Incidence of Inborn Errors of Metabolism in British Columbia, 1969–1996

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ABSTRACT. Objective. To determine how many children with specific types of inborn errors of metabolism are born each year in British Columbia, Canada. This population provides a relatively unique setting for collection of accurate and uniform incidence data because the diagnoses are all made through one laboratory in a population with universal access to government-funded medical care.

Methodology. We used the records of the Biochemical Diseases Laboratory, Children’s Hospital, Vancouver (the central referral point for all metabolic diagnoses in British Columbia) to identify all patients diagnosed with the metabolic diseases defined below. We obtained incidence figures by including only the children diagnosed with the diseases covered in this article who were confirmed as having been born within the province for the years 1969 to 1996. The diseases covered were diseases of amino acids, organic acids, the urea cycle, galactosemia, primary lactic acidoses, glycogen storage diseases, lysosomal storage diseases, and diseases involving specifically peroxisomal and mitochondrial respiratory chain dysfunction. Because the technology needed for diagnosis of specific disease groups was in place at different times our data for the different disease groups correspond to different time frames. We have also adjusted the time frames used to allow for the likelihood that some diseases may not come to medical attention for some time after birth. For instance the incidence of amino acid diseases was assessed throughout the whole of this time frame but the incidence of peroxisomal diseases was restricted to 1984 to 1996 because this was the time frame during which the technology needed for diagnosis was in place and reliable. Most disease group statistics included at least 400 000 births.

Results. The overall minimum incidence of the metabolic diseases surveyed in children born in British Columbia is ~40 cases per 100 000 live births. This includes phenylketonuria (PKU) and galactosemia which are detected by a newborn screening program. Metabolic diseases, which were not screened for at birth, ie, those with PKU and galactosemia subtracted from the total, have a minimal incidence of ~30 cases per 100 000 live births. This diagnostic dilemma group would present to pediatricians for diagnosis. Not all metabolic diseases have been surveyed and our data are restricted to the following metabolic disease groups. Approximately 24 children per 100 000 births (~60% of the total disease groups surveyed) have a disease involving amino acids (including PKU), organic acids, primary lactic acidosis, galactosemia, or a urea cycle disease. These children all have metabolic diseases involving small molecules. Approximately 2.3 children per 100 000 births (~5%) have some form of glycogen storage disease. Approximately 8 per 100 000 births (20%) have a lysosomal storage disease; ~3 per 100 000 births (7%–8%) have a respiratory chain-based, mitochondrial disease and ~3 to 4 per 100 000 (7%–8%) of births have a peroxisomal disease. The diseases involving subcellular organelles represent approximately half of the diagnostic dilemma group. The incidence of each of the specific diseases diagnosed, including apparently rare diseases such as nonketotic hyperglycinemia, is to be found in the text. The metabolic diseases reported in this survey represent over 10% of the total number of single gene disorders in our population.

Conclusions. Our data provide a good estimate of metabolic disease incidence, for the disease groups surveyed, in a predominantly Caucasian population. Incidence data for metabolic diseases are hard to collect because in very few centers are diagnoses centralized for a population with uniform access to modern health care and this has been the case for our population during the course of the study. We foresee a need for accurate information on the incidence of metabolic diseases as a guide to how to provide diagnostic and therapeutic services for metabolic diseases and the figures should help in assessing such needs in similar populations. Pediatrics 2000; 105(1). URL: http://www.pediatrics.org/cgi/content/full/105/1/e10; incidence data, metabolic diseases, lysosomal, peroxisomal, mitochondrial, small molecule.

ABBREVIATION. PKU, phenylketonuria.

In 1988, Baird and colleagues1 published data on the overall incidence of a broad range of genetic diseases in British Columbia, Canada, and quoted an expected incidence of ~360 single gene disorders per 100 000 births.

We used the database of the Biochemical Diseases Laboratory to obtain data on the incidence of specific groups of metabolic diseases in our population, using only British Columbia-born patients between 1969 and 1996. Our study allows some breakdown of the earlier figure to highlight the numbers of single gene disorders which involve specific metabolic diseases. The data include diseases involving amino acid and organic acid metabolism, urea cycle dis-

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Received for publication Mar 2, 1999; accepted Jul 14, 1999.

