Hum Genet (1999) 105 : 151–156
Digital Object Identifier (DOI) 10.1007/s004399900075

ORIGINAL INVESTIGATION

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The frequency of lysosomal storage diseases in The Netherlands

Received: 23 February 1999 /Accepted: 27 April 1999 / Published online: 18 June 1999

Abstract We have calculated the relative frequency and the birth prevalence of lysosomal storage diseases (LSDs) in The Netherlands based on all 963 enzymatically confirmed cases diagnosed during the period 1970–1996. The combined birth prevalence for all LSDs is 14 per 100,000 live births. Glycogenosis type II is the most frequent LSD with a birth prevalence of 2.0 per 100,000 live births, representing 17% of all diagnosed cases. Within the group of lipidoses, metachromatic leukodystrophy (MLD) is the most frequent LSD. MLD was diagnosed in 24% of lipidoses and the calculated birth prevalence was 1.42 per 100,000 for all types combined. Krabbe disease, diagnosed in 17% of cases, also belongs to the more frequent lipid storage diseases in The Netherlands with a birth prevalence of 1.35 per 100,000. The birth prevalence of Gaucher disease, commonly regarded as the most frequent lipid storage disease is 1.16 per 100,000 for all types combined. The combined birth prevalence for all lipid storage diseases is 6.2 per 100,000 live births. Within the group of mucopolysaccharidoses (MPSs), MPS I has the highest calculated birth prevalence of 1.19 per 100,000 (25% of all cases of MPS diagnosed), which is slightly more frequent than MPS IIIA with an estimated birth prevalence of 1.16 per 100,000. As a group, MPS III comprises 47% of all MPS cases diagnosed and the combined birth prevalence is 1.89 per 100,000 live births. The birth prevalence of MPS II is 0.67 per 100,000 (1.30 per 100,000 male live births). All other MPSs are rare. The combined birth prevalence for all MPSs is 4.5 per 100,000 live births. Mucolipidoses and oligosaccharidoses are very rare with birth prevalences between 0.04 and 0.20 for individual diseases. Only 49 cases were diagnosed between 1970 and 1996. Their combined birth prevalence is 1.0 per 100,000 live births.

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Introduction

Although much is known about the biochemical and molecular basis of lysosomal storage diseases (LSDs), few data are available on the frequency of these disorders, because of the rarity of these diseases, the long observation period necessary to collect sufficient cases to make reliable frequency estimations and the incomplete ascertainment of cases. Some information on the relative frequency of LSDs in different areas of the world can be derived from the frequency at which specific diagnoses are made by reference laboratories for the diagnosis of LSDs (Coelho et al. 1997; Di Natale et al. 1993; Krasnopolskaya et al. 1997; Michelakakis et al. 1995; Sewell 1988; Whiteman and Young 1977). However, in only a few instances has the number of diagnosed cases been related to demographic data allowing an estimation of the birth prevalence to be made (Lowry et al. 1990; Meikle et al. 1999; Nelson 1997; Terry and Linker 1964). Here, we present data on the relative frequency and the birth prevalence of LSDs in The Netherlands based on 963 cases diagnosed between 1970 and 1996 assuming complete ascertainment. The data should be of interest to clinical geneticists, health care authorities, patients and their families, patient societies and laboratories involved in the diagnosis of LSDs. In addition, they should provide useful information for scientists and industries involved in developing therapies for LSDs and for decision makers when it comes to estimating the social and genetic burden of these diseases

to society or to considering the implementation of newborn screening programs for LSDs.

Patients and methods

The records from the laboratories of the clinical genetic centres involved in the post- and prenatal diagnosis of LSDs in The Netherlands were used as sources of ascertainment. These were judged to be complete and reliable for the observation period of 1970–1996. The main referral laboratories for the diagnosis of LSDs, viz. the clinical genetics centres of Leiden, Nijmegen and Rotterdam, contributed 95% of all cases. Additional information was obtained from the other contributing laboratories. The authors believe that these records represent as complete an ascertainment as possible of all cases of LSDs for the following reasons: (1) the intense coverage of complete postnatal and prenatal diagnostic facilities (metabolite and enzyme analysis and cell bank facilities) in The Netherlands during the ascertainment period 1970–1996; (2) the awareness of these diseases among clinicians in The Netherlands and the special efforts to ascertain all cases (also retrospectively); (3) the research efforts with regard to clinical and genetic aspects of various LSDs, such as mucopolysaccharidosis III (MPS III; van de Kamp 1979; Weber et al. 1998), Gaucher disease (Boot et al. 1997), glycogenosis type II (Reuser et al. 1995) and other LSDs.

