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A Family Study of the Late Infantile and Juvenile Forms of Metachromatic Leucodystrophy

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Classification within the disorder formerly known as diffuse sclerosis has been much improved in the past decade. Lumsden pointed out in 1951 that Schilder (1912, 1913, 1924) had described three distinct conditions, the one in his 1913 paper corresponding to what is now known as familial metachromatic leucodystrophy. In 1957 Hirsch and Peiffer introduced a new stain for metachromasia (cresyl violet in 1% acetic acid giving a golden brown colour), re-examined (Peiffer, 1962) the necropsy material from several earlier cases, and reclassified them in the group of metachromatic leucodystrophy.

The age of onset of metachromatic leucodystrophy extends from infancy to adult life. The most homogeneous group of these is the late infantile, in which the age of onset is between 7 and 36 months, with a mode at 11–24 months. The child develops a progressive weakness, incoordination of limb and eye movements, dysphagia, and then increasing spasticity and dementia. The latest age at death recorded in this group is 7 years, apart from one survivor at 8 years. Without exception, the affected sibs of patients with this form of the disease have had a similar form of the disease. There has been little discussion of the genetics of the condition, with the exception of Jervis (1960) who suggested that the condition was autosomal recessive, and no family study of a consecutive series of index patients has yet been reported.

The group of leucodystrophies with a later onset is heterogeneous. In a few families there is clear evidence of a dominant mode of inheritance with a wide range of age of onset, and the duration of the illness may be more than 20 years (Poser, Dewulf, and van Bogaert, 1957). Other families (Scholz, 1925; Walthard, 1933; Pfister, 1936; Curtius, 1930; Hoefnagel, van den Noort, and Ingbar, 1962) show a probable recessive X-linked inheritance with occasional manifestation in females: in this group there may be clinical evidence of skin pigmentation and, at necropsy, adrenal atrophy. Other adult cases are isolated.

When these three subgroups are excluded, the remainder appears to form a homogeneous group, with age of onset between 4 and 10 years, the duration of the illness from 1 to 11 years, and the earliest recorded age at death 7 years; there is, however, a male preponderance.

Present Study

No families suggesting dominant inheritance or X-linked inheritance were seen in this series from a children's hospital, and all the patients studied in this series may be classed as late infantile or juvenile.

Material. The index patients for this family study were all those in whom the diagnosis of metachromatic leucodystrophy had been established on clinical and histological evidence at The Hospital for Sick Children from 1950 through 1963. There were 17 such patients, including two pairs of sibs. The histological and clinical findings on these index patients are summarized in Table I. The nerve conduction times recorded in the right hand column of the table were done by Fullerton (1964), who has reported the findings in 7 of them.

Twelve (4 boys and 8 girls) may be readily classified as 'late infantile', all with an onset between 12 and 24 months. Of these, 9 are dead, all dying at ages between $2\frac{1}{2}$ years and $5\frac{1}{2}$ years. Another male index patient (No. 8) had an early onset (16 months), and was the elder brother of a girl typical of the infantile form of the disease, but did not die until aged 7 years 8 months. He has been included among the late infantile cases. The remaining 2 were still alive at the ages of 4 years 5 months and 5 years 8 months.

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TABLE I

Serial No.	Sex	Date Admitted	Date of Birth	Age at Onset (mth.)	Age at Death* Yr.	Mth.	Metachromasia on Biopsy or at Necropsy† Urine or Kidney	Rectal Biopsy or Gastro-intestinal	Nerve	Brain	Skin	Lowered Nerve Conduction
1	M	5/50	3/45	18	5	2	+	+	+	+		
2	M	3/54	1/52	14	2	7	+	+		+		
3	F	4/54	2/52	16	4	0				+		
4	M	3/56	1/53	21	4	4	+			+		
5	F	6/56	4/50	24	6	4				+		
6	M	7/57	11/55	12	3	3	+	+		+		
7	F	10/59	11/55	24	4	8	+			+		
8	M	12/57	6/56	16	7	8	+	+	+	+	+	+
9	F	11/62	8/58	12	4	9	+	+	+		+	+
10	F	4/62	3/60	16	4	9	+	+	+		+	+
11	F	5/63	1/61	20	2	7	+	+	+		+	+
12	F	8/63	1/60	18	(4	5)	+			+		−
13	F	9/63	11/59	18	(5	8)	+	+	+		+	+
14	M	4/54	10/50	6 yrs.	10	4	+			+		
15	M	5/62	12/53	6 ,,	(11	1)	+	+		+	+	−
16	M	3/63	5/58	4 ,,	(6	1)		+	+		+	+
17	F	4/63	5/54	4 ,,	(10	6)	+	+	+	+	+	+

* Those still alive are in parentheses.
† If examined and found negative they are shown as −.