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http://www.pediatrics.org/cgi/content/full/105/1/e10

PEDIATRICS Vol. 105 No. 1 January 2000 1 of 6

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eases, and all forms of glycogen storage disease, lysosomal storage diseases, peroxisomal, and mitochondrial diseases. The mitochondrial diseases included in this survey are defined as those which affect the respiratory chain as proven either by mitochondrial enzymology assays or mitochondrial DNA analysis.

Because Canada has universal health care and there is a consistent standard of medical care throughout British Columbia we believe that our data are representative of the actual disease incidence. Investigations for metabolic diseases in children in British Columbia are centralized in the Biochemical Diseases Laboratory of the Children’s Hospital in Vancouver so that it has been possible to evaluate minimal disease incidence for our whole population. Children’s Hospital is the only children’s hospital in British Columbia so it is available to all physicians for medical testing and care for all children in the province. Diagnoses may well have been made when children were in outlying hospitals but the only referral laboratory in our province, for laboratory confirmation of a metabolic disease, is our laboratory at British Columbia’s Children’s Hospital. Cases may be referred to other laboratories when appropriate assays are not available in Vancouver but the laboratory itself is always responsible for such referrals. Newborn screening for phenylketonuria (PKU) has been in effect since 1964 and galactosemia screening has been done since 1984. For all diseases final clinical diagnosis was made by medical personnel from the Children’s Hospital, in Vancouver, which is the teaching hospital of the University of British Columbia, Department of Pediatrics. Only diagnoses confirmed by both laboratory and clinical investigations have been included in our data. British Columbia averaged ~41,000 births per year during the 28-year period selected for data collection.

The figures should be capable of extrapolation to other populations with a similar ethnic mixture to our predominantly (at the time the data were collected) Caucasian population.

MATERIALS AND METHODS

The fact that all the patients in this survey were actually born in British Columbia was established initially from the birth records of the British Columbia Vital Statistics Agency. For patients not in the records of this agency (presumably in such circumstance as a family name changing after the infant left the birth hospital, and so forth) we contacted families of all our diagnosed patients by mail to establish the province of birth.

Cases diagnosed prenatally are included in our statistics. In such cases a proband had been diagnosed within the family and the family was living in British Columbia at the time of the prenatal diagnosis.

Our data relate only to conditions which cause a clinical disease state. Where a metabolite assay was used to make a likely diagnosis, cases (except PKU) were further confirmed by appropriate enzyme or DNA mutation assay. All cases included in this survey have met appropriate present criteria for diagnosis of a genetically inherited metabolic disease. These included appropriate family studies of the metabolic defect. In all cases the clinical findings and response to therapy, in which therapy is possible, were consistent with the stated diagnosis.

Laboratory tests used for the initial diagnosis and detection of diseases include the following: quantitative plasma and cerebrospinal fluid amino acid analyses; urine organic acids by gas chromatography-mass spectrometry; very long-chain fatty acids and phytanic acid for diagnosis of peroxisomal diseases; specific enzyme assays for all diseases, including galactosemia, glycogen storage diseases, lysosomal storage diseases, and diseases involving defects of the mitochondrial respiratory chain. Mutation analysis was performed on white blood cells, fibroblast, or tissue DNA for point mutations and deletions of mitochondrial DNA, for the common DNA mutation in medium chain acyl CoA dehydrogenase deficiency, and in some patients with classical galactosemia.

Diseases have been tabulated in the group in which the disease has its primary pathogenesis. For example, cystinosis is counted as a lysosomal storage disease and not as an amino acid disease. Disorders of cobalamin metabolism (cobalamin C and F diseases, 2 cases) are the only disorders counted in 2 groups—as amino acid disorders (because they demonstrate homocystinuria) and organic acid diseases (because they demonstrate methylmalonic aciduria). Benign renal tubular aminoacidurias, such as cystathioninuria and iminoglycinuria have not been counted in our statistics. It is worth noting that during the time of data collection most of the primary diagnostic tests for metabolic diseases were biochemical. The commonest exceptions are the common DNA mutations in mitochondrial DNA.

