

Sex-Linked Hereditary Ataxic Diplegia, the Borderland Between Cerebral Palsy and Pelizaeus-Merzbacher Disease

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SUMMARY: *After a review of the literature concerning hereditary cases of cerebral palsy, a family is reported in which ataxic diplegia appears to be inherited as a sex-linked and probably recessive condition occurring in 3 males in successive generations. This ataxic diplegia, occurring after an unremarkable perinatal course, is associated with mild to moderate mental retardation, congenital nystagmus and significantly small stature and prevents the acquisition of free walking. Associated extrapyramidal features may gradually become more marked, while the nystagmus may subside. The condition is similar to that*

described in three previous reports in the literature. No evidence of linkage with other sex-linked disorders has been found, Xg^a typing showed that recombination between the Xg locus and the locus for hereditary ataxic diplegia has occurred once out of three possible opportunities. In the absence of neuropathological findings or specific biochemical tests, the differential diagnosis from Pelizaeus-Merzbacher disease cannot be made with certainty. The differentiation from other progressive sex-linked neurological disorders is discussed.

RÉSUMÉ: *Après une revue de la littérature sur les cas héréditaires de paralysie cérébrale, la cas d'une famille, dans laquelle une ataxie diplégique apparaît de façon héréditaire à être liée au sexe et probablement chez 3 mâles de 3 générations successives, est rapporté. Cette ataxie diplégique survenant après une période périnatale peu remarquable, est associée à un retard mental léger, à un nystagmus congénital, à une petite taille et ne permet pas l'acquisition d'une démarche libre. Les signes extrapyramidaux associés peuvent graduellement devenir plus marqués pendant que le nystagmus peut*

s'atténuer. La condition est presque similaire à celle décrite dans trois rapports antérieurs de la littérature. Aucune évidence n'a été donnée du lien avec les autres désordres liés au sexe. Un typage Xg^a montrait que la recombinaison entre le locus Xg et le locus pour l'ataxie diplégique est survenu une fois sur trois possibilités. En l'absence de constatations neuropathologiques ou de tests biochimiques spéciaux, le diagnostic différentiel de maladie de Pelizaeus-Merzbacher ne peut pas être fait avec certitude. La différenciation des autres désordres neurologiques liés au sexe est aussi discutée.

The importance of genetic factors in the etiology of cerebral palsy is still somewhat controversial, though occasional cases have a clear family history of similar disability. With regard to spastic forms, Paskind and Stone in 1933 were able to analyze 152 families in the literature, in whom familial cases had been described. Among these, spastic paralysis had been found in two generations in 32 instances and in 3 or more generations in 13 instances. The literature has also been reviewed by Rhein (1916), Bell and Carmichael (1939), Polani (1963), Ingram (1964) and Glenting (1970). The exact frequency of hereditary cases is hard to determine since the mere occurrence of cerebral palsy in siblings may be due to environmental factors like prematurity or maternal toxemia, rather than genetic causes. Also, the frequency depends on the definition of the cerebral palsy syndrome; as most recent authors insist that this should strictly exclude any progressive lesions, conditions like hereditary spastic paraplegia cannot be considered in this context (MacKeith et al 1959, Bax 1964, Glenting 1970).

In surveys of cerebral palsy the prevalence of the condition in siblings has been found to range from about 3% to 5% (Blumel et al 1957, Mitchell 1961, Ingram 1964). The prevalence in all relatives in direct descent of the grandparents has been found to be about 10% (Ingram 1964, Glenting 1970). In general, cerebral palsy tended to affect members of the family in a horizontal rather than vertical direction on the pedigree, thus suggesting mostly recessive inheritance. However, environmental factors could then not be excluded, and Glenting (1970) noted that the

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incidence of consanguinity among parents was only 1.2%, compared to 2.1% among the general population. A closer investigation of etiological possibilities in his survey showed that a tendency to premature birth might be related to the condition, but that otherwise birth factors could not be considered significant. He concluded cautiously that genetic factors might well be responsible for some cases of spastic cerebral palsy, and that some familial cases might be part of hereditary syndromes. Twin studies (Gedda 1955, Hansen 1960, Glenting, 1970) and the finding of chromosome defects among possibly 1% of cerebral palsied patients with severe mental retardation (Polani 1963) point towards the same conclusion. Neuro-pathological studies demonstrating developmental brain defects in familial cases would be of great value in supporting the hereditary nature of the condition but have rarely been available (Paskind and Stone 1933, Christensen and Melchior 1967). In a Swedish survey, Gustavsson et al (1969) concluded that about 1.5% of all cases of cerebral palsy were inherited as an autosomal recessive, while other modes of inheritance were rarer.

In ataxic forms of cerebral palsy the proportion of hereditary cases appears greater than in the purely spastic type. Ingram (1962) suggested that two major categories of ataxic cerebral palsy could be defined, namely "ataxia" and "ataxic diplegia." The former tends to be accompanied by persistent hypotonia dating from birth, while the latter shows some features of spastic diplegia associated with the ataxia. In an analysis of 29 patients with congenital ataxia and 33 patients with ataxic diplegia, Ingram found that about one-half of each group had been delivered normally after normal pregnancies and that one-half of the mothers' previous pregnancies had resulted in abortion, perinatal or infant death, or the birth of an abnormal child. Also, about 20% of the ataxic children had associated major developmental malformations. Skatvedt (1958) had previously pointed out that patients