Of the other index patients, 4 (3 boys and 1 girl) may be readily classified as belonging to the juvenile form with onset between 4 years and 7 years; one of these patients died at the age of 10 years and 4 months, and the other 3 were still alive at the ages of 6 years 1 month, 10 years 6 months, and 11 years 1 month.

The post-mortem histological features of 4 of these children and the biopsy findings on 4 others have been reported (Bodian and Lake, 1963). Their post-mortem Cases 1, 2, 7, and 5, and their surgical Cases 1, 2, 3, and 4 are our patients 1, 2, 3, 6, 15, 10, 8, and 9, respectively.

Methods. The families of the index patients were visited in their own homes and a family history was taken, paying special attention to the possibility of consanguinity. Hospital records and death certificates were obtained on sibs and other relatives who were possibly affected.

Genetic Findings

Sex Ratio. The sex ratio of the index patients, 5 male to 8 female for the late infantile, and 3 to 1 for the juvenile, does not differ significantly from unity.

Parental Consanguinity. None of the parents seen were known to be blood relatives, and there is no suggestion that grand-parents of affected individuals came unduly often from any particular part of Britain.

Twins. None of the index patients was twin born.

Sibs. The sibships of the index patients are tabulated in Appendix I and are summarized in Table II (excluding two dying in infancy) for the infantile and juvenile series, respectively. Of 25 sibs of the late infantile index patients, 7 had similar late infantile metachromatic leucodystrophy, and 3 of the 5 sibs of the juvenile type index patients had the juvenile form of the disease.

Information on the sibs classed as probably affected is summarized in Appendix II.

Half-sibs. 7 male and 3 female half-sibs of the late infantile patients were all unaffected.

TABLE II

SIBS OF INDEX PATIENTS WITH LATE INFANTILE AND JUVENILE FORMS OF METACHROMATIC LEUCODYSTROPHY (NUMBER AFFECTED SHOWN IN BRACKETS)

	Sibs Before Index Patient		Sibs After Index Patient		Total
	Male	Female	Male	Female	
Late infantile (13 cases)	10 (4)	10 (2)	2 (0)	3 (1)	25 (7)
Juvenile (5 cases)	0 (0)	1 (1)	2 (2)	2 (0)	5 (3)

Other Relatives. No other relatives were found affected. For the late infantile group the numbers of other relatives (counting the family with two index patients twice) were: mother's brothers and sisters 13 and 39, father's brothers and sisters 25 and 24, mother's brother's sons and daughters 9 and 10, mother's sister's sons and daughters 25 and 37, father's brother's sons and daughters 25 and 22, father's sister's sons and daughters 20 and 18. For the juvenile cases, again using a double count for the family with two index patients, the number of relatives were 10 and 5, 4 and 1, 6 and 7, 1 and 1, 3 and 2, 0 and 3, respectively. In the two families with only male index patients, the mothers had 8 brothers who were all normal, and 1 mother had a sister's son who was normal.

Discussion

The 46 previously published reports, not all

studied by modern histological methods, but generally accepted as the late infantile form of metachromatic leucodystrophy, are listed in Appendix IIIA. Assuming one index patient per sibship, these patients between them had 82 sibs, of whom 25 were proved or probably affected. In 2 instances the parents were consanguineous (first cousins: Marggraf, 1939; second cousins: Hariga, 1960); consanguinity was absent in 20 and not recorded in 24. The proportion of sibs affected is higher than 1 in 4, but this is to be expected in the early years of recognition of a disease when the diagnosis is facilitated by a familial incidence and where the family history is incompletely reported. The sex ratio, 36 male to 34 female (not stated in 1) is close to unity. There are only two reports of a relative other than a sib being affected, one was of a male second cousin (Hagberg, Sourander, Svennerholm, and Voss, 1960), the other was of two cousins of a patient reported by Austin (1957).

The recessive inheritance suggested by these case reports of the late infantile form is strongly supported by the proportion of sibs affected in the present series. If one assumes that the two index patients in the same family in our series were independently ascertained, this proportion is 7 in 25, or, if one assumes that only 1 of these 2 children was truly an index patient, the proportion is 6 in 24. The sex ratio, 5 male to 8 female for the index patients, and 3 male to 2 female for affected sibs other than index patients, does not differ significantly from unity. The absence of parental consanguinity is perhaps surprising, but the cousin marriage rate in England is now probably very low indeed.