Stringent criteria were applied to patients classified as having biochemical evidence of mitochondrial disease for this article. All had either a strictly defined enzyme deficiency of one or more of the muscle mitochondrial respiratory chain enzymes or proof of a mtDNA mutation in mtDNA. We have only included cases in which the respiratory chain activity of at least 1 of the mitochondrial complexes I, II, or IV, expressed as a ratio to citrate synthase, had a value of <20% of the mean activity for control muscle samples (in the normal range for control muscle samples the lowest control value was 53% of the mean). All the patients had clinical findings consistent with mitochondrial disease.

RESULTS

The results obtained for incidence figures of various diseases are given in Table 1 and Fig 1. More details of the actual diagnoses follow. Following the name of each disease the total number of patients diagnosed with each disease is in parentheses followed by the number of affected prenatal diagnoses.

Amino acid diseases, for patients born in years 1969 to 1996, (1, 142, 912 births) included the following: cobalamin C and F (2 cases), cystinuria (17 cases), formiminoglutamic aciduria (2 cases), ornithine alpha amino transferase deficiency (gyrate atrophy of the retina) (2 cases), histidinemia (8 cases), homocystinuria (cystathionine synthase deficiency) (6 cases), lysinemia (2 cases), maple syrup urine disease (2 cases), nonketotic hyperglycinemia (18 cases, 2 diagnosed prenatally), sulfite oxidase deficiency (3 cases, 2 diagnosed prenatally) and hereditary tyrosinemia (8 cases). PKU patients (198 cases) are those with a plasma phenylalanine at diagnosis of >600 micromolar and who require a continual low phenylalanine diet to normalize their phenylalanine levels. Twenty-six cases of hyperphenylalaninemia, who did not require ongoing dietary management, are not included in the data.

Urea cycle diseases (for years 1979–1996; 966 901 births) included the following: carbamyl phosphate synthetase deficiency (3 cases), ornithine transcarbamylase deficiency (9 cases), citrullinemia (3 cases), argininosuccinic aciduria (3 cases). One prenatal diagnosis, for citrullinemia, was done and the affected fetus carried to term.

Organic acid diseases (for years 1979–1996; 785 400 births) included the following: alkaptotonuria (3 cases); biotinidase deficiency (5 cases); cobalamin C and F diseases (2 cases; also counted in the amino
acid group) and transcobalamin II deficiency; hydroxylutaric acidemia; glutaric acidemia type I (3 cases); isovaleric acidemia (2 cases); ketothiolase deficiency (2 cases); medium chain acyl CoA dehydrogenase deficiency; methylmalonic acidemia (2 cases); propionic acidemia; pyroglutamic aciduria; glycerol kinase deficiency; and hyperoxaluria type I (3 cases), while being also an organic acid disease has been counted, for statistical purposes, in the peroxisomal disease group. We detected several fatty acid oxidation diseases classified loosely as glutaric acidemia type II but which are not yet enzymatically diagnosed. These do not form part of our statistics. There were no affected prenatal diagnoses in the organic acid group.

Galactosemia has been identified by a newborn screening program since 1984. We have included only cases in which there was an absence of erythrocyte galactose 1-phosphate uridyl transferase activity. Cases of likely Duarte variants are not included in our data (see “Discussion” section).

Primary lactic acidosis cases consisted of pyruvate carboxylase deficiency (2 cases, 1 diagnosed prenatally and both from the same family) and pyruvate dehydrogenase deficiency (4 cases).14