with ataxic forms of cerebral palsy often had defects of vision, eye movements, hearing and speech, and Ingram noted that only 36% of those with ataxia and 21% of those with ataxic diplegia had normal intelligence. He concluded that a developmental malformation of the brain was probably more important than birth injury in the majority of patients with ataxic forms of cerebral palsy. Such a malformation (sometimes associated with hydrocephalus) might then be genetically determined or due to teratogenic factors in early pregnancy. In 1964, Ingram mentioned that among 12 patients with ataxic diplegia, 5 had a family history of possible significance. In 2 of these the mother also had ataxic diplegia, suggesting that the disease was inherited in a dominant manner. In their Swedish survey, Gustavsson and his collaborators (1969) collected 43 families in whom more than one member had cerebral palsy, and these included 16 families with identical syndromes and a history of normal pregnancy, delivery and perinatal period. Among these 16 families, which were of main genetic

importance, there were 10 with congenital non-progressive ataxia and mental retardation, and 3 with ataxic diplegia. The ataxia and mental retardation appeared to be inherited as an autosomal recessive condition; in one of the 3 families with ataxic diplegia, the disease appeared to be due to a dominant gene, possibly with varying expressivity. One family with only a brother and sister affected by ataxic diplegia was subsequently published in detail by Hagberg et al (1970), since the patients were also found to have deficient cellular immunity.

We report a family in whom ataxic diplegia appears to be inherited as a sex-linked and probably recessive condition. We have found only three previous reports in the literature concerning this mode of inheritance in ataxic diplegia, and in all three families the clinical picture was remarkably similar to that in our patients (Wolfslast 1943, Blumel et al 1957, Baar and Gabriel 1966). However, the condition may also be clinically indistinguishable from Pelizaeus-Merzbacher disease with a very slow course.

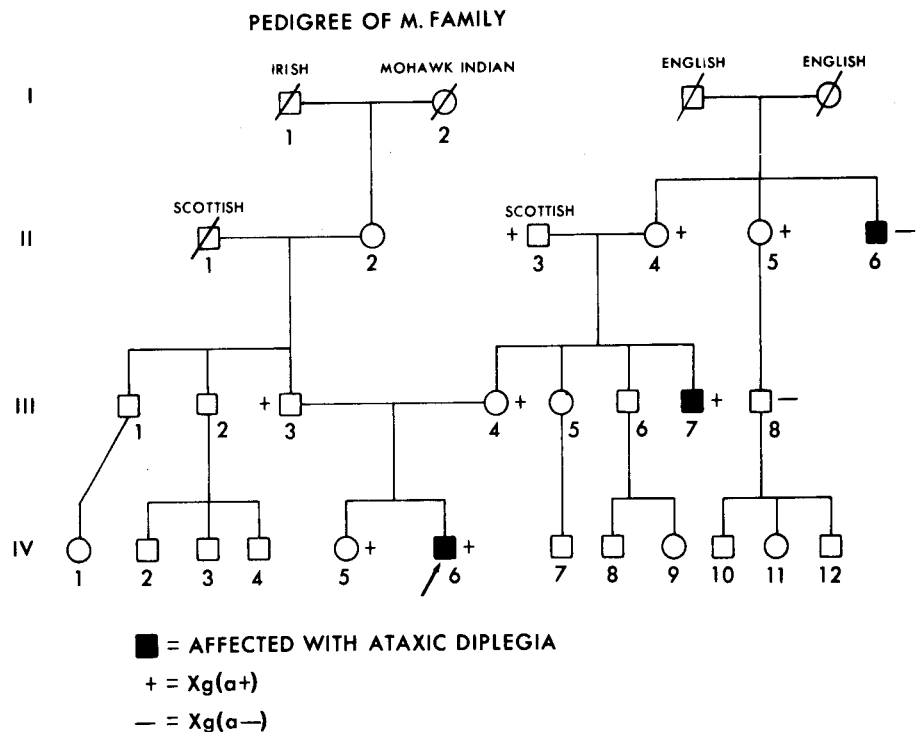


Figure 1. Pedigree of patients' family.

CASE 1 (IV. 6)

C.M., a Canadian boy, is the younger of 2 children, and his older sister and parents are healthy (Fig. 1). The pregnancy was unremarkable. He was delivered normally 2 days after term, and though the cord was said to have been tight around the neck, he cried well and obtained an Apgar score of 8 at 1 minute. The birth weight was 7 lbs. 8 ozs. (3,403 g.). After discharge from hospital at the age of 5 days, he had some projectile vomits and cried excessively, but gained weight satisfactorily.

About one week after birth the infant was first noted to have "wobbly eyes." He smiled in response at 5 months, and mental retardation was suspected at 8 months when he first learned to roll over. At 15 months he began to crawl. He said the first words with meaning at 1½ years. He learned to remain sitting unsupported at 20 months, to pull himself to sitting at 22 months and to standing at 3 years. After that he began to take steps with support, but he never learned to walk freely without supports or appliances.

At 1½ years cerebral palsy was diagnosed, and physiotherapy was arranged. At 3 years he was temperamental and easily frustrated and obtained a D.Q. of 52 on the Cattell Infant Intelligence Scale, whereas he had been assessed as

having a D.Q. of 65-75 on the same test a year earlier. Chromosome analysis then showed him and his mother to have a normal karyotype.

Physical examination at 3 years 10 months showed an auburn-haired, fairly alert and happy but irritable little boy. His length of 92 cm was about 3 S.D. below the mean, and his weight of 14.5 kg was satisfactory for the length-age. The head circumference of 48.5 cm was about 2 S.D. below the mean. He had a slight anti-mongoloid slant of the palpebral fissures and an inexpressive facies (Fig. 2), with excessive drooling. The hands were mostly fisted but at times adopted an "avoidance" position. The dermatoglyphs on the hands showed a radial loop on the right middle finger and double axial triradius and concomitant A^u/L^{dr} pattern in the right hypothenar area and were otherwise unremarkable (Table I). He sat with a long C kyphosis, and the hip adductors, hamstrings and heelcords were tight.