The 16 reported families of juvenile metachromatic leucodystrophy, excluding patients with clearly dominant or X-linked pedigrees, are listed in Appendix IIIB. There is a male preponderance, 18 male : 9 female (3 not recorded), though this does not differ significantly from unity. Assuming one index patient per sibship, these patients between them had 45 sibs of whom 14 were affected. There were no instances of parental consanguinity for the 8 families where information on this point was given. Recessive inheritance is suggested, but it is probable that some instances of X-linked recessive inheritance, not revealed by the pedigree, have been included, since not all such cases have pigmentation and the state of the adrenals at necropsy is not always reported.

Again the findings in the present small series of juvenile cases is compatible with recessive inheritance. There were affected 3 in 5 sibs, or 2 in 4 sibs, if only one of the family which includes Cases 16 and 17 is regarded as an index patient. The sex ratio of 3 male to 1 female index patient with one other male sib affected adds slightly to the male preponderance seen in the reported cases.

In this series affected sibs, as shown in Appendix II, without exception have run a course very similar to that of the index patient.

Summary

Between 1950 and 1963 at The Hospital for Sick Children, London, 17 patients have been admitted with the clinical features of metachromatic leucodystrophy, and in all these the diagnosis has been confirmed by modern methods of staining. Of these, 13 may be classified as examples of the 'late infantile' form of the disease with onset between the ages of 12 and 24 months, and death in the first decade. The other 4 may be classed as examples of the 'juvenile type' with onset between the ages of 4 and 10 years.

The proportion of sibs affected in the families of this consecutive series of index patients suggests autosomal recessive inheritance for both the 'late infantile' and 'juvenile' forms of the disorder; but there were no instances of parental consanguinity.

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APPENDIX I

Index patients are marked with an asterisk; affected sibs are in italics
M = male, F = female, m = miscarriage, [ ] = twins

Serial No.	Patient, date of birth, and sibship	Half-sibs		Date of Birth	
		Maternal	Paternal	Mother	Father
Late Infantile Metachromatic Leucodystrophy					
	One-child families				
10	*F** 3.60 (d. 12.64)			1/41	1/36
3	*F** 2.52 (d. 2.56)	MMF	MMMFF	9/15	/07
	Two-child families				
8, 9	m 6.55; *M** 6.56 (d. 2.64); *F** 8.58 (d. 5.63)			12/31	/30
2	*M* 6.47 (d. 3.50); m −.50; *M** 1.52 (d. 8.54)			6/23	10/20
13	*F** 11.59; *M* 7.62			9/34	10/33
	Three-child families				
1	M 1.33; M −.37 (d. −.40); *M** 3.45 (d. 5.50)			3/13	7/08
5	F 7.45; *F** 4.50 (d. 8.56); F 12.51			9/21	/11
	Four-child families				
12	m −.56; [M 1.58 (d. 1.58); M 1.58 (d. 1.58)]; *F** 1.60; M 6.61			1/31	12/28
7	*F* 5.53 (d. 10.57); M 10.54; *F** 11.55 (d. 7.60); F 12.59			2/23	9/22
	Five-child families				
4	M 3.38; F 1.46; M 5.47; F 12.51; *M** 1.53 (d. 5.57)			9/13	5/13
6	*M* 10.49 (d. 3.52); M 2.51; *F* 10.53 (d. 4.57); F 10.54; *M** 11.55 (d. 2.59)	M	MF	12/12	5/06
	Six-child families				
11	F 9.38; *M* 10.40 (d. 3.44); F 8.42; F 1.44; F 9.47; *F** 1.61 (d. 8.63)			3/20	10/09
Juvenile Metachromatic Leucodystrophy					
	Two-child families				
16, 17	m −.53; *F** 5.54; *M** 5.58			8/23	/20
14	*M** 10.50 (d. 2.61); F 12.53			8/20	5/20
	Three-child families				
15	m −.52; *M** 12.53; *M* 4.57; F 7.59			5/29	12/28

APPENDIX II

Affected Sibs of Index Cases (excluding those who are themselves index cases)