A total of 963 patients were entered into the study. Familial cases and affected fetuses diagnosed prenatally were included. For all patients, the following data were available: date of birth, sex and year of diagnosis. The birth prevalence of an LSD was defined as the total number of cases with a particular LSD born within a certain period of time divided by the total number of live births within the same period. The latter data were collected from the Dutch Central Bureau of Statistics.

This approach is most reliable when a patient group consists of a sufficient number of patients with a homogeneous clinical presentation, such as Krabbe disease. When a patient group consisted of subgroups of sufficient patients with a distinct clinical phenotype, we calculated the birth prevalence of the subgroups separately and estimated the overall birth prevalence by adding the birth prevalences of the subgroups. Examples of this approach are metachromatic leukodystrophy(MLD), glycogenosis type II and Niemann-Pick disease types A and B. The age of presentation of Gaucher disease type 1 in the study group varied between 3 and 78 years of age. Although Gaucher disease type 1 is not formally classified into subgroups according to phenotype, calculation based on such a heterogeneous group of patients would lead to an underestimation of the birth prevalence. Therefore, we subdivided the Gaucher type 1 patients into a group with early presentation diagnosed when less than 15 years of age and a group with late presentation diagnosed at more than 15 years of age. In practice, virtually all of the latter patients presented at adult age.

Not all patients diagnosed between 1970–1996 were included in the calculation of the birth prevalence. For example, MPS IIIA patients with year of birth before 1960 were excluded. Inclusion of these patients would have led to an underestimation of the birth prevalence, because analysis of the age at diagnosis showed that, in that cohort, severe patients were significantly under-represented. The same also applied to some other diseases. A few patients diagnosed shortly before 1970 were included in the calculation of the birth prevalence of MPS II and MPS IIIC.

When diseases are very rare, such as the oligosaccharidoses and the mucolipidoses, non-ascertainment of even single cases may significantly influence the accuracy of the calculated birth prevalence. There is also more uncertainty about the correct time period that one should use to calculate the total number of live births, i.e. the denominator used to calculate the birth prevalence. For some of the rarer LSDs, the metabolic defect only became known during the course of the ascertainment period of 1970–1996. Examples are mucolipidosis I (1977), β-mannosidosis (1986), N-acetyl-α-N-galactosaminidase deficiency (1987), MPS IIID (1980) and lipidosis variants attributable to an activator protein deficiency (1979–1989); the reader is referred to the relevant chapters and references cited in Scriver et al. (1995) regarding these LSDs. For these diseases, the actual ascertainment period is considerably shorter than for the more common LSDs.

Results

The frequency distribution of the four main groups of LSDs for the 963 cases ascertained during the observation period of 1970–1996 is shown in Table 1. Lipidoses as a group are the most frequent LSDs followed by MPSs. Mucolipidoses and oligosaccharidoses are very rare. Glycogenosis type II is the most frequent single LSD. The combined birth prevalence for all LSDs is 14 per 100,000 live births.

The frequency distribution of the individual lipidoses is shown in Table 2. MLD, Krabbe and Gaucher diseases are the most frequent disorders. No cases of Wolman/cholesteryl ester storage disease or Farber disease were diagnosed in 1970–1996. Moreover, no cases of lipidosis attributable to an activator protein deficiency were found.

Within the group of MPSs, MPS I and MPS IIIA are the most frequent diseases (Table 3). MPS II and MPS IIIB also belong to the more common MPSs in The Netherlands. MPS III has a birth prevalence of 1.89 for all types combined. Other MPSs are rare. All individual mucolipidoses and oligosaccharidoses are also very rare (Table 4). The number of diagnosed patients and the birth prevalence for the clinical subgroups of glycogenosis type II (Pompe disease), the most frequent LSD in The Netherlands, is shown in Table 5.

