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The inheritance of primary lymphoedema

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SUMMARY A family study is reported on 312 index patients who had primary lymphoedema with onset before 36 years. All had been investigated at St Thomas's Hospital, London, between 1965 and 1980. Most of the information was obtained by questionnaire, but 70 patients were also interviewed to check the reliability of the answers to the questionnaire. The frequency at birth of those who will develop primary lymphoedema is estimated to be about 1 in 6000, with a sex ratio of about one male to three females. Approximately 10% of children of index patients and 10% of sibs were affected when these relatives were at least five years older than the age of onset in the index patient. The proportion of female relatives affected was between two and four times that of males affected. The proportion of parents affected was about 10%. The proportion of grandparents, aunts, and uncles was about 2·5%. Where the index patient had an affected parent, the proportion affected of sibs and children was about 20%. The risk to relatives of male index patients was about 50% higher than for female index patients.

Lymphoedema is defined as a swelling in some part of the body owing to a fault in the lymphatic system.[1] Primary lymphoedema is due to a pathology affecting the lymphatics directly. The vast majority of patients complain of swelling of the lower limbs and this may be present in one or both legs and be present at birth or develop at any age afterwards, but with a peak between the ages of 10 and 25 years. The major classification of lymphoedema is by lymphographic findings and is as follows.[2]

(1) Distal hypoplasia: lymph vessels too small or too few in limbs.

(2) Proximal hypoplasia: vessels and nodes too small or too few in groin and pelvis. Vessels in limb numerous, tortuous, and dilated (that is obstructed and distended).

(3) Distal and proximal hypoplasia: a combination of (1) and (2), that is, vessels and nodes too small and few in limb and pelvis.

(4) Hyperplasia. (a) Bilateral: numerous, tortuous lymphatics in both limbs with many large nodes in groins and trunk. Non-filling or distorted thoracic duct. (b) Megalymphatics: many large, tortuous, varicose lymphatics in limbs and trunk. Nodes diffuse, scattered, often numerous, almost always unilateral.

Inheritance has been thought to be one of the causes of primary lymphoedema since 1892 when Milroy[3] described a family with the condition passing through six generations. The inheritance has been thought to be through a dominant gene and this has been supported by studies into small numbers of selected families.[4,5] The proportion of patients inheriting the condition has not previously been described and, more importantly, the risk to relatives of such patients remained unquantified.

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Material and methods

A study of the incidence of lymphoedema in the relatives of 312 patients was carried out to check the mode of inheritance of lymphoedema and also to identify the proportion of patients likely to pass on the trait. All the patients were seen at St Thomas's Hospital, London, between 1965 and 1980, and represent the number contacted by ourselves out of a total of 467 patients identified as suitable for the study. The patients were unselected as regards the presence or absence of a positive family history; 35% of respondents had a positive family history and this compares favourably with an expected 37%, the proportion found in previous studies carried out at the hospital. Patients were excluded from the survey only if (1) their age of onset of symptoms was greater than 35 years as such patients only have a 3·6% incidence of a positive family history; and (2) if they had megalymphatics, as

defined by lymphography, there being no incidence of a positive family history in this small group. An attempt was made to contact all the patients by questionnaire and 312 patients replied. Seventy of these patients were also interviewed to check that the data obtained were accurate. It was found that the correlation between the two sources of information was good for first and second degree relatives, but major discrepancies occurred with more distant relatives. At the interviews it became clear that usually one member of the family had a very clear idea about who did or did not have lymphoedema. Where someone had to be seen to confirm the diagnosis (in three subjects) then the diagnosis was always confirmed. All in all it became clear that patients had a very clear idea as to who had lymphoedema and who did not.

Results

The results were considered against the type of preceding family history, that is, where a parent was affected, where parents were unaffected but a preceding second degree relative was affected, and where there was no preceding family history. The figures are given for normal relatives and those with lymphoedema and a ratio calculated from these. In table 1 the overall figures are given and from this table the following observations can be made. (1) The risk is highest when a parent of the proband is affected. (2) Female relatives are at greater risk than males. (3) Even if there is no preceding family history sibs and children of the proband are still at risk of developing lymphoedema.

Lymphoedema has a complex and wide distribution of its age of onset of symptoms and may appear in relatives up to an age of 30 years. In table 2 a correction has been made to take account of the short fall in affected relatives who are young, that is, mainly children and sibs. It was found that children and sibs who had reached five years in excess of the age at which the proband had developed lymphoedema gave a more accurate picture of the incidence. This is supported by the observation that there is a correlation within families for the age of onset, and in our studies it was found that 66% of patients who will eventually develop lymphoedema will have done so using this correction for age. In table 2 the figures with this correction are given, and from this it can be seen that the overall risk to children and sibs is about 1 in 10, which is the risk to parents overall, and thus the risk to first degree relatives is similar. In addition, where a parent is affected the risk to sibs and children is in the order of 1 in 4.