The boy appeared right-handed. His speech consisted mostly of single words which were poorly articulated. On the Gesell scale of behavioral development he had mastered all the non-motor items at the 18 months' level except toilet control by day. He also accomplished about half the expected non-motor skills at the 2-year level but hardly any beyond that.

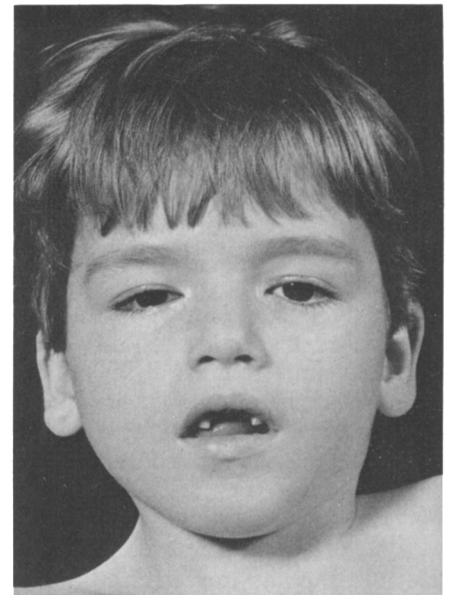


Figure 2. Photograph of Case 1 at 6½ years.

The optic fundi were normal apart from mild pallor of the optic discs. The range of eye movements was full, but there was a fine pendular and somewhat rotary nystagmus, noticeable on forward gaze, with superadded jerk component on lateral gaze. The mouth was often open, facial movement restricted. He appeared to hear satisfactorily, and the

	Digital patterns and ridge counts						Palms					Hypothen.	Then I ₁	I ₂	I ₃	I ₄	Soles Hal			
	5	4	3	2	1	(L) Total	(R)	1	2	3	4							5	Axial triradius (atd)	
II.3, father of Case 2	U	U	U	U	U			W	W	U	W	U	(L) t' (36°), t' (32°)	A ^u /A ^c	O	O	L ^d	D	L ^d	
	13	13	14	12	15	67	154	87	18	19	13	21	16	(R) t' (38°)	L ^u /A ^c	O	O	L ^d	O	L ^d
II.4, mother of Case 2	U	U	U	U	U			U	R	U	W	W	(L) t' (42°)	A ^u /A ^c	O	O	V	O	L ^d	
	17	17	13	12	16	75	159	84	16	15	13	17	23	(R) t' (42°)	A ^u /A ^c	O	O	O	O	L ^d
II.6, Case 3	U	W	U	W	U			W	W	W	W	U	(L) t' (51°)	L ^d /A ^c	O	O	O	L ^d	—	
	14	15	14	11	18	72	140	68	20	14	11	12	11	(R) t' (36°)	A ^r /O	O	O	O	L ^d	—
III.4, mother of Case 1	U	U	U	U	U			W	R	U	W	U	(L) t (35°)	O	O	O	O	L ^d /L ^d	O/O	
	17	16	9	11	19	72	147	75	18	13	11	17	16	(R) t (38°)	O	O	O	O	L ^d /L ^d	L ^d
III.5, sister of Case 2	W	W	U	W	W			W	W	U	W	W	(L) t' (41°)	A ^u /A ^c	O	O	O	L ^d	L ^d	
	24	23	13	20	21	101	196	95	20	21	12	21	21	(R) t' (37°)	A ^u /A ^c	O	O	O	L ^d	L ^d
III.7, Case 2	U	W	W	W	U			W	W	R	W	U	(L) t' (46°)	A ^u /A ^c	O	O	O	L ^d	W	
	17	25	24	17	24	107	218	111	27	21	21	21	21	(R) t' (40°)	A ^u /A ^c	O	O	L ^d	O	O/O
IV.6, Case 1	U	U	U	R	U			W	R	R	U	U	(L) t (36°)	A ^u /A ^c	O	O	O	L ^d	O/O	
	13	12	4	2	15	46	129	83	21	13	13	19	17	(R) t (38°), t (38°)	A ^u /L ^{dr}	O	O	L ^d	O	O/O
IV.7, son of III.5	U	U	R	R	U			U	R	U	U	U	(L) t' (58°)	A ^u /A ^c	O	O	O	L ^d	L ^d	
	17	19	4	17	12	69	153	84	19	15	12	22	16	(R) t' (55°)	A ^u /A ^c	O	O	O	L ^d	L ^d

Table I — Dermatoglyphic patterns

remaining cranial nerves were unremarkable.

The upper limbs were mildly hypertonic, with excessive resistance to passive supination. Seizing of objects was awkward and jerky, with primitive spreading of fingers. The tendon reflexes were present symmetrically, and no sensory defect was demonstrated. Sitting balance was poor, unless he sat between his flexed legs, and there was slight truncal tremor and head titubation.

The lower limbs were moderately hypertonic with brisk tendon reflexes and bilateral sustained ankle clonus. The plantar and Chaddock responses were extensor on both sides. When one ankle was elevated in the Collis test, the opposite leg tended to remain adducted and often extended. There was no proper