Table 1 Relative frequency and birth prevalence of lysosomal storage diseases in The Netherlands

Disease	No. of patients 1970–1996	% of total	Birth prevalence[a] (per 100,000)	Relative rate (%)
Lipidoses	424	44	6.2	45
Mucopolysaccharidoses	331	34	4.5	33
Mucolipidoses plus oligosaccharidoses	49	5	1.0	7
Glycogenosis type II	159	17	2.0	15
Total	963		14	

[a] Taken from Tables 2, 3, 4 and 5

Table 2 Relative frequency and birth prevalence of lipidoses in The Netherlands

Disease	No. of patients 1970–1996	% of total	Years of birth	No. of live births	No. of patients	Birth prevalence (per 100,000)	Relative rate (%)
MLD late infantile	–	–	1965–1991	5,346,384	28	0.52	–
MLD juvenile	–	–	1954–1991	7,982,018	41	0.51	–
MLD adult	–	–	1927–1970	9,517,068	23	0.24	–
MLD unspecified	–	–	1957–1992	7,489,865	11	0.15	–
MLD (all types)	103	24	–	–	–	1.42	23.0
Fabry	27	6	1926–1986	12,634,905 (6,495,078)[a]	27	0.21 (0.42)[a]	3.5
GM1-gangliosidosis	20	5	1973–1996	4,426,936	18	0.41	6.5
GM2-Tay Sachs	31	7	1960–1995	7,358,444	30	0.41	6.5
GM2-Sandhoff	18	4	1970–1994	4,726,261	16	0.34	5.5
Niemann-Pick A	–	–	1974–1992	3,459,695	14	0.40	–
Niemann-Pick A or B	–	–	1943–1988	9,989,220	13	0.13	–
Niemann-Pick A + B	27	6	–	–	–	0.53	8.5
Niemann-Pick C	26	6	1957–1990	7,094,466	25	0.35	5.5
Gaucher type 1, early	–	–	1956–1993	7,917,105	21	0.26	–
Gaucher type 1, late	–	–	1918–1970	11,148,824	70	0.64	–
Gaucher type 2 and 3	–	–	1974–1996	4,231,943	11	0.26	–
Gaucher (all types)	102	24	–	–	–	1.16	19.0
Krabbe	70	17	1971–1995	4,677,849	63	1.35	22.0
All types	424	–	–	–	–	6.2	–

[a] Male live births

Table 3 Relative frequency and birth prevalence of mucopolysaccharidoses in The Netherlands

Disease	No. of patients 1970–1996	% of total	Years of birth	No. of live births	No. of patients	Birth prevalence (per 100,000)	Relative rate (%)
MPS I	82	25.0	1962–1995	6,871,909	82	1.19	26.0
MPS II	52	15.5	1955–1995	8,532,427 (4,373,713)[a]	57	0.67 (1.30)[a]	15.0
MPS IIIA	93	28.0	1960–1993	6,972,344	81	1.16	26.0
MPS IIIB	47	14.0	1940–1991	11,131,609	47	0.42	9.0
MPS IIIC	13	4.0	1949–1980	7,119,276	15	0.21	5.0
MPS IIID	3	1.0	1970–1985	2,994,743	3	0.10	2.0
MPS III (all types)	156	47.0	–	–	–	1.89	42.0
MPS IVA	22	6.5	1951–1996	9,639,257	21	0.22	5.0
MPS IVB	5	1.5	1960–1975	3,680,759	5	0.14	3.0
MPS VI	6	2.0	1970–1990	3,939,514	6	0.15	3.0
MPS VII	6	2.0	1985–1995	2,100,154	5	0.24	5.5
MSD	2	0.5	1975–1995	3,855,561	2	0.05	1.0
All types	331	–	–	–	–	4.5	–

[a] Male live births

Discussion

Few data are available on the population frequency of lipidoses. For the infantile type of MLD, the estimated birth prevalence varies from 1:40,000 in Northern Sweden and Washington State to 1:130,000 in France. An overall figure for MLD of 1:100,000 is given as an estimate based on the personal experience of a referral laboratory in the United States (Scriver et al. 1995). These figures compare well with the overall birth prevalence for all types of MLD of 1.42 per 100,000 live births (1:70,000) found in our study and of 1.09 per 100,000 (1:92,000) recently reported for Australia (Meikle et al. 1999).

Gaucher disease type 1 is particularly prevalent in the Ashkenazi Jewish population with a disease frequency of clinically affected cases of at least 1:10,000. Gene frequency assessments suggest a much higher frequency but, in many cases, homozygotes for the 1226G mutation appear to have no or only minor clinical symptoms and probably do not come to medical attention (Scriver et al. 1995). The birth prevalence that we have calculated for

Table 4 Relative frequency and birth prevalence of mucolipidoses and oligosaccharidoses in The Netherlands