Lymphoedema is more common in women and, to give some idea of the influence of sex, in tables 3

TABLE 1 *Risk to relatives: all patients.*

Index patient	*Parents affected (n=62)*	*G'parent, uncle, or aunt affected (n=24)*	*No previous family history (n=226)*	*All patients (n=312)*
Brothers Normal	75	29	257	361
	1 in 7·3	1 in 15·5	1 in 258	1 in 25·1
L'dema	12	2	1	15
Sisters Normal	60	15	284	359
	1 in 3·1	1 in 8·5	1 in 26·8	1 in 9·8
L'dema	28	2	11	41
Sibs Normal	135	44	541	720
	1 in 4·4	1 in 12	1 in 46·1	1 in 13·9
L'dema	40	4	12	56
Sons Normal	38	22	145	205
	1 in 13·7		1 in 30	1 in 26·6
L'dema	3	0	5	8
Daughters Normal	33	11	121	165
	1 in 17·5	1 in 12	1 in 11·1	1 in 12
L'dema	2	1	12	15
Children Normal	71	33	266	370
	1 in 15·2	1 in 34	1 in 16·6	1 in 17·1
L'dema	5	1	17	23
Fathers Normal	50			298
	1 in 5·2			1 in 25·8
L'dema	12			12
Mothers Normal	12			260
	1 in 1·2			1 in 6·2
L'dema	50			50
Grandparents Normal	214	85		1195
	1 in 10·7	1 in 8·7		1 in 37·2
L'dema	22	11		33
Grandchildren Normal	24	17	128	169
			1 in 65	1 in 85·5
L'dema	0	0	2	2
Aunts, uncles Normal	399	143	1362	1904
	1 in 15·3	1 in 9·4		1 in 43·3
L'dema	28	17	0	45
Nephews, nieces Normal	216	48	795	1059
	1 in 37		1 in 266	1 in 119
L'dema	6	0	3	9

TABLE 2 *Risk to sibs and children 5 years older than onset age of index patient.*

Index patient	*Parents affected*	*G'parent, uncle, or aunt affected*	*No previous family history*	*All patients*
Brothers Normal	44	14	117	175
	1 in 8·3	1 in 15	1 in 118	1 in 23
L'dema	6	1	1,	8
Sisters Normal	36	7	117	160
	1 in 3·1	1 in 8	1 in 24	1 in 8
L'dema	17	1	5	23
Sibs Normal	80	21	134	335
	1 in 4·5	1 in 11·5	1 in 40	1 in 11·8
L'dema	23	2	6	31
Sons Normal	8	2	26	36
	1 in 9		1 in 27	1 in 12·3
L'dema	1	0	1	2
Daughters Normal	6	2	19	27
	1 in 4		1 in 7·3	1 in 6·4
L'dema	2	0	3	5
Children Normal	14	4	45	63
	1 in 5·7		1 in 12·3	1 in 10
L'dema	3	0	4	7

TABLE 3 *Risk to relatives: all male index patients.*

Index patient	*Parents affected (n=25)*	*G'parent, uncle, or aunt affected (n=5)*	*No previous family history (n=48)*	*All patients (n=78)*
Brothers Normal	32	5	52	89
	1 in 5·6	1 in 6	1 in 53	1 in 10·9
L'dema	7	1	1	9
Sisters Normal	29	4	55	88
	1 in 3·9	1 in 5	1 in 56	1 in 8·3
L'dema	10	1	1	12
Sibs Normal	61	9	107	177
	1 in 4·6	1 in 5·5	1 in 54·5	1 in 9·4
L'dema	17	2	2	21
Sons Normal	15	5	21	41
	1 in 8·5		1 in 8	1 in 9·2
L'dema	2	0	3	5
Daughters Normal	6	4	17	27
			1 in 18	1 in 28
L'dema	0	0	1	1
Children Normal	21	9	38	68
	1 in 11·5		1 in 10·5	1 in 12·3
L'dema	2	0	4	6
Fathers Normal	19			72
	1 in 4·2			1 in 13
L'dema	6			6
Mothers Normal	6			58
	1 in 1·3			1 in 4·1
L'dema	19			19
Grandparents				
Normal	85	28		286
	1 in 8·7	1 in 10·3		1 in 21·4
L'dema	11	3		14
Grandchildren				
Normal	6	5	25	36
			1 in 13·5	1 in 19
L'dema	0	0	2	2
Aunts, uncles				
Normal	130	31	246	407
	1 in 11·8	1 in 16·5		1 in 30·1
L'dema	12	2	0	14
Nephews, nieces				
Normal	85	17	124	226
	1 in 43·5		1 in 125	1 in 76·3
L'dema	2	0	1	3

