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A Hungarian study on Werdnig-Hoffmann disease

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SUMMARY The prevalence of Werdnig-Hoffmann disease was found to be 0·66 per 10 000 livebirths in Hungary from 1973 to 1980. However, the true prevalence is estimated to be 1 per 10 000 livebirths, which exceeds the level of a previously published English study. There was no higher fetal death rate in previous and subsequent pregnancies of index patients' mothers. The occurrence in sibs was 32%, probably because of greater ascertainment in families with more than one affected child.

Cystic fibrosis and Werdnig-Hoffmann disease are the two most common monogenic disorders encountered in our Genetic Counselling Clinic in Budapest.[1] Of nearly 1000 probands affected by autosomal recessive disorders, 10% had Werdnig-Hoffmann disease (WHD). This high number prompted us to set up a genetic epidemiological study in the early 1980s. The purposes of this study were to determine the birth prevalence of WHD in Hungary and to delineate its epidemiological characteristics.

WHD is the severe infantile form of proximal spinal muscular atrophy. It was described by Werdnig[2 3] and Hoffmann[4 5] independently as progressive muscle weakness beginning in the first year of life and terminating in death in early childhood, usually before the age of four years. There is degeneration in the anterior horn cells, that is, the lower motor neurones of the spinal cord, distinguishing the disease from the primary muscular dystrophies. Family studies of patients have indicated autosomal recessive inheritance.[6 7]

Materials and methods

To ascertain the index patients born in Hungary during the study period of 1970 to 1980 the heads of all pathology, paediatric, and general neurology departments were asked to inform us about cases of WHD and to send us their medical documentation, including necropsy records and histological examination. As a check on the ascertainment, cases of WHD born in the study period were selected from the records of all genetic counselling clinics and the Hungarian Congenital Malformation Registry.

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In the second step of the study the parents of index patients were invited to our department or visited at home for a personal interview in order to confirm the diagnosis of WHD and to obtain epidemiological data with the help of a purpose designed, printed questionnaire.

The criteria for WHD were the following: (1) the start of wasting, proximal muscular weakness, and hypotonia with absence of deep tendon reflexes in the first year of life; (2) the index patient was never able to sit without support; (3) death before the age of four years; (4) no other congenital anomalies (for example, arthrogryposis, microcephaly, etc) or neurological features (for example, ophthalmoplegia, deafness, etc); (5) histological verification. Unfortunately, there is no centralised system in Hungary for patients with WHD or for dealing with their documentation.

Results

In total, 128 cases were ascertained (66 cases were reported twice and three cases three times). All cases recorded in the Hungarian Congenital Malformation Registry were reported. However, three cases from genetic counselling clinics were not notified.

Out of the 128 cases, 24 were excluded owing to misdiagnosis on the basis of the usual classification of WHD.[8] Thus, the proportion of misdiagnosed cases (for example, spinal muscular atrophy with arthrogryposis multiplex congenita) was 18·8%. Four excluded cases with the typical clinical pattern of WHD survived the age limit of four years. These cases were diagnosed as the intermediate form of spinal muscular atrophy.[9] Finally, 104 index patients with WHD, that is, the severe infantile type of proximal spinal muscular atrophy, were evaluated.

TABLE 1 *Annual prevalence per 10 000 livebirths of Werdnig-Hoffman disease in Hungary, 1970 to 1980.*

Year	*Livebirths*	*No of index patients*	*Livebirth prevalence*
1970	151 819	6	0·40
1971	150 640	3	0·20
1972	153 265	4	0·26
1973	156 224	10	0·64
1974	186 288	14	0·75
1975	195 240	11	0·57
1976	185 405	17	0·92
1977	177 574	9	0·51
1978	168 160	13	0·77
1979	160 364	9	0·56
1980	148 673	8	0·53
Total	1 832 652	104	0·57
Subtotal in 1973–1980	1 376 928	91	0·66

However, appropriate histological evidence checked by one of us (JH) was available in only 56 cases (54%). Nevertheless, cases without histological findings but with all the other four criteria were accepted as cases of WHD.

The distribution of the annual livebirth prevalence of index patients studied showed a significant deviation from the mean: 0·57 per 10 000 livebirths (table 1). However, for the first three years there had been obvious underascertainment. The birth prevalence of WHD was 0·66 from 1973 to 1980; the maximum 0·92 occurred in 1976.

The geographical distribution of index patients also showed significant differences in prevalence (figure). The main cause of these may be the difference in diagnosis and reporting in different areas. It was noted that two counties with maximum prevalence (Nógrád, 1·48; Vas, 1·01) have neurology and pathology institutions interested in neurological disorders. Thus the estimated true birth prevalence of WHD may be about 1 per 10 000 livebirths in Hungary. The sex ratio 0·51 agrees with the usual sex ratio of newborns.

