Increased prevalence of hereditary metabolic diseases among native Indians in Manitoba and northwestern Ontario

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Objective: To compare the prevalence of hereditary metabolic diseases in the native and non-native populations of Manitoba and northwestern Ontario.
Design: Retrospective analysis.
Setting: Children's Hospital, Winnipeg.
Patients: Patients were selected by three methods: laboratory tests designed to screen patients suspected of having a metabolic disease, laboratory investigation of newborn infants with abnormalities detected through screening, and investigation of near relatives of probands with disease.
Results: A total of 138 patients with organic acid, amino acid and carbohydrate disorders were seen from 1960 to 1990. Of these, 49 (36%) were native Indians (Algonkian linguistic group). This was in sharp contrast to the proportion of native Indians in the total study population (5.8%). Congenital lactic acidosis due to pyruvate carboxylase deficiency (13 patients), glutaric aciduria type I (14 patients) and primary hyperoxaluria type II (8 patients) were the most common disorders detected. Other rare disorders included glutaric aciduria type II (one patient), 2-hydroxyglutaric aciduria (one patient) and sarcosinemia (one patient). Underreporting, especially of glutaric aciduria type I and hyperoxaluria type II, was likely in the native population.
Conclusions: Hereditary metabolic diseases are greatly overrepresented in the native population of Manitoba and northwestern Ontario. We recommend that native children who present with illnesses involving disturbances of acid–base balance or with neurologic, renal or liver disease of unknown cause be investigated for a possible metabolic disorder.

Objectif : Comparer la prévalence des maladies héréditaires du métabolisme chez les populations autochtones et non autochtones du Manitoba et du nord-ouest de l'Ontario.
Conception : Analyse rétrospective.
Contexte : Hôpital pour enfants, Winnipeg.
Patients : On a choisi les patients de trois façons : tests de laboratoire conçus pour dépister les patients soupçonnés de souffrir d'une maladie du métabolisme, examen de laboratoire des nouveau-nés victimes d'anomalies décelées par dépistage et investigation des parents proches des probants malades.
Résultats : Entre 1960 et 1990, on a vu 138 patients atteints de troubles des acides organiques, des acides aminés et des glucides. Ce groupe comptait 49 (36 %) Indiens autochtones (du groupe linguistique algonquin). Ce chiffre représente un contraste frappant par rapport à la proportion d'Indiens autochtones dans la population totale de l'étude (5,8 %). Les troubles les plus fréquents décelés ont été l'acidose lactique congénitale causée par un déficit de la pyruvate-carboxylase (13 patients), l'acidurie glutarique de type I (14 patients) et l'hyperoxalurie primaire de type II (8 patients).

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Parmi les autres troubles rares, on comptait l'acidurie glutarique de type II (un patient), l'acidurie 2-hydroxyglutarique (un patient) et la sarcosinémie (un patient). Les rapports étaient probablement incomplets chez la population autochtone, et particulièrement dans le cas de l'acidurie glutarique de type I et de l'hyperoxalurie de type II.

Conclusions : Les maladies héréditaires du métabolisme sont très surreprésentées dans la population autochtone du Manitoba et du nord-ouest de l'Ontario. Nous recommandons de soumettre à un examen de dépistage de troubles métaboliques possibles les enfants autochtones qui présentent des symptômes de maladie comportant des troubles de l'équilibre acido-basique ou de maladies neurologiques, rénales ou hépatiques d'origine inconnue.

During the past few decades the health of native Indians in Canada has improved, as demonstrated by the decreasing death rates, although they are still considerably higher than the rates among non-natives. In Manitoba, for example, the number of deaths among Indian children aged 29 days to 14 years decreased from 260 per 100 000 population in 1977 to 150 per 100 000 in 1985;[1] the corresponding rates among other children were 60 and 40 per 100 000 population. The main causes of death in the native population as a whole have shifted from infectious diseases to chronic diseases, such as circulatory diseases, cancer and diabetes.[2]

Hereditary metabolic diseases have so far not received much attention as causes of illness and death among native children. The Children's Hospital, Winnipeg, one of the centres for the diagnosis and treatment of such diseases in Canada,[3] provides service to Manitoba and northwestern Ontario. We report our experience with this group of diseases among native Indians in those regions from 1960 to 1990.