TABLE 4 *Risk to relatives: all female index patients.*

Index patient	*Parents affected (n=37)*	*G'parent, uncle, or aunt affected (n=19)*	*No previous family history (n=178)*	*All patients (n=234)*
Brothers Normal	43	24	205	272
	1 in 9·6	1 in 25		1 in 46·3
L'dema	5	1	0	6
Sisters Normal	31	11	229	271
	1 in 2·7	1 in 12	1 in 23·9	1 in 10·3
L'dema	18	1	10	29
Sibs Normal	74	35	434	543
	1 in 4·2	1 in 18·5	1 in 44·4	1 in 16·5
L'dema	23	2	10	35
Sons Normal	23	17	124	164
	1 in 24		1 in 63	1 in 55·7
L'dema	1	0	2	3
Daughters Normal	27	7	104	138
	1 in 14·5	1 in 8	1 in 10·5	1 in 10·9
L'dema	2	1	11	14
Children Normal	50	24	223	302
	1 in 17·7	1 in 25	1 in 18·5	1 in 18·8
L'dema	3	1	13	17
Fathers Normal	31			226
	1 in 6·2			1 in 38·7
L'dema	6			6
Mothers Normal	6			202
	1 in 1·2			1 in 7·5
L'dema	31			31
Grandparents				
Normal	129	57		909
	1 in 12·7	1 in 8·1		1 in 48·8
L'dema	11	8		19
Grandchildren				
Normal	18	12	103	133
L'dema	0	0	0	0
Aunts, uncles				
Normal	269	112	1116	1497
	1 in 17·8	1 in 8·5		1 in 49·3
L'dema	16	15	0	31
Nephews, nieces				
Normal	131	31	671	833
	1 in 33·8		1 in 337	1 in 140
L'dema	4	0	2	6

and 4 a comparison can be made between the risk to relatives of male and female probands. From this it is clear that the risk is increased in both sexes when the proband is male.

Discussion

It is clear from these results that lymphoedema passes from generation to generation. The proportion of children affected is similar to that of sibs and the condition can pass from father to son; thus both recessive and sex linked inheritance are excluded. True dominant inheritance is not the explanation either, as this trait skips generations and does not give a 1 in 2 risk to sibs and children. This leaves either multifactorial inheritance or modified dominant autosomal inheritance as the possible modes of transmission of the trait.

Multifactorial inheritance is superficially an attractive proposition. Lymphoedema has a variable clinical onset, progress, and picture; it has a high incidence in females with an increased onset in the ages associated with the menarche and child bearing, and all this could well represent a multifactorial condition. However, the criteria for multifactorial inheritance include the following. (1) The risk to first degree relatives is approximately the square root of the population frequency of the trait.[6] (2) When the condition has a population frequency of 1 in 1000 or less the risk to relatives declines sharply with increasingly remote degrees of relationship.

There are no reliable morbidity figures for lymphoedema, but an estimate of its prevalence has been made from the patients who attended St Thomas's from the London area which puts the population frequency at less than 1 in 6000, confirm-

ing the clinical impression that it is an uncommon condition. Multifactorial inheritance is unlikely because the incidence in first and second degree relatives is too high when considered against the prevalence of the condition. Finally, the fall in the risk to second degree relatives is not great enough for a condition with a prevalence below 1 in 1000. In one way the criteria are met, and that is that the recurrence risk is increased where males are affected, they being the less susceptible sex,[7] but this is not a sufficient reason to label the condition as a multifactorial condition.

Modified dominant autosomal inheritance remains the explanation for the transmission of this trait. These figures prove what has long been accepted from our studies of individual families. Reduced penetrance produces a rate of expression lower than the expected 1 in 2 with skipping of generations. The concept of reduced penetrance is an accepted genetic concept and, in addition, the difference in expression between the sexes represents sex limitation, again recognised in such conditions as baldness. Modified dominant inheritance with sex influence and variable expressivity does explain the inheritance of lymphoedema. Thus, a subject with the trait has a 1 in 2 chance of passing the genotype to each of the next generation, but it would only be expressed in about half those with the genotype. This represents a 1 in 4 risk to children of those with lymphoedema. Daughters, however, will express the condition more readily than sons, but if sons do develop the condition then they carry a stronger genetic predisposition and this will be reflected in the greater proportion of their relatives affected. It is easy, therefore, to advise patients who have a known family history on the genetics of the condition, but the remainder, who represent the majority, still have a risk of having a heritable trait. They can obtain the trait in two ways. Firstly, by inheriting it through parents and grandparents who have not suffered from lymphoedema, particularly if it has come down through the male line. Secondly, they may well develop the condition through the action of a new mutation.

