridge R, Anayiotos CP, Schlesinger S, Cowen D, Bever C, Patronas N, McFarland H (1984): Hereditary adult-onset leukodystrophy simulating chronic progressive multiple sclerosis. N Engl J Med 311:948-953.
- Farnsworth D (1943): The Farnsworth-Munsell 100-hue and dichromatous tests for color vision. J Opt Soc Am 33:568-578.
- Ferguson F, Critchley M (1929): A clinical study of a heredofamilial disease resembling disseminated sclerosis. Brain 52:203-221.
- Fischbeck KH, Shi Y, Ritter A, Bird T, Jankovic J, Puckett C (1987): Linkage studies of X-linked spastic paraplegia. Am J Hum Genet 41:A165.
- Garland HG, Astley CE (1950): Hereditary spastic paraplegia with amyotrophy and pes cavus. J Neurol Neurosurg Psychiatry 13:130-133.
- Gilman S, Horenstein S (1964): Familial amyotrophic dystonic paraplegia. Brain 87:51-66.
- Gutmann DH, Fischbeck KH, Kamholz J (1989): Complicated hereditary spastic paraparesis with cerebral white matter lesions: Lack of linkage to Xq28. Am J Hum Genet 45:A47.
- Henkes HE, Deutman AF, Busch HFM (1972): Behr disease. In Vinken PJ, Bruyn GW (eds): "Handbook of Clinical Neurology." New York: American Elsevier Publishing Co., Vol 13, pp 88-93.

Complicated Hereditary Spastic Paraparesis 257

- Holmes G (1905): Familial spastic paraparesis associated with amyotrophy. Rev Neurol Psychiatry 3:257-263.
- Holmes GL, Shaywitz BA (1977): Strümpell's pure familial spastic paraplegia: Case study and review of the literature. J Neurol Neurosurg Psychiatry 40:1003-1008.
- Johnston AW, McKusick VA (1962): A sex-linked recessive form of spastic paraplegia. Am J Hum Genet 14:83-94.
- Kenwrick S, Ionasescu V, Ionasescu G, Searby C, King A, Dubowitz M, Davies KE (1986): Linkage studies of X-linked recessive spastic paraplegia using DNA probes. Hum Genet 41:933-943.
- Keppen LD, Leppert MF, O'Connell P, Nakamura Y, Stauffer D, Lathrop M, Lalouely M, White R (1987): Etiological heterogeneity in X-linked spastic paraparesis. Am J Human Genet 41:933-943.
- Kjellin K (1959): Familial spastic paraplegia with amyotrophy, oligophrenia and central retinal degeneration. Arch Neurol 1:133-140.
- Koenig RH, Spiro AJ (1970): Hereditary spastic paraparesis with sensory neuropathy. Dev Med Child Neurol 12:576-581.
- Kolodny EH, Raghavan SS (1983): GM2-gangliosidosis. Hexosaminidase mutations not of the Tay-Sachs type produce unusual clinical variants. Trends Neurosci 6:16-20.
- Konigsmark BW, Weiner LP (1970): The olivopontocerebellar atrophies: A review. Medicine 49:227-241.
- Konishi Y, Kamoshita S (1975): An autopsy case of classical Pelizaeus-Merzbacher's disease. Acta Neuropathol (Berl) 31:267-270.
- Matalon R, Michaels K, Sebesta D, Deanching M, Gashkoff P, Casanova J (1988): Aspartoacylase deficiency and N-acetylaspartic aciduria in patients with Canavan disease. Am J Med Genet 29:463-471.
- McKusick VA (1988): "Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes." Eighth edition. Baltimore: The Johns Hopkins University Press.
- Moser HW, Moser AE, Singh I, O'Neill BP (1984): Adrenoleukodystrophy: Survey of 303 cases. Ann Neurol 16:628-641.
- Norman R, Urich H, Tingey A (1960): Metachromatic leuko-encephalopathy: A form of lipidosis. Brain 83:369-380.
- O'Neill BP, Swanson JW, Brown FR, Griffin JW, Moser HW (1985): Familial spastic paraparesis: An adrenoleukodystrophy phenotype? Neurology 35:1233-1235.
- Penner MW, Li KC, Gebarski SS, Allen RJ (1987): MR imaging of Pelizaeus-Merzbacher disease. J Comput Assist Tomogr 11:591-592.
- Poser CM, Dewulf A, Van Bogaert L (1957): Atypical cerebellar degeneration associated with leukodystrophy. J Neuropathol Exp Neurol 16:209–237.
- Silver JR (1966): Familial spastic paraplegia with amyotrophy of hands. Ann Hum Genet 30:69-73.
- Stewart RM, Tunnell G, Ehle A (1981): Familial spastic paraplegia, peripheral neuropathy and crural hypopigmentation: A new neurocutaneous syndrome. Neurology 31:754-757.
- Suzuki K, Suzuki Y (1970): Globoid cell leukodystrophy: Deficiency of galactocerebrosidase-beta-galactosidase. Proc Natl Acad Sci USA 66:302-309.
- Thurman TF, Walker BA, Scott CI, Abbott MH (1971): Two kindreds with a sex-linked recessive form of spastic paraplegia. In Bergsma D (ed): "BD:OAS." Baltimore: Williams and Wilkins, Vol VII, Part VI (#1), pp 219-221.
- Wells CR, Jankovic J (1986): Familial spastic paraparesis and deafness. A new X-linked neurodegenerative disorder. Arch Neurol 43:943–946.
- Went LN (1964): A sex-linked heredo-degenerative neurological disorder associated with Leber's optic atrophy. Part II. Laboratory investigations. J Neurol Sci 1:81–87.