Population characteristics

The population of Manitoba and northwestern Ontario is about 1.1 million. The native Indian population is 56 000 in Manitoba (5% of the provincial population) and about 10 000 in northwestern Ontario (about 18% of the provincial population west of Thunder Bay).[4]

Of the nine major linguistic groups of native Indians, three are found in the two regions under study: the Algonkian linguistic group, by far the largest, inhabits the central area of Manitoba and northwestern Ontario; the Dakota, part of the plains Indians, live in southwestern Manitoba; and the Dene live in the far north. The Algonkian linguistic group comprises many tribes, including the Cree and Saulteaux (also called Ojibway or Chippewa), stretching from the Maritimes to Alberta. All of the inherited metabolic disorders described herein occurred among the Cree and Saulteaux.

Methods

We included patients with organic acid, amino acid and carbohydrate disorders who were born and living in Manitoba and northwestern Ontario. Lysosomal, peroxisomal, connective-tissue and other types of metabolic disorders were not included. Most patients in whom these disorders were diagnosed would in all likelihood have been referred to the Children's Hospital, although we cannot exclude the possibility that a small number might have been referred to tertiary care centres in other provinces.

Patients with hereditary metabolic disorders were ascertained as follows.

- Through laboratory screening tests designed to identify patients suspected of having a metabolic disease, such as patients with unexplained mental retardation or other neurologic abnormalities. The screening methods changed over the years as new technologies became available. Before 1984 the methods included qualitative amino acid analysis by one-dimensional (for plasma samples) and two-dimensional (for urine samples) thin-layer chromatography. Since then amino acids in plasma and urine have been quantitated with the use of an automated amino acid analyser, urine organic acids have been screened semiquantitatively by means of gas chromatography–mass spectrometry, and urine has been tested for reducing substances and for keto acids.
- Through definitive laboratory investigation of newborns with abnormalities identified through screening. Since 1966 the Manitoba Newborn Screening Program has screened blood samples from all babies born in the province for phenylketonuria and other amino acid disorders and for galactosemia. Screening of urine samples was added in 1977.[5]
- Through family studies in the presence of a previously diagnosed metabolic disorder. (Several of the patients with glutaric aciduria type I and L-glyceric aciduria were ascertained in this way.)

Results

During the study period we saw 138 patients from Manitoba and northwestern Ontario with organic acid, amino acid and carbohydrate disorders; 49 (36%) were native Indians (Table 1). These disorders were thus overrepresented in the native

population, given that Indians constitute only 5.8% of the total population. The disorders in the native Indians are summarized as follows.

Lactic acidosis

In 1964 two unrelated native Indian children were identified with metabolic acidosis, mental retardation and seizures associated with greatly increased blood levels of lactate and pyruvate.[6] One was a member of a large kindred in a remote area of northwestern Ontario. Two of the youngest siblings in that family were later found to have congenital lactic acidosis as well. All 3 died at home before 2 years of age, as had another 5 of the 12 children. The symptoms preceding death in the eight children were remarkably similar: rapid breathing, convulsions, episodes of unconsciousness, occasional vomiting and cough. The five children who died earlier likely also had lactic acidosis. Metabolic studies suggested that these children had a defect in pyruvate metabolism,[7] but techniques to measure enzyme activity were unavailable at that time.

In the early 1970s we saw an Ontario family in which three children had congenital lactic acidosis. Initial enzyme assays of cultured fibroblasts indicated low activities of pyruvate dehydrogenase and α-ketoglutarate dehydrogenase in the youngest of the patients.[8] Subsequent analysis of fibroblasts from two of the siblings (by Dr. Brian H. Robinson, Toronto) showed normal levels of pyruvate dehydrogenase complex but low activity levels of pyruvate carboxylase.[9]

We diagnosed lactic acidosis in an additional six patients (two of them siblings), all of whom were found to have pyruvate carboxylase deficiency

Table 1: Hereditary metabolic disorders in Manitoba and northwestern Ontario from 1960 to 1990