Disease	No. of patients 1970–1996	% of total	Years of birth	No. of live births	No. of patients	Birth prevalence (per 100,000)	Relative rate (%)
Mucolipidosis I	4	8	1950–1990	8,701,328	4	0.05	5
Mucolipidosis II	6	12	1975–1995	3,855,561	6	0.16	16
Mucolipidosis III	9	19	1940–1990	10,932,944	9	0.08	8
Fucosidosis	5	10	1950–1995	9,678,575	5	0.05	5
α-Mannosidosis	9	20	1950–1995	9,678,575	9	0.09	9
β-Mannosidosis	3	6	1978–1990	2,350,052	3	0.13	13
Galactosialidosis	4	8	1944–1995	11,144,032	4	0.04	4
Aspartylglucosaminuria	5	10	1970–1990	3,939,514	5	0.13	13
Sialic acid storage diseases	2	4	1980–1995	2,976,770	2	0.07	7
α-N-acetyl galacto-saminidase deficiency	2	4	1990–1994	984,712	2	0.20	20
All types	49	–	–	–	–	1.0	–

Table 5 Relative frequency and birth prevalence of Pompe disease in The Netherlands

Disease	No. of patients 1970–1996	% of total	Years of birth	No. of live births	No. of patients	Birth prevalence (per 100,000)	Relative rate (%)
Glycogenosis type II infantile	67	42	1970–1996	5,107,161	67	1.31	65
Glycogenosis type II juvenile and adult	92	58	1916–1979	13,195,587	92	0.70	35
Glycogenosis type II (all types)	159	–	–	–	–	2.0	–

Gaucher disease type 1 in The Netherlands is 0.9 per 100,000. Although the 1226G mutation is particularly prevalent in the Dutch population, homozygosity for the 1226G mutation has been found to be extremely rare among Gaucher patients in The Netherlands (Boot et al. 1997). This has to be taken into account when making carrier frequency estimations for Gaucher disease based on prevalence figures such as those given by Scriver et al. (1995). The neuronopathic forms of Gaucher disease (types 2 and 3) are rare. Recently, a few cases of very severe Gaucher disease with hydrops fetalis and the collodion baby phenotype were diagnosed in our laboratories (Tayebi et al. 1997; unpublished). These phenotypes are probably under-represented in the current survey.

Hagberg et al. (1969) have reported a birth prevalence of 1.9 per 100,000 for Krabbe disease in Sweden, where this disease is particularly prevalent, and estimates of 1:150,000 (0.67 per 100,000) for France, 1:100,000–200,000 (0.5–1.0 per 100,000) for Japan (Scriver et al. 1995) and 1:141,000 (0.71 per 100,0000 for Australia (Meikle et al. 1999) have been given. Our estimate of 1.35 per 100,000 falls in between the estimates for Sweden and France; Krabbe disease belongs to the more frequent lipidoses in The Netherlands.

For Tay-Sachs and Sandhoff disease, the birth prevalences reported here are close to those expected in non-Jewish individuals (Scriver et al. 1995) and similar to those found in Australia (Meikle et al. 1999). For the other lipidoses, no population frequency estimates have been made so far, apart from genetic isolates with high frequencies and for Australia (Meikle et al. 1999).

The available data on the population frequencies of MPSs have recently been reviewed (see Table 1 in Nelson 1997, and page 2480 in Scriver et al. 1995). In addition, the cumulative experience of several referral laboratories for the diagnosis of LSDs gives some insight into the frequencies of MPSs and other LSDs (Coelho et al. 1997; Di Natale et al. 1993; Krasnopolskaya et al. 1997; Michelakakis et al. 1995; Sewell 1988; Whiteman and Young 1977) but these data have not been related to demographic data except those recently published for Australia (Meikle et al. 1999). MPS I and MPS IIIA are the MPSs with the highest birth prevalence in The Netherlands. Our study confirms previous observations by van de Kamp (1979), viz. that MPS III (all types combined) has the highest birth prevalence of all MPSs. His estimates of 1:73,000 and 1:47,000, obtained by using two different approaches, are based on much smaller numbers of ascertained cases than in the current study where we find a combined birth prevalence of 1:53,000 (1.89 per 100,000 live births). These previous estimates and the assumptions made in the calculations have recently been discussed in detail by Nelson (1997) in view of the low incidence of MPS III in Northern Ireland. Our data also suggest that the third and most frequently cited estimate of 1:24,000 obtained by van de Kamp (1979) by comparing the number of patients in 13 mental institutions with the number of patients with phenylketonuria is probably an overestimation of the true birth prevalence. Nevertheless, the birth prevalence of MPS III in The Netherlands is much higher than that obtained in Northern Ireland (1:280,000; 0.36 per 100,000; Nelson 1997), British Colombia (1:325,000; 0.31 per