	Late Infantile Form
Family 2	Elder brother, born 6·47, died 2 years 9 months; onset age 24 months; signs of progressive cerebral degeneration; diagnosis at Chester City Hospital—Schilder's disease
Family 7	Elder sister, born 5.53, died 4 years 5 months; onset age 3 years; signs of progressive cerebral degeneration; diagnosis at Southampton General Hospital—'encephalitis or some form of Schilder's disease'
Family 6	Elder brother, born 10.49, died 2 years 5 months; onset age 23 months; diagnosis at The Hospital for Sick Children—Schilder's disease Elder sister, born 10.53, died 3 years 6 months; signs of progressive cerebral degeneration; brain biopsy at The National Hospital showed metachromatic leucodystrophy
Family 11	Elder brother, born 10.40, died 3 years 6 months; onset age 20 months; mother's description of illness very much like that of index patient; death certified as due to 'spastic diplegia'
	Juvenile Form
Family 15	Younger brother, born 4.57, still alive aged 8 years 2 months; onset age 6 years 9 months: diagnosis confirmed by metachromatic granules in urine at age 7 years 5 months

APPENDIX III

Published Reports of Late Infantile Metachromatic Leucodystrophy and of Juvenile Metachromatic Leucodystrophy

M = male, F = female, N = sex not stated, italics = affected, — = no consanguinity, n.r. = not reported, + = consanguinity, [ ] = twins, ? = not possible to check original paper.

Author	Cases	Consanguinity
A: *Late infantile Metachromatic Leucodystrophy*		
Van Bogaert and Scholz (1932)	M *F F F*	—
Greenfield (1933)	*F*	n.r.
	M M F *M*	n.r.
Heuyer, Vogt, and Roudinesco (1933)	M *F* F M *M F* N	—
Heuyer, Lhermitte, and Vogt (1934)		
Marggraf (1939)	N *M*	—
	F	+
Brandberg and Sjövall (1940)	*M M F*	—
Frank (1947)	*F*	—
Jacobi (1947)	*M*	n.r.
Dubois and Ley (1949)	*M* M	—
Brain and Greenfield (1950)	*M*	n.r.
	F F F *F*	n.r.
	F	n.r.
	F	n.r.
Scheidegger (1950)	*M*	n.r.
Leslie (1952)	*M*	—
Bertrand, Thieffry, and Bargeton (1954)	*M M*	—
Vries (1954)	*F*	n.r.
Austin (1957)	*M M M*	n.r.
	M F	n.r.
Cogan, Kuwabara, Richardson, and Lyon (1958)	*F F*	n.r.
Hain and LaVeck (1958)	*F* F F	n.r.
Wohlwill and Paine (1958)	*F F*	—
Peiffer (1959)	*M* F F *M M* M	—
	M F F	—
	M F F M	—
	F M	—
Thieffry and Lyon (1959)	F N *F* N	—
Hagberg, Sourander, Svennerholm, and Voss(1960)	F *M* F *M*	—
Jervis (1960)	*F* N	—
	F N N	—
Norman, Urich, and Tingey (1960)	[N N] *M* F *F*	n.r.
Hariga (1960)	*M M*	+
Ogawa (1961)	*F*	n.r.
Mossakowski, Mathieson, and Cumings (1961)	*M F F* [M M]	—
Black and Cumings (1961)	*F* N	n.r.
Hansen, Olsen, and Plum (1961)	*F* N *M*	—
Christensen, Melchior, and Negri (1961)	N N N NN *M*N *M* N NN *M* N	n.r.
Allen, McCusker, and Tourtellotte (1962)	*M* M	n.r.
Prot and Sobkowicz (1963)	*M*	—
Abraham and Lampert (1963)	N *M* N	n.r.
	F M	
	F	
Isler, Bischoff, and Esslen (1963)	*F*	n.r.
Wolfe and Pietra (1964a)	*M* N N N N N	n.r.
Wolfe and Pietra (1964b)	*N* N N *F* N	n.r.
B: *Juvenile Metachromatic Leucodystrophy*		
Gasul (1930)	N N N N N N N *M*	n.r.
Van Bogaert and Bertrand (1933)	*M* F F F *M* M	—
	F M	—
Valdes and Piantoni (1933)	*N N N* N N N N	?
Jakob and Gonzalez (1936)	F F *M* M *M* M M *M* M	—
Slaczka (1938)	*M M*	n.r.
Gareiso, Pereyra Käfer, Pedace, and Rascovsky (1938)	*M* M	—
Lange (1946)	M *M F*	—
Lange (1947)	F F *M M*	—
Brusa (1952)	*F* F	n.r.
Kufs, Lange-Cosack, and Suckow (1954)	*F F F* F M	—
Cumings (1955)	*F*	n.r.
Diezel (1957) } Cogan *et al.* (1958) }	*M M*	n.r.
Scheidegger (1959)	*M*	n.r.
Lyon, Arthuis, and Thieffry (1961)	N *F M* N N	—
Kalicanin (1962)	*M F*	—

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