Disorder	Biochemical defect	No. of patients	
		Native	Non-native
Organic acid			
Lactic acidosis	Pyruvate carboxylase	13	0
Glutaric aciduria type I	Glutaryl–coenzyme A dehydrogenase	14	1
Primary hyperoxaluria			
Type II	D-glycerate dehydrogenase and glyoxylate reductase	8	0
Type undetermined	–	1	1
Glutaric aciduria type II	Electron transfer flavoprotein–ubiquinone oxidoreductase	1	0
2-hydroxyglutaric aciduria	Unknown	1	0
Amino acid			
Tyrosinemia			
Type I	Fumarylacetoacetate hydrolase	1	0
Type II	Tyrosine aminotransferase	1	0
Maple syrup urine disease	Branched-chain α-keto acid dehydrogenase	0	2
Homocystinuria	Cystathionine β-synthase	2	0
Hyperphenylalaninemia	Phenylalanine hydroxylase	0	36
Histidinemia	Histidase	1	21
Nonketotic hyperglycinemia	Glycine cleavage system	0	1
Hyperprolinemia	Proline oxidase or pyrroline-5-carboxylate dehydrogenase	3	0
Ornithine transcarbamylase deficiency	Ornithine transcarbamylase	0	2
Sarcosinemia	Sarcosine dehydrogenase	1	0
Carbohydrate			
Galactosemia	Galactose-1-phosphate uridyl transferase	2	8
Hereditary fructose intolerance	Fructose-1-phosphate aldolase	0	3
Glycogen storage disease			
Type I	Glucose-6-phosphatase	0	5
Type II	Acid α-glucosidase	0	1
Type III	Amylo-1,6-glucosidase	0	4
Type VII	Muscle phosphofructokinase	0	1
Type IX	Liver phosphorylase *b* kinase	0	2
Type unknown	–	0	1
Total		49	89

(through enzyme assays performed by Dr. Robinson). The five families were not related and lived in different communities. Two of the six patients died. The ages of the survivors were from 9 months to 12 years; all were mentally retarded and required frequent admissions to hospital for treatment of acute acidosis, usually precipitated by minor stress such as infection. Oral sodium bicarbonate therapy was used to control the acidosis between the acute episodes. Other forms of treatment, including changes in diet and administration of vitamin cofactors (in large doses), dichloroacetate, arginine and propionic acid, had no effect on the disease.[10]

Five of the 13 patients had not undergone enzyme analysis. Nevertheless, one was a sibling of two children with enzymically proven pyruvate carboxylase deficiency, and all had clinical and biochemical features almost identical to those in the cases we described. Therefore, we believe that these five also had pyruvate carboxylase deficiency.

Glutaric aciduria type I

In 1982 we saw a 1-year-old native girl living in a remote Manitoba community. Her development had been relatively normal until she was 6 months old, when seizures, muscular hypotonia, dystonia and involuntary movements occurred and her development regressed. Laboratory screening tests revealed small amounts of glutaric and 3-hydroxyglutaric acids in her urine. An assay of cultured dermal fibroblasts and lymphocytes for glutaryl coenzyme A (CoA) dehydrogenase (which catalyzes a step in the degradation of lysine, hydroxylysine and tryptophan) showed an activity level of less than 10% of normal. Three other members of her family were later found to have the same disease.

We diagnosed a total of 14 cases of glutaric aciduria type I in five native Indian kindreds in the study regions.[11] The clinical features varied, even within the families. Eight of the cases followed the typical clinical course of normal early growth and development until the onset of neurologic abnormalities between 6 weeks and 7 months of age. Five of the patients had early developmental delay, and one was thought to be healthy until 8 years of age. Four patients died, seven were severely handicapped mentally and physically, and four had only mild mental retardation or incoordination. Computed tomography of the brain gave abnormal results in 11 of 12 patients.

Although all of the patients excreted increased amounts of glutaric and 3-hydroxyglutaric acid in their urine, the amounts were much lower than in most other reported cases. Indeed, in some patients the levels barely exceeded the upper limit of normal.

Primary hyperoxaluria

Type II: Also known as L-glyceric aciduria this condition occurred in eight patients during the past 2 years. The ages were from 6 months to 18 years, and six patients were boys. Four of the patients presented with renal calculi; the other four were asymptomatic. All excreted large amounts of glyceric and oxalic acid in their urine. Enzyme analysis of liver tissue from one patient showed deficiencies of D-glycerate dehydrogenase and glyoxylate reductase. Only one of the four patients with nephrolithiasis had recurrent stone formation after surgery.[12]

Type undetermined: About 10 years before we began to recognize hyperoxaluria type II we saw a male native Indian infant with acidosis and renal failure. Renal biopsy showed the changes consistent with oxalosis. The baby died at 2 months of age.