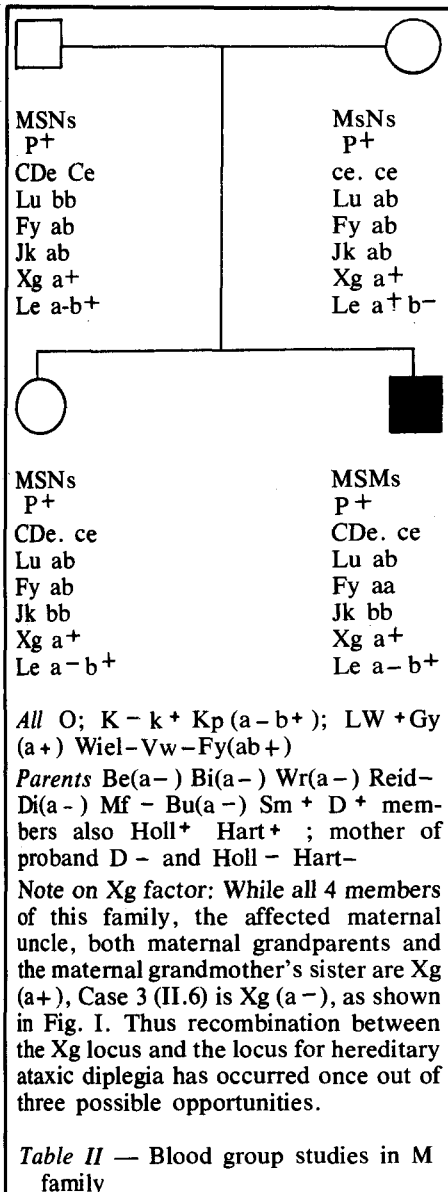
crawling but only a "bunny hop." When supported in the standing position, the boy showed marked truncal ataxia and tended to stand on tiptoe or on the inner borders of the feet. He took a few steps with "scissoring."

At 5 years, he was examined by an ophthalmologist who noted that he could find a 6 mm white ball almost anywhere in space, indicating generally satisfactory vision and visual fields. There was no marked unilateral suppression on testing with the Worth 4-color elimination dots. The presence of a fine pendular type of nystagmus in the direction of gaze was confirmed, and a jerk component appeared to develop on peripheral gaze. Cycloplegic refraction revealed moderate bilateral hyperopic astigmatism. Funduscopy showed no abnormality apart from a localized whitish appearance of both optic nerve heads attributed to gliosis. Corrective glasses were prescribed.

Investigations: X-ray examination of the left hand and wrist indicated a significantly retarded bone age of 2 years at a chronological age of 3 years 10 months. Films of the skull and pelvis showed no abnormality. An electroencephalogram

at that age showed poorly regulated and sustained alpha rhythm of 8 to 9½ Hz and also much 4 to 7 Hz activity of low voltage in both occipital leads. Thus the record was somewhat dysrhythmic in the waking state, whereas the sleep record was unremarkable. The following investigations had normal results: urine osmolality and tests for specific gravity, reducing sugars and protein; urine screening for excessive amounts of keto acids or mucopolysaccharides and for abnormal amino acids (on two-dimensional paper chromatography); complete blood count, assay of Factors VIII and IX, and of glucose-6-phosphate dehydrogenase (by Brilliant Cresyl Blue method); serum levels of calcium, phosphate, alkaline phosphatase, uric acid and protein, and electrophoretic pattern of proteins. The mother's blood count, serum calcium, phosphate, alkaline phosphatase and uric acid levels were also normal. The blood grouping of the family is shown in Table II, and the serum immunoglobulin levels are listed in Table III.

Later, at 7 years, pure tone screening at 15 db showed hearing within normal limits in both ears. Electronystagmo-



	Age (yrs)	IgG (mg.%)	IgA (mg.%)	IgM (mg.%)
II.3, father of Case 2	86	<u>1700</u> (710-1540)	<u>670</u> (60-490)	45 (37-204)
II.4, mother of Case 2	67	1400 (710-1540)	490 (60-490)	215 (42-261)
II.5, sister of Case 3	65	1250 (710-1540)	410 (60-490)	252 (42-261)
II.6, Case 3	45	<u>1700</u> (710-1540)	280 (60-490)	100 (37-204)
III.3, father of Case 1	38	<u>650-700</u> (710-1540)	426 (60-490)	87 (37-204)
III.4, mother of Case 1	36	<u>650-700</u> (710-1540)	170 (60-490)	110 (42-261)
III.7, Case 2	25	1250 (710-1540)	300 (60-490)	145 (37-204)
III.8, son of II.5	40	890 (710-1540)	180 (60-490)	120 (37-204)
IV.5, sister of Case 1	10	<u>600-650</u> (720-1600)	85 (48-368)	120 (36-256)
IV.6, Case 1	4½	500-550 (550-1490)	<u>344</u> (36-232)	74 (36-204)
	6½	550-600 (550-1490)	<u>290</u> (36-232)	80 (36-204)
		<u>450-500</u> (620-1550)	<u>310</u> (46-284)	43 (36-208)

Note: Underlined values are outside normal range for age of patient.

Table III Serum immunoglobulin levels in members of family (normal range for age according to Allansmith et al [1968] in brackets)

graphy (Dr. R. P. Gannon) showed some large amplitude saccades with the eyes open and closed, and a slow right-beating nystagmus with the patient blindfolded in the dark. Gaze testing did not demonstrate any significant nystagmus, but both command and pursuit movements were performed poorly. Superimposed on all the eye movements was a fine oscillation of roughly sinusoidal pattern with a frequency of about 4 per second, not significantly affected by eye opening or closure. Caloric responses to irrigation at 30 and 44 C. showed that both labyrinths were functioning normally, but while a right-beating nystagmus was induced normally from either ear, any induced left-beating nystagmus was either distorted or absent, thus indicating extreme directional preponderance, presumably of brain stem origin. Electronystagmography also demonstrated a significant positional nystagmus and directional preponderance to the right in the proband's healthy sister (IV.5) but not in the mother (III.4).

Conduction in the motor and sensory fibers of the right median nerve and in the motor fibers of the right lateral popliteal nerve was normal. Electromyography of the right tibialis anterior muscle was unremarkable apart from features consistent with an upper motor neuron lesion. Lumbar puncture showed clear colorless fluid with an opening pressure of 180 mm, white blood cells 3 per cu mm (75% polymorphonuclears), red blood cells 120 per cu mm, protein 19 mg per 100 ml and gamma globulin 1.6 mg per 100 ml (8.5% of total protein), glucose level normal, V.D.R.L. non-reactive, colloidal gold curve 112110.