TABLE 2 *Outcome of previous and subsequent pregnancies.*

Outcome	*Induced abortion*		*Spontaneous abortion*		*Livebirth*	*Total*
	No	*%*	*No*	*%**		
Previous pregnancies	16	13·3	10	9·6	94	120
Subsequent pregnancies	30	25·4	8	9·3	78	118
Total	46	19·3	18	9·5	72	238

*Induced abortions excluded.

The previous and subsequent pregnancies of index patients' mothers (table 2) did not show any increase in the rate of spontaneous abortions (stillbirths were not noted). The lack of prenatal selection in sibs proves that the harmful effect of WHD exists only after birth and that postnatal recurrence is not distorted by prenatal loss of sibs. Thus, livebirth prevalence is equal to the incidence. However, there was a significantly higher rate of induced abortions after the birth of index patients, which may reflect the effect of genetic counselling. Of 172 liveborn sibs, 55 were affected by WHD; thus, the recurrence in sibs was 32%. (Additionally, death from unknown causes before the age of one year was mentioned in two sibs.) The observed 32% recur-

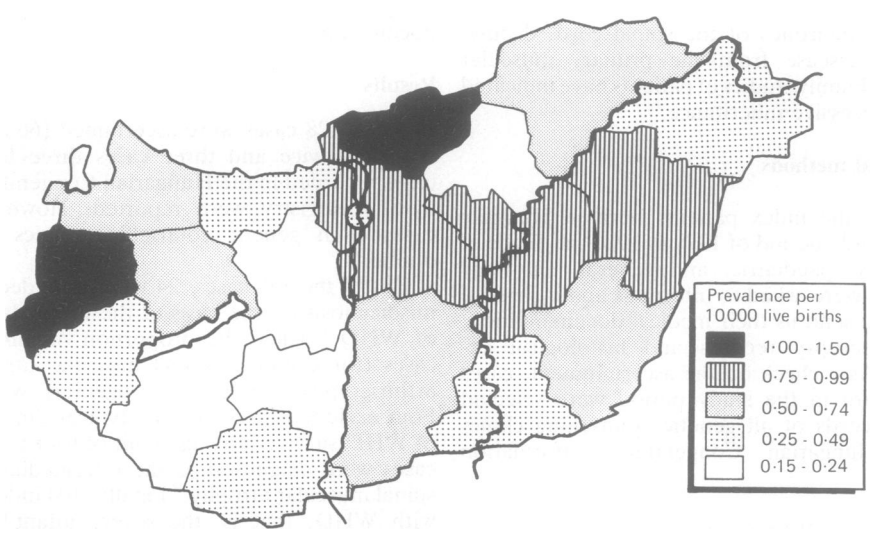

FIGURE *Territorial distribution of Werdnig-Hoffmann disease in Hungary, 1970 to 1980.*

rence rate exceeds the expected 25%; however, the explanation may be ascertainment bias, in that there is a higher chance of ascertaining families with more than one index patient. Fifty-seven families had one, 19 had two, and three had three index patients. The total number of 104 index patients occurred in 79 families and the proportion of affected sibs was similar in previous and subsequent pregnancies.

Among 79 parents three second cousin couples were found. This rate of 3·8% is 13 times higher than the Hungarian population figure.[10]

Discussion

The frequency of all forms of spinal muscular atrophy was found to be at least 0·5 per 10 000 livebirths by Brandt.[7] The livebirth prevalence of the infantile form (WHD) was reported as 0·39 per 10 000 in north-east England,[11] the incidence being 1 per 25 708 livebirths. The observed population based Hungarian figure of proximal infantile spinal muscular atrophy without other anomalies or additional neurological symptoms (WHD) was 0·66 per 10 000 from 1973 to 1980. Thus, the Hungarian incidence was 1 per 15 131 livebirths. Furthermore the estimated Hungarian figure was 1 per 10 000 livebirths, exceeding the population prevalence in north-east England. We were unable to find any data on the birth frequency of WHD from other central or eastern European countries.

Territorial clustering of WHD was recorded in Egyptian Karaite infants (1 in 400) caused by inbreeding[12] and in the European population of Réunion Island (1 in 1263)[13] explained by a founder effect.[14]

This disease is the second or third most common lethal disease of childhood in Britain,[15] while it is the second commonest in Hungary. Thus, the Hungarian gene frequency of WHD is likely to be 0·008 to 0·01, compared to the English figure of 0·006. The occurrence of consanguinity is relatively low in Hungary.[10] This Hungarian study has confirmed the autosomal recessive inheritance of WHD.

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