Glutaric aciduria type II

A male newborn was dysmorphic and had intrauterine growth retardation. He presented with hypotonia, hypoglycemia and metabolic acidosis at a few hours of age and died at 4 weeks of progressive renal failure. Autopsy revealed diffuse fatty infiltration of the heart and skeletal muscles as well as bilateral renal cortical atrophy with cysts. He had abnormal urine organic acid levels and other biochemical abnormalities characteristic of glutaric aciduria type II. Studies of cultured fibroblasts showed deficiency of electron transfer flavoprotein (ETF)–ubiquinone oxidoreductase.[13,14]

2-hydroxyglutaric aciduria

We saw one case of this disorder, in a growth-retarded female newborn with dysmorphic facial features, hepatosplenomegaly and tricuspid regurgitation. Gas chromatography–mass spectrometry revealed massive amounts of 2-hydroxyglutaric acid in the urine but no other abnormalities. She died at a few days of age. Investigation is in progress to determine whether the acid was the L or the D isomer.

Tyrosinemia

We excluded the numerous native babies with transient neonatal hypertyrosinemia. Oral vitamin C therapy was usually effective in lowering the plasma tyrosine level. Two children had persistent hypertyrosinemia. The first had all the characteristics of type I tyrosinemia and died of liver disease at 7 months of age. At the time, we were unable to measure urinary succinylacetone levels, and fumarylacetoacetate hydrolase activity was not

assayed. The other patient presented with mental retardation and seizures and had cytosolic tyrosine aminotransferase deficiency.[15]

Homocystinuria

Two children, half-siblings, had this disorder. They had vitamin-B_6-nonresponsive homocystinuria due to presumed cystathionine β-synthase deficiency. One had severe and the other mild mental retardation.

Histidinemia and hyperprolinemia

One patient with histidinemia and three with hyperprolinemia were identified by the screening program and the diagnosis confirmed through quantitative amino acid analysis. They were asymptomatic and, because of the distance they lived from Winnipeg, were not investigated further.

Sarcosinemia

A 6-month-old infant with cerebro-oculofacio-skeletal (COFS) syndrome[16] was found to excrete massive amounts of sarcosine (*N*-methyl glycine) in her urine. The plasma sarcosine level was 364 μmol/L (normally not detectable). A liver biopsy specimen was not available for measurement of the sarcosine dehydrogenase activity. A sibling also had COFS syndrome but not sarcosinemia. It is unlikely that the two conditions were related.

Galactosemia

Two children, who were first cousins once removed, presented with classic galactosemia due to a deficiency of galactose-1-phosphate uridyl transferase.

Discussion

There are few reports of hereditary metabolic diseases in the native Indian population of Canada. An annotated bibliography published in 1986 contained no reference to these diseases except for lactic acidosis.[17] Perry and associates[18] described five patients with prolinemia in an inbred band of the Suswap Indians in British Columbia. Six cases of the milder form of pyruvate carboxylase deficiency have been reported among the Algonkian linguistic Indians in Nova Scotia, northwestern Ontario and northern Saskatchewan.[19]

The number of Indians with hereditary metabolic diseases seen at the Children's Hospital since 1960 greatly exceeded the number expected from the proportion of Indians in the total population. Even if one excludes the predominant diseases (lactic acidosis, glutaric aciduria and primary hyperoxaluria type II) there is still overrepresentation in the native population (10%). Although ascertainment of hereditary metabolic diseases is likely incomplete in native and non-native groups, it is probably less complete in the native group, because many live in remote areas and have limited access to the diagnostic facilities of a tertiary care hospital. One factor that might increase ascertainment in the native population is the large average size of the families. We believe that glutaric aciduria type I and hyperoxaluria type II, for example, are underdiagnosed in the native population.

The reason for the relatively high frequency of three rare metabolic diseases (pyruvate carboxylase deficiency, glutaric aciduria type I and primary hyperoxaluria type II) among the Ojibway/Saulteaux Indians requires further investigation. Like the other disorders these three are inherited as autosomal recessive traits and may illustrate the "founder effect" in these isolated communities in which consanguineous matings are frequent. Whether there is any heterozygote advantage of the mutant genes for the three diseases is unknown, but it seems very unlikely. In addition, further investigation is needed to determine the defects at the molecular level.