Course. A diagnosis of ataxic diplegia with mild mental retardation, congenital nystagmus and significantly small stature was made. The boy continued to make slow progress in his physical and mental development while attending a pre-school class and receiving physiotherapy and speech stimulation. He gradually developed some choreo-athetoid movements of the hands, whereas the nystagmus diminished. At 4 years sitting balance had improved, and below-knee braces were used. At 4 years 3 months he achieved an I.Q. score of 48 on the Stanford-Binet (Form L-M) test. At 5 years he was fitted with above-knee braces, as his attitude of hip and knee flexion had increased. At 6½ years a proximal hamstring release operation was performed. At 7 years he was beginning to form 3-word sentences. At 7 years 5 months his abilities were increasing very slowly, and the Stanford-Binet

I.Q. score was about 38. The Peabody Picture Vocabulary Test showed vocabulary recognition corresponding to an I.Q. of 66. He could then walk short distances precariously in his braces with a paraplegic walker. His truncal ataxia, titubation of the head and choreoathetosis were accompanied by considerable intention tremor and were worse on walking.

CASE 2 (III.7)

D.C., the maternal uncle of Case 1 (see Fig. 1), also had a normal pre-natal and birth history. His birth weight was about 6 lbs. 5 ozs. (2,863 gm) at term. Nystagmus was noted during the first 6 months, and then the mother became concerned at his failure to learn how to remain sitting. He always used his hands better than his legs. At 3 years he was diagnosed as having cerebral palsy and had become fully toilet-trained. At 5 years he began to attend a cerebral palsy center, where he received physiotherapy. At 8-9 years he had learned to walk with crutches. Bilateral subtalar arthrodeses were then performed, but he gradually lost his ability to walk freely. He managed to feed himself with a spoon, though unsteadily, and he was described as cheerful and relating well to other children. He formed long sentences, but articulated poorly. He was thought to have an I.Q. of 77 on the Stanford-Binet scale at the age of 7 years, but of only 52 at nearly 11 years, and a full-scale I.Q. of only 46 (Verbal Score 53, Performance Score 44) on the Wechsler Intelligence Scale for Children at 14½ years. The reason for this appar-

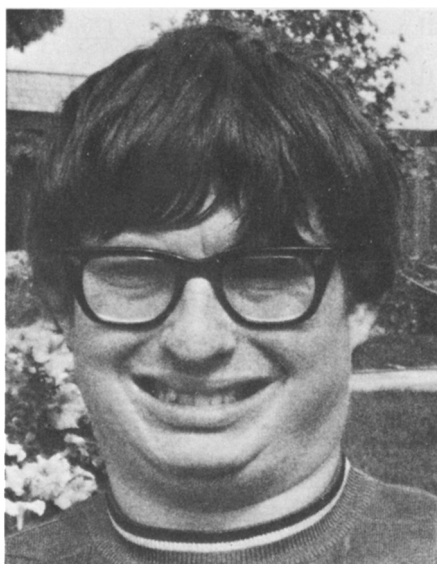


Figure 3. Photograph of Case 2 at 25 years.

ent fall in ability was considered to be that the later tests were more heavily weighted with tasks requiring abstract thinking, and it was not thought that there was any real fall in ability. By the age of 14 years, a mixed form of cerebral palsy had been diagnosed with spasticity (chiefly in the legs), ataxia and athetosis, and mild secondary flexion contracture of the hips and knees. Glasses were prescribed for a refractive error.

This lad was reported to be a good, steady worker in the cerebral palsy workshop, but was very dependent and had difficulty with fine hand movements. He was wheelchair-bound, but he could transfer to and from bed and toilet, crawled and got around on his knees at home. He had some limited ability to read, write and do simple arithmetic, but added little to this in his teen years. At 19 years he was discharged from the cerebral palsy center and continued to attend a sheltered workshop. At 24 years he was admitted to a residence for handicapped persons in Ontario. Like his maternal uncle (Case 3) he was said to be fond of music.

Physical examination at the age of 22 years showed a pleasant, well-nourished, dull lad with brown hair and blepharitis (Fig. 3). His height of 153 cm was significantly small (more than 4 S.D. below the mean). The head circumference of 55 cm was within normal limits. Many teeth had been filled; the lower wisdom teeth had erupted. The dermatoglyphs showed a radial loop in the right middle finger (as in Case 1) and an unusually high digital ridge count (as in his sister III.5) but were otherwise normal (Table I). The finger joints were unusually extensible, the operated feet were somewhat fixed in mild pes planus. There were moderate flexion contractures at the hips and knees, and the hip adductors were tense, with intertrigo of the left groin. The spine showed slight dorsal kyphosis. The deltoids, biceps brachii and thigh muscles were well-developed, whereas the calves were small. The heelcords were only moderately tight, and both ankles could be dorsiflexed passively beyond 90°.

D. C. was right-handed and right-eyed. His speech consisted of sentences, but was uttered slowly and monotonously with staccato quality. He was able to add small numbers, to print slowly and to draw simple big figures clumsily, but he could not name coins. Stereognosis was only fair in both hands. He also had some apraxia, e.g. for rubbing his hands when washing with soap.

Visual acuity appeared satisfactory with glasses, and color vision was grossly intact. The optic fundi were normal apart from mild pallor of both optic discs. There was fixation nystagmus, and jerk nystagmus was noted in the directions of lateral gaze; pursuit movements of the eyes were saccadic but appeared conjugate. The face was somewhat inexpressive. Hearing was normal for whisper and wrist watch. Otherwise, apart from dysarthria and slow protrusion of the tongue, the cranial nerves appeared intact.