Lysosomal storage diseases (for years 1972–1996; 1 035 816 births) included the following: cobalamin F disease (1 case), cystinosis (7 cases, 1 prenatal diagnosis), Fabry (3 cases), galactosialidosis,16 Gaucher (4 cases),17–19 GM1 gangliosidosis (2 cases), Pompe disease (9 cases, 1 prenatal diagnosis), Sandhoff (2 cases, 1 prenatal diagnosis), Tay-Sachs (3 cases; 2 born to non-Jewish parents), mucolipidoses II and III (3 cases), Krabbe (3 cases, 1 prenatal diagnosis), mannosidosis (2 cases),20 metachromatic leucodystrophy (6 cases, 1 prenatal diagnosis), Hurler Scheie (6 cases),22 Hunter (1 case, prenatal diagnosis), Moroteaux-Lamy; Morquio A (5 cases, 1 prenatal diagnosis),23 Sandhoff disease (2 cases, 1 prenatal diagnosis), Sanfilippo A (3 cases), Sly (3 cases), multiple sulfatase deficiency (1 case), Niemann-Pick (4 cases), sialidase deficiency (2 cases), Wolman (6 cases, 4 prenatal diagnoses), and 1 case of carbohydrate deficient glycoprotein disease (classified here as a lysosomal storage disease as a temporary expedient until we know more about this disease).

Glycogen storage diseases (for years 1972 to 1996; 1 035 816 births) excluding Pompe (cited in lysosomal storage diseases), glycogenoses I (5 cases, 3 cases type Ia, 1 case of Ib, and 1 case of Ic), III, IV (3 cases), V and VI together with 4 cases of histologically or chemically proven cases with glycogen storage in liver without a defined enzymologic diagnosis. There was 1 affected prenatal diagnosis for glycogen storage disease type IV in this group.

Peroxisomal diseases (for years 1984 –1996; 579 196 births) included: neonatal adrenoleucodystrophy or infantile Refsum disease (2 cases), Zellweger (8 cases, 1 prenatal diagnosis), X-linked adrenoleucodystrophy or adrenomyeloneuropathy (4 cases), rhizomelic
chondrodysplasia punctata (3 cases, 1 prenatal diagnosis), type I hyperoxaluria (3 cases), and 1 unclassified patient who also had congenital rubella syndrome.

Mitochondrial disease cases (for years 1988–1996; 408,667 births) included only patients in which there was either a severe deficient activity of one or more of the respiratory chain enzyme activities confirmed by enzyme assay on a biopsy of vastus lateralis muscle or a defined point mutation of mitochondrial DNA. For our criteria for diagnosis within this group see the “Materials and Methods” section. There were no prenatal diagnoses in this group. The actual case results were as follows: decreased complex I (2 cases), decreased complex IV (3 cases), decreases in both complex I and IV (3 cases), and decreases in complex I and III (1 case). For mtDNA errors, 1 case of NARP (mtDNA 8993 T→G), 2 cases of mtDNA depletion syndrome in 2 brothers.

DISCUSSION

The criteria used for diagnoses included in this survey have been covered in the “Introduction” and “Materials and Methods” sections. It is important to specify what disease groups are not covered. Our data do not include diseases of collagen, such as osteogenesis imperfecta; disorders of metal metabolism, such as Menkes or Wilson’s disease; diseases of porphyrin metabolism or any of the blood lipid diseases, such as hypercholesterolemia (other than the lysosomal storage diseases involving glycolipids). All these diseases, or others not specified, may be present in significant amounts in some populations but our laboratory has concentrated mostly on the classical inborn errors of metabolism already enumerated in this article.

The results in Table 1 and Fig 1 include data for different disease groups collected during different time periods according to the availability of testing methods during the total 28-year period used for data collection. The years chosen for individual groups of diseases depended on the availability or reliability of the diagnostic technology used for each disease group during the years chosen. For instance, amino acid diseases have been accurately diagnosed since approximately 1969 whereas mitochondrial diseases have only been definitively diagnosed by enzyme or molecular assays, in our laboratory, since approximately 1988. Therefore, the denominator, of births per year, is different for different groups of diseases. The birth years used were 1969 to 1996 for amino acid diseases, 1974 to 1996 for urea cycle diseases (separated from amino acid diseases in the statistics but clearly also diagnosed by amino acid assays), 1979 to 1996 for organic acid diseases, 1978 to 1996 for lysosomal diseases, 1972 to 1996 for glycogen storage diseases, 1986 to 1996 for peroxisomal diseases, and 1988 to 1996 for mitochondrial diseases. The year 1996 was chosen as the cutoff year of births to allow a time window for ascertainment although the actual laboratory diagnoses were made up to the end of 1997.