The classification of lymphoedema implies that there may be fundamental differences between groups of patients. If the index patients are separated according to the lymphographic classification then some differences are noted. Those relatives of index patients with either form of proximal hypoplasia and those with distal hypoplasia are essentially similar to one another and the overall picture, and they make up the majority. Relatives of the 20 patients classified as suffering from bilateral hyperplasia (table 5) appear to differ in that only those who have an affected parent are at risk and the sex influence is either lost or perhaps even reversed. The number in this group, however, is small.

TABLE 5 *Risk to relatives: all patients with hyperplasia.*

Index patient	*Parents affected (n=8)*	*G'parent, uncle, or aunt affected (n=0)*	*No previous family history (n=12)*	*All patients (n=20)*
Brothers Normal	2	0	15	17
	1 in 2			1 in 9·5
L'dema	2	0	0	2
Sisters Normal	6	0	22	28
	1 in 7			1 in 29
L'dema	1	0	0	1
Sibs Normal	8	0	37	45
	1 in 3·7			1 in 16
L'dema	3	0	0	3
Sons Normal	3	0	5	8
	1 in 4			1 in 9
L'dema	1	0	0	1
Daughters Normal	7	0	3	10
L'dema	0	0	0	0
Children Normal	10	0	8	18
	1 in 11			1 in 19
L'dema	1	0	0	1
Fathers Normal	4			16
	1 in 2			1 in 5
L'dema	4			4
Mothers Normal	4			16
	1 in 2			1 in 5
L'dema	4			4
Grandparents Normal	29	0		77
	1 in 10·7			1 in 26·7
L'dema	3	0		3
Grandchildren Normal	0	0	0	0
L'dema	0	0	0	0
Aunts, uncles Normal	40	0	65	105
	1 in 7·7			1 in 18·5
L'dema	6	0	0	6
Nephews, nieces Normal	9	0	50	59
L'dema	0	0	0	0

About a quarter of patients who inherit lymphoedema do so from parents and grandparents who have not expressed the condition and any information on the preceding generations is likely to be unreliable. These patients, however, appear with those with no preceding family history.

All genes are subject to a certain mutation rate and that of lymphoedema is no exception. It would be expected, therefore, that a proportion of patients will develop a heritable trait because of a new mutation. This is likely to be a low proportion overall, as an estimate of the reproductive fitness of our patients was 1·94, which compares closely with the expected figure of 1·9 from the Office of Population Census and Statistics for 1980. There is no evidence of an increasing proportion of patients with lymphoedema and it is hard, therefore, to assign a major role to new mutations in the sudden appearance of lymphoedema in a family.

Conclusions

In those patients with a genetic origin of their lymphoedema, the form of inheritance is that of a modified dominant single autosomal gene. On average, half the offspring of these subjects will carry the gene. The expression of this dominant gene approaches 50% and in those patients who develop lymphoedema the majority will have done so by the age of 30 years. The expression of lymphoedema is sex influenced and is much higher in females than males, 66% and 30% respectively. This sex influence is not seen in those patients with bilateral hyperplasia where it is either lost or may be reversed with males predominating. In those patients who have no preceding family history probably only a small proportion have received a new mutation, thus creating a risk to children in this group which is higher than to sibs. In those patients with no preceding family history the risk to children is about 1 in 12.

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References

1 Kinmonth JB. *The lymphatics, diseases, lymphography and surgery*. London: Edward Arnold, 1982:83–144.
2 Kinmonth JB, Wolfe JH. Fibrosis in lymph nodes in primary lymphoedema. *Ann R Coll Surg Engl* 1980;**62**:344–54.
3 Milroy WF. An undescribed variety of hereditary oedema. *NY Med J* 1892;**56**:505–8.
4 Esterley JR. Congenital hereditary lymphoedema. *J Med Genet* 1965;**2**:93–8.
5 Schroeder E, Hewleg-Larsen HF. Chronic hereditary lymphoedema (Nonne-Milroy-Meige's disease). *Acta Med Scand* 1950;**137**:198–216.
6 Edwards JH. The simulation of Mendelism. *Acta Genet* 1960;**10**:63–70.
7 Carter CO, Evans KA. Inheritance of congenital pyloric stenosis. *J Med Genet* 1969;**6**:233–54.

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