The upper limbs were mildly hypertonic with fair power and brisk tendon reflexes. Arm and hand movements were slow and ataxic with dysmetria and action tremor. He was able to throw a ball, but could not catch it. Grasp and pinch were strong. The outstretched hands showed some athetoid posturing. No sensory defect was demonstrable apart from slightly impaired stereognosis and doubtful vibration sense in the fingers. The abdominal skin responses were absent. The lower limbs were markedly hypertonic, with grossly exaggerated knee and ankle jerks, sustained ankle clonus, crossed adductor responses, extensor plantar and Chaddock responses, and diminished power, especially in muscles below the knees. He managed to stand and turn unsteadily with support and with the legs flexed and adducted, but had very little ability to make movements of progression.

The only investigations performed on D.C. were for Xg blood factor and serum immunoglobulins. He proved to be Xg (a+) like both his parents. The immunoglobulin levels are listed in Table III.

CASE 3 (II.6)

A.D., maternal great-uncle of Case 1 and maternal uncle of Case 2 (Fig. 1) was born in Lancashire, England, in 1928. His father and mother are reported to have been in good health and to have died at 72 and 71 years, respectively. According to his older sister (II.5) the mother was one of 8 children, including only one male, and there was no nervous disease among any of these or among their offspring, except that one sister's daughter died of meningitis. However, it may be noteworthy that 3 of the mother's sisters, though married, had no children. A.D.'s father was evidently the 7th son among 10 children, and again there was no family history of nervous disease except that one of his sisters had a retarded son who did not have cerebral palsy.

Little is known about A.D.'s delivery, but he was evidently considered healthy initially and was brought to Canada at the age of one year. He was slow to talk and never learned to walk freely, but as a boy got around with a walker, dragging his feet. He spoke mostly in single words, but managed to form short sentences, especially when excited. Until the age of about 10 years he was noted to have an "eye wobble." He did not attend any pre-school or school, became wheelchair-bound and gradually developed a moderate spinal deformity and flexion contractures.

At 33 years he was admitted to a residential institution for the aged and handicapped in Ontario. On admission it was noted that he was an "imbecile" and unable to read, but had toilet control, was able to feed himself solids, used crayons and knew colors. The blood pressure was 110/60, and a chest x-ray showed no abnormality.

Physical examination at the age of 42 years showed a crippled man who was greying prematurely and appeared to have moderate acne rosacea and blepharitis (Fig. 4). His length of about 132 cm was significantly small. The head circumference of 52 cm was near the lower limit of the normal range for an adult. The teeth consisted mostly of carious stumps. In addition to the blepharitis he had a small marginal corneal ulcer and circumcorneal injection in the left eye. The tongue appeared somewhat prominent. The spine exhibited marked kyphoscoliosis, convex

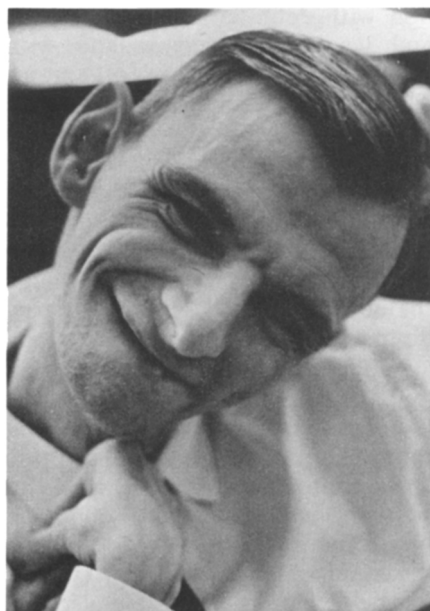


Figure 4. Photograph of Case 3 at 42 years.

toward the right in the dorsal and toward the left in the lumbar region, while the legs were both held together toward the left side. The hips and knees exhibited flexion contractures. As in Case 2, the deltoid and biceps brachii muscles were well-developed and strong, whereas the calves and forearms were thin. The heelcords were tight and shortened, the feet flat, with flexed toes. The dermatoglyphs were unremarkable and did not show a radial loop on the right 3rd digit as in Cases 1 and 2. The hands were elongated, fingers hyperextensible. The heart and lungs were normal, B.P. 100/60. The left testis was undescended.

A.D. was friendly and appeared moderately orientated but dull. He was right-handed and right-eyed. His speech was slow and slurred and consisted mostly of single words. He understood colors and other simple concepts like "up" and "down." He used his hands fairly well, whereas the legs were stiff in flexion. No asymmetrical tonic neck response could be demonstrated.

The optic fundi were normal apart from mild pallor and cupping of the discs. The eyes followed poorly in pursuit, but the eye movements appeared coordinated, and no nystagmus was evident. Opticokinetic nystagmus could not be elicited. The pupils appeared normal. Facial expression was somewhat restricted. Chewing and lip closure appeared slow. The gag response was brisk. The tongue was protruded centrally to a moderate extent. Otherwise the cranial nerves appeared intact.

The upper limbs were slightly hypertonic, biceps and supinator jerks brisk. Power was fair, but hand movements were slow with mild dysmetria and poor coordination of fingers. Position and touch sensation in the fingers appeared intact, vibration sense doubtful. Abdominal and cremaster skin responses could not be elicited.

The lower limbs were markedly hypertonic, especially the hip adductors and heelcords. Spontaneous clonus of the whole legs was observed at times. Flexion contractures at the hips and knees restricted even passive movements, and the ankles could not be dorsiflexed beyond 90°. The knee and ankle jerks were very brisk, with sustained ankle clonus and crossed adductor responses. The plantar and Chaddock responses were extensor. A.D. had to be held in the standing position and was unable to take any steps. He appeared quite unsteady on his feet; the heel-shin test could not be performed. Pain, touch and position

sense in the toes appeared intact, while vibration sense was doubtful.