Only classical galactosemia cases are included in our data. Classical galactosemia patients were identified by an absence, in erythrocytes, of enzyme activity for galactose 1-phosphate uridyl transferase. We have not included 16 newborns who were probable Duarte/classical galactosemia compound heterozygotes with a low level of galactose uridyl transferase activity detected by newborn screening and high levels of erythrocyte galactose 1-phosphate. For 7 of these cases, the presence of the Duarte, N314D, mutation was confirmed and for the remainder no sample was available for DNA analysis, so we elected not to include likely Duarte galactosemia cases in our table and figure.

In Fig 1 the data are subdivided into groups which include small molecule diseases and organelle diseases. Small molecule diseases tend to be diseases in which newborn screening detects the disease (PKU and galactosemia) or diseases in which diagnosis can be made by requesting assay of a metabolite group such as amino acids or organic acids. This method of testing allows diagnosis of any one of many possible diseases in a single test. For organelle diseases, defined as involving lysosomal storage or peroxisomal or mitochondrial dysfunction, the diagnostic protocols are much less easily defined. Diseases involving mitochondrial enzymes responsible for fatty acid oxidation could logically be classified as either mitochondrial diseases or small molecule diseases. We have chosen to define mitochondrial disease specifi-
cally as involving only those diseases which affect, as a primary pathogenesis, the mitochondrial respiratory chain. Other diseases involving mitochondrial housekeeping enzymes such as diseases of fatty acid oxidation or the urea cycle have been classified in the small molecule disease group.

Some diseases can be classified in more than one group. For example, Pompe disease can be classified under glycogen storage disease or as a lysosomal storage disease and cystinosis could be counted as an amino acid disease or a lysosomal storage disease. In all such cases the total incidence is calculated only from the rows in the table which have an asterisk in the extreme right column. This will allow the reader to see in which group we have counted a disease. Urea cycle diseases are also counted separately although we recognize that most frequently the diagnosis must rely on amino acid assay.

We deliberately made our laboratory criteria for classification of a patient as having a primary mitochondrial disease fairly rigorous by only including cases in which the activity of at least one component of the mitochondrial respiratory chain was <20% of the mean of our controls. We have used criteria published by Walker et al7 for the biochemical categorization of a muscle enzyme result as having likely clinical significance. For this report we have only listed the patients whose muscle biochemistry fits the criterion given above. We have at least as many cases again in which the enzyme activity of one or more of the respiratory chain complexes had a value below the mean and the patient was likely, on clinical grounds, to have a primary mitochondrial disease. Proof that a respiratory chain enzyme deficit is a primary cause of disease requires many evidence-based criteria. We have not included such patients until evidence-based criteria for diagnosis of a mitochondrial disease have more uniform acceptance. Until there are better criteria we realize that our figures on the incidence of primary mitochondrial diseases are likely to be underestimates.

Our data do include cases diagnosed by prenatal diagnosis in families in which an index case had led to this request. All prenatal diagnoses were confirmed by analysis of abortus tissue in which the prenatal diagnoses resulted in termination of pregnancy.

Any attempt at generating accurate prevalence or incidence figures based on years of birth will always be subject to problems of underdiagnosis because there will always be some patients who present with signs or symptoms of their inborn disease later in life than the time period surveyed. Our data are pediatric data and do not take into account the, intuitively observed, increasing numbers of adults with mitochondrial diseases which we believe will greatly swell incidence figures of metabolic diseases in the future. Nevertheless, we have available, in British Columbia, a fully comprehensive, Medicare system of a standard comparable to that found elsewhere in the developed world. Our population has uniform access to these services so that it is likely that these figures are a good indication of minimal disease incidence. It is recognized that it is likely they are minimal incidence figures because a proportion of cases will not be ascertained and die before diagnosis. There is also the aspect to consider of affected infants who move out of the Province before diagnosis. For the disorders which would be symptomatic less than one year of age, it is likely that the proportion lost by this out-migration is comparable to the out migration rate in a year in the population as a whole which is ~2% or less. For diseases presenting later it is harder to quantify loss by out-migration so our data represent only the beginnings of attempts to estimate the accurate incidence of metabolic diseases in a predominantly Caucasian population.