100,000; Lowry et al. 1990) and Utah (1 : 10,000–200,000; Terry and Linker 1964) but in the same order as the figure of 1 : 66,000 (1.51 per 100,000) calculated for Australia (Meikle et al. 1999). MPS IIIA has the highest birth prevalence of all types of MPS III, confirming that this is the most frequent form of MPS III in north-west Europe (van de Kamp 1979; Sewell 1988; Whiteman and Young 1977). In contrast MPS IIIB is the more common type of MPS III in south-east Europe (Michelakakis et al. 1995). In our study, a birth prevalence of 0.42 per 100,000 (1 : 238,000) has been found, which is about 3 times lower than that for MPS IIIA and comparable to the Australian figures (Meikle et al. 1999).

Our patient population of MPS I comprises 58 patients classified as having the Hurler phenotype and 24 cases of the milder Hurler-Scheie and Scheie phenotypes. Since these phenotypes are part of a continuous spectrum of phenotypes of MPS I attributable to different combinations of mutations in the α-L-iduronidase gene (Scott et al. 1993) and since the diagnoses of the milder patients were made early in life, we have treated all MPS I patients as a single group in the calculation of the birth prevalence. The birth prevalence of 1.19 per 100,000 live births (1 : 84,000) compares with a birth prevalence of 0.90 for Australia (Meikle et al. 1999) and older estimates 0.69 per 100,000 in British Columbia, and to 1.3 and 0.36 per 100,000 for MPS I Hurler and Hurler/Scheie disease in Northern Ireland (Lowry et al. 1990; Nelson 1997).

The birth prevalence of 1.30 per 100,000 male live births for MPS II compares well with the figures of 1.43 for Australia and 1.39 in Northern Ireland and 0.9 for British Columbia. A lower figure of 1 per 132,000 (0.76 per 100,000) male live births was calculated for the United Kingdom by Young and Harper (1982), possibly related to incomplete ascertainment (Nelson 1997). MPS IVA and B, VI and VII belong to the less frequent MPSs in most populations except for Brazil, where MPS VI appears to be relatively frequent (Coelho et al. 1997), and Northern Ireland with a relatively high birth prevalence of MPS IVA (Nelson 1997). The birth prevalence of MPS VII was calculated on the basis of a relatively short period of time (1985–1995) and was probably under-diagnosed during the first part of the ascertainment period of 1970–1984. This is related to the recent awareness that this MPS may present more frequently than other MPSs with hydrops fetalis (Vervoort et al. 1996). Indeed, all patients diagnosed with MPS VII belonged to the early presenting group and none had the classic MPS phenotype described in the first patient with MPS VII (Scriver et al. 1995).

The overall birth prevalence of all MPSs as a group is estimated as 4.5 per 100,000 live births (1 : 22,000), which is very close to the previous estimates of 1:25 000 for British Columbia and Münster (Spranger 1972), 1: 24,692 for Northern Ireland (Nelson 1997) and 1 : 22,000 for Australia (Meikle et al. 1999).

No population frequency data are available for the mucolipidoses and the oligosaccharidoses except for aspartylglucosaminuria, which is particularly frequent in Finland, where the carrier frequency has been determined as 1 in 36 (see Scriver et al. 1995). All these diseases are very rare in The Netherlands and, as stated above, the calculations of the birth prevalence are only based on a few cases. The overall birth prevalence for this group of LSDs was estimated to be 1 per 100,000 live births. Glycogenosis type II (Pompe disease) is the most frequent single LSD in The Netherlands. The age of diagnosis in the adult patient group varied from 11–64 years of age suggesting great variation in clinical severity extending into a very mild phenotype expressing itself at an advanced age. Indeed, the very mild phenotype may go unrecognized. This means that, as with Gaucher disease, patients with very mild complaints may be under-represented in this survey and the birth prevalence of 0.7 per 100,000 for adult Pompe disease is probably a minimum estimate.

In conclusion, our data represent the most comprehensive survey on the frequency of LSDs in a given population. The population of The Netherlands is sufficiently large and the number of patients sufficiently high to make reasonably reliable estimations of the birth prevalence for the more common LSDs. Given the provisos mentioned above, our figures for the rarer LSDs represent the best possible approximation to date.

Acknowledgements We thank all our clinical colleagues for referring patient material. The invaluable help of G. Mantel in converting the initial data to a manageable form is gratefully acknowledged.

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