This man was seen by an ophthalmologist who considered his eye movements full and adequately coordinated. The presence of fairly severe squamous blepharitis with marginal ulceration of the left cornea was confirmed. The corneae were otherwise clear and the anterior chambers of average depth. The pupils and their light reaction were considered normal, reaction to accommodation could not be tested. After instillation of mydriatic the lenses were seen to be in normal position, media clear. There was mild pallor and cupping of the optic nerve heads, resembling in mild form the changes seen in patients with long-standing glaucoma. The retinal vessels appeared grossly normal, and the intraocular pressure felt normal to fingers, but accurate tonometry was impossible.

On investigation this man proved to be Xg(a-), whereas his sister (II.5) was Xg(a+) like Cases 1 and 2. The serum immunoglobulin levels are listed in Table III.

DISCUSSION

The clinical features of our three patients may be summarized as follows:

1. Non-progressive or slowly progressive ataxic diplegia after unremarkable perinatal course, with inability to walk freely without supports or appliances, ultimately making the patient wheelchair-bound. Sometimes mild associated extrapyramidal features, e.g. choreoathetosis of hands, titubation of head, static truncal tremor.
2. Non-progressive or slowly progressive mild to moderate mental retardation.
3. Congenital nystagmus, rotary or pendular or jerky, often subsiding with age.
4. Significantly small stature. (Retarded bone age also demonstrated in Case 1.)
5. Slight gliosis of optic nerve heads without definite optic atrophy.

In reviewing the literature we encountered three reports of similar families. Wolfslast (1943) described 5 affected males in 2 generations in a

German family. The proband was noted at the age of 9 months to have horizontal-rotary nystagmus, a "weak neck," inability to remain sitting, flexor hypertonus and increased tendon reflexes (particularly in the legs). Later, he exhibited mild head tremor and dysarthria, and at 6 years was able to get around with a walker, but was still unable to stand freely. A pneumoencephalogram was reported to show cortical atrophy. His older brother, aged 10 years, presented similar findings and also bilateral choreoathetosis, inability to sit freely, ankle clonus and extensor plantar responses. Neither this brother nor an affected cousin, aged 19 years, received any schooling, but the cousin did know his age and weight. An affected retarded maternal uncle, aged 43 years, was in an institution and also exhibited head shaking, nystagmus, dysarthria and ataxia of both arms as well as "spastic paraplegia" with secondary contractures. Blumel and her associates (1957) reported 4 affected males in 2 generations in a Mexican family. The proband was a full-term child who had no difficulty at or after birth. He passed his milestones of development with delay and at 10½ years was still unable to stand freely. He had slight nystagmus and essentially spastic paraplegia. His younger brother had a similar condition with definite lateral nystagmus and was considered spastic with cerebellar pathway involvement. The maternal uncle was said to have the same type of cerebral palsy, including eye involvement. Baar and Gabriel (1966) published a brief account of the most extensively affected family, in which 13 males in 5 generations had a condition which the authors termed sex-linked spastic paraplegia. As noted by Knox (1967) it is clear from the description that all four limbs were affected, but the legs more than the arms, and thus the term diplegia would be more appropriate. The proband, a boy of 14 years, was wheelchair-bound and was found to have an I.Q. of 35 on the Stanford-Binet and an I.Q. of 36 on the Columbia Scale. He also had marked dorsal kyphoscoliosis, nystagmus, impaired facial movements,

extremely active gag response and spastic tongue. Athetotic movements and marked cerebellar signs were present in the upper limbs. The spinal fluid was evidently normal, with a protein level of 40 mg.%. Skull films showed a very small cranium with poor development of frontal fossa. An electroencephalogram was reported as very abnormal, with severe cerebral dysrhythmia but without any focal changes. The younger brother, aged 12 years, was similarly affected and was thought to have I.Q.s of only 20 and 18 on the Stanford-Binet and an I.Q. of 26 on the Columbia Scale. His spinal fluid was similarly normal, while an electroencephalogram was said to be within normal limits. The blood levels of glucose-6-phosphate dehydrogenase and plasma fibrinogen concentration were checked in both brothers and were normal; both boys were Xg(a-). The authors state that the affected males in the family appeared normal at birth and subsequently developed signs of cerebral palsy; the mother was able to predict this because the eyes were unsteady and shaky. The age of onset was under 1 year in all affected males, and they were all retarded and had similar physical findings. There was no sign of color blindness. Thus, there was no evidence of any associated sex-linked disorder.

It is evident that all these cases in the literature fit into the same sex-linked syndrome, though no details of stature, optic fundi, dermatoglyphic patterns or bone age were reported. It is also of interest that none of these patients had any seizures, whereas children with ataxic diplegia who have had difficulties at birth often exhibit neonatal convulsions (Ingram, 1964).

The family described by Johnston and McKusick (1962) is different, since the affected males initially had a pure spastic paraplegia which gradually spread over many years to involve the upper extremities, brain stem, optic nerves and cerebral cortex. Nystagmus was variable, and there was evidently no gross mental retardation, at least among the children.

The question may next be asked whether this sex-linked ataxic diplegia is really a non-progressive condition qualifying for the term cerebral palsy. The mother of our proband and other intelligent observers have not been convinced that the patients show intellectual deterioration, and the increasing physical disability may be due largely to contractures. The falling I.Q. scores are also of doubtful significance. On the other hand, it must be admitted that the patients appear to make little physical or intellectual progress after the age of about 10 years. Also, while the nystagmus tends to diminish, the extrapyramidal features may gradually increase. The spinal fluid in our Case 1 and in the two brothers described by Baar and Gabriel (1966) did not show any excess of protein, and in our patient the level of gamma globulin was also normal, while the colloidal gold curve of 112110 may be described as of doubtful significance. Thus a slowly progressive disorder cannot be excluded, but, in the absence of neuropathological studies and of any definite evidence of demyelination in the brain or peripheral nerves, it seems legitimate to retain the condition among the cerebral palsy syndromes for the present.