Before 1991, the majority of British Columbians were of British or European origin. According to Census Canada the British group comprised 58%, whereas other European populations comprised 29%. Chinese at that time comprised 2% of the population, North American Indians 2.4%, East Indians .9%, and Japanese .6%. Since 1991 there has been a significant influx of people of Chinese and Indo-Pakistani origin, but the majority of the population is still of British or European origin.

It is possible to get approximate figures for birth incidences of any of the diseases described in the written portions of the “Results” section but it is likely that for most of these single gene diseases the numbers of cases may not reach a statistically significant figure so we have preferred to quote incidence figures for disease groups. Nevertheless, for some diseases, such as nonketotic hyperglycinemia there are no comparable data. For nonketotic hyperglycinemia the incidence in our population is 1 in 63 000. Our data might have similar utility for others interested in specific diseases provided our caveats concerning paucity of cases of individual diseases are kept in mind.

The Baird study1 quoted in the “Introduction” reported an expected incidence of ~360 single gene disorders per 100 000 births for British Columbia. Our data suggest that of this total ~40 children in 100 000 births can be expected to have one of the metabolic diseases included in our survey. This is over 10% of the total number of single gene disorders. Children with PKU and galactosemia make up approximately a quarter of metabolic diseases in the group of diseases surveyed here. Approximately half are diseases involving subcellular organelles. There is a smaller group of patients with primary lactic acidosis and glycogen storage disease.

Our data can be viewed as a guide to how we can provide diagnostic and therapeutic services for metabolic diseases in the future. They do not accurately represent the complete workload of a metabolic laboratory. For instance, our laboratory analyzes many more samples for amino and organic acids than the relatively few numbers of positive diagnoses. An informal cross-Canada survey suggested that the ratio of urinary organic acid samples analyzed to diagnose each case was at least 300 to 1. Our data do not, therefore, provide figures for expected workloads of metabolic laboratories. They do provide some evidence for speculation about how we can
make diagnoses in the future. Because approximately half of the cases of metabolic disease involve increases in small molecule metabolites it is reasonable to expect that many of these diseases will be diagnosable by the increasing use, and sensitivity of, tandem mass spectrometry when it is used in mass population screening of newborns or at-risk populations. As the sensitivity of these methods increases, tandem mass spectrometry will, presumably, be able to diagnose peroxisomal diseases by screening for either very long chain fatty acids or bile acids in blood samples. Lysosomal storage diseases are already screened for in Australia by one major laboratory in Adelaide which uses a panel of lysosomal assays to detect most of the lysosomal storage diseases described in our data. Whereas many centers will continue to attempt a diagnosis of a lysosomal storage disease by the classical comparison of signs and symptoms with knowledge of the diseases corresponding to these signs and symptoms the per diem costs of hospital admissions may make it cheaper to use this enzyme screening approach (see chapter 4 in Applegarth et al25). Overall it may be feasible to use screening approaches to diagnose most of the metabolic diseases discussed in this article. The major remaining diagnostic dilemma remains how to diagnose mitochondrial disease most efficaciously.

ACKNOWLEDGMENTS

This survey was based on clinical and laboratory investigations by the clinical staff of British Columbia’s Children’s Hospital. Our ability to publish this laboratory-based survey comes from close collaboration with the Biochemical Diseases Clinical Service headed by Dr George Davidson, whose staff include Drs Lawrence Wong and Lorne Clarke, the physicians and staff of the Clinical Genetics unit headed by Dr Sylvie Langlois, the physicians and staff of Pathology, British Columbia’s Children’s Hospital and those of Neurology, headed by Dr Alan Hill. The sheer number of such clinical colleagues precludes individual recognition but we must stress that only with their diagnostic skill was this tabulation of data possible. We owe heartfelt thanks to them by the clinical staff of British Columbia’s Children’s Hospital. Our thanks also go to the excellent secretarial expertise for an extended period of our data collations. The Biochemical Diseases Laboratory was founded, in 1968, with the visionary foresight of Drs Sydney Israel and David Hardwick. Their vision made our data collection possible.

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Pediatrics 2000;105;e10

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