Wolfslast (1943) was concerned about the differential diagnosis from Pelizaeus-Merzbacher disease, which is considered to be a degenerative disorder and is usually inherited as a sex-linked recessive condition in males. In the classical form of that disease the clinical features can also be described as an ataxic diplegia with superadded head tremor, bradyphasia, athetotic movements and other extrapyramidal manifestations, and with pallor of the optic discs and secondary skeletal abnormalities. Usually, nystagmus does not commence before the 3rd month of life, and the course is more distinctly progressive, leading to death in the second decade (Diezel and Huth 1963, Ford 1966, Seitelberger 1970). A congenital ("connatal") form was described by Seitelberger (1954), and in this form the nystagmus and other features are noticeable from birth, but there is

almost total cerebral demyelination and complete failure of psychomotor development, with death before the age of 8 years. Recently, Seitelberger (1970) added a third type of the disease which is a transitional form between the classical and congenital categories. In this type the longest survival was to the age of 18 years 10 months. However, occasional cases of Pelizaeus-Merzbacher disease with very slow evolution have been recorded. Thus a patient described by Blackwood and Cumings (1954, Case 2) began like a congenital case but lived to the age of 41 years, when the diagnosis was confirmed by autopsy. Another male patient with superadded proportional dwarfism, testicular atrophy and tapeto-retinal degeneration survived to 42 years (Lüthy and Bischoff 1961). One of Tyler's (1958) patients with the classical type of the disease is reported to have lived to the age of 51 years. The heredity and clinical features in the families described by Batten and Wilkinson (1914) and by Tyler (1958) showed a considerable resemblance to those reported here, though the affected males were usually more severely handicapped and died earlier. Thus it is hard to exclude the possibility that our patients and the similar ones in the literature may have Pelizaeus-Merzbacher disease, unless neuropathological studies become available or some appropriate biochemical test for that disorder is discovered.

In their review of spastic ataxia Bell and Carmichael (1939) encountered only two reports of families suggesting a sex-linked inheritance. The cases described by Turner and Roberts (1938) are suggestive of Friedreich's ataxia, and those described by Mastin (1887) were somewhat similar, though associated with dementia and not with nystagmus. The manifestations and course of the illness in both these reports are notably different from those in our patients. Nayrac et al. (1957) described a family in which Friedreich's ataxia with optic atrophy and mental retardation was thought to be inherited by an autosomal but sex-influenced recessive

gene, and here also the clinical picture was different. Finally, Malamud and Cohen (1958) described an unusual syndrome of cerebellar ataxia with sex-linked inheritance which was characterized by a marked clinical change from initial cerebellar to extrapyramidal manifestations with dementia. Autopsy in one case showed a degenerative process involving both the cerebellum and basal ganglia in addition to the red nucleus, optic tracts and thalamus. Again, the clinical course in that family was more rapid after more normal initial development than in our family.

As has been pointed out previously with regard to sex-linked mental deficiency (Allan et al. 1944, Dunn et al. 1963), it is generally impossible to distinguish categorically between sex-linked recessive and autosomal dominant male-limited transmission when the disease is so severe as to prevent the reproduction of affected individuals. However, Johnston and McKusick (1962) noted with respect to sex-linked spastic paraplegia that male-limited autosomal dominant inheritance seemed less plausible, because there was no obvious mechanism by which the neurological manifestation of the autosomal gene could be limited to males. In any case, it seems important to look for associated sex-linked defects attributed to abnormal genes on the X chromosome. In the present family there is no evidence of color blindness, hemophilia, Christmas disease, glucose-6-phosphate dehydrogenase deficiency, nephrogenic diabetes insipidus or any other sex-linked disorder with which the ataxic diplegia might be linked. Searching for an association with an abnormal dermatoglyphic pattern, we were interested to note that Cases 1 and 2 both had a radial loop pattern on the right middle finger, but this was not found in Case 3 and the presence of a radial loop on the left middle finger of the unaffected boy IV.7 suggests that this may be a familial trait unrelated to hereditary ataxic diplegia. We also looked for an associated abnormality of serum immunoglobulins, but Table III shows that no

clear pattern emerges. The IgG level is low in Case 1 and in his mother and sister, but also in his father, whereas it is high in Case 3 and in the father of Case 2. The IgA level is somewhat high in Case 1 and in his unaffected maternal grandfather II.3, but not in the other patients. A more notable marker may be the presence of positional nystagmus and directional preponderance in the proband's sister, but this was not found in the mother, and before it is accepted as a sign of heterozygosity in children (possibly disappearing later) it will have to be confirmed and checked in other members of affected families.

The data in Fig 1 would fit the possibility of the gene for sex-linked hereditary ataxic diplegia and the allele Xg^a being on the same chromosome in Cases 1 and 2, while Case 3 may represent a crossover event causing the gene for the disease and the Xg allele to be associated on the same chromosome. While the sample is too small to allow any conjecture about the distance between the two loci concerned, the data are recorded here for the use of future investigators of like families.

In practice, the most important point at present is that any child with congenital ataxia or ataxic diplegia must be considered to have a possible genetic defect, particularly if pregnancy and delivery were unremarkable. In the case of a boy with ataxic diplegia the possibility of sex-linked inheritance must be considered, particularly in the presence of congenital nystagmus, and the family history must be investigated accordingly. If the history is positive for sex-linked inheritance of the condition, the mother must be a heterozygote and any subsequent children would have a 50% chance of having the disease if they are males and of being heterozygote carriers if they are females. If the family history is negative or the patient is a girl, the defect may be due to a recessive autosomal gene, with its 25% chance of recurrence in subsequent siblings. Genetic counselling should be given accordingly.

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