No more than about 20 patients with glutaric aciduria type I have previously been described in the world literature.[20] We saw one patient in the non-native population. This child exhibited the common biochemical features of the disease, with massive urinary excretion of glutaric acid, and had no residual enzyme activity in fibroblasts or lymphocytes. In contrast, the 14 Indian patients excreted much lower amounts of glutaric acid and had some residual enzyme activity. Different mutations were likely involved, but this remains to be determined. We saw no patients with pyruvate carboxylase deficiency or primary hyperoxaluria type II in the non-native population. On the other hand, we did not see any hyperphenylalaninemia or glycogen storage disease in the Indian population, as compared with 36 and 14 cases respectively in the non-native population.

We believe that infants and children with unexplained acute illness, especially those with neurologic disease, should be investigated for hereditary metabolic disorders. We recommend that glutaric aciduria type I be considered in native children with unexplained cerebral-palsy-like disorders, especially if computed tomography gives abnormal results. Analysis of the urine for organic acid should be done on such patients, and if there is a suspicion of glutaric aciduria the glutaryl CoA dehydrogenase level should be measured in fibroblasts or lymphocytes even if the urine glutaric acid level is not increased.[11]

Primary hyperoxaluria type II is a rare disease (only eight patients having been described in the world literature[21,22]). It is caused by deficiencies of D-glycerate dehydrogenase, which catalyzes the interconversion of hydroxypyruvate and D-glycerate, and glyoxalate reductase, which converts glyoxalate to glycolate, a deficiency of which causes excess oxalate formation from glycolate. As in hyperoxaluria type I (which is caused by deficiency of the peroxisomal enzyme alanine:glyoxylate aminotransferase) the main clinical manifestation is calcium oxalate nephrolithiasis. Our experience, supported by the limited data in the literature, suggests that hyperoxaluria type II is a milder disease with a better long-term prognosis than type I, which in its severe form with onset in childhood frequently results in progressive renal insufficiency and death before the age of 20. We recommend that native Indians presenting with renal calculi be investigated for glyceric aciduria. We also recommend that all those with primary hyperoxaluria be carefully investigated to determine whether they have type I or type II disease, since the prognosis may differ.[12]

In diseases such as glutaric aciduria type II 2-hydroxyglutaric acid is found with other organic acids. However, as far as we know it has been described as the sole abnormal urinary metabolite in only two cases: L-2-hydroxyglutaric aciduria was described in a 5-year-old boy with psychomotor retardation and dystrophy[23] and D-2-hydroxyglutaric aciduria in an 8½-year-old boy with protein-losing enteropathy.[24] Whether these are inborn errors of metabolism is unknown. Our patient with 2-hydroxyglutaric aciduria probably died of heart disease; we do not know whether the metabolic defect contributed to his death. Investigation of urine samples from this child is continuing.

Glutaric aciduria type II is an inborn error of fatty acid and amino acid metabolism caused by deficiency of either ETF or ETF-ubiquinone oxidoreductase. The latter defect was the abnormality in our patient.[13,14]

The incidence of sarcosinemia is reported to be 1 in 350 000 in New England and 1 in 43 000 in Quebec.[25] Unfortunately we were unable to investigate our patient further.

Although none of these metabolic diseases individually contributed significantly to the illness and death rates among the native children in our area, as a group they have caused a significant burden on tertiary care resources, especially during the past decade. In particular the children with lactic acidosis and glutaric aciduria have required frequent, and in some cases prolonged, admission to acute and chronic care hospitals.

We recommend that native infants and children who present with acute illnesses involving disturbances of acid–base balance or with neurologic, renal or liver disease of unknown cause be investigated for possible metabolic disorders.

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Conferences

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Sept. 20-23, 1991: Canadian Paediatric Society 68th Annual General Meeting
Quebec
Dr. Victor Marchessault, executive vice-president, Canadian Paediatric Society, Children's Hospital of Eastern Ontario, 401 Smyth Rd., Ottawa, ON K1H 8L1; (613) 737-2728, fax (613) 737-2794

Sept. 20-23, 1991: Royal College of Physicians and Surgeons of Canada 60th Annual Meeting
Convention Centre, Quebec
Anna Lee Chabot, head, Meetings and Assemblies Section, Office of Fellowship Affairs, Royal College of Physicians and Surgeons of Canada, 74 Stanley St., Ottawa, ON K1M 1P4; (613) 746-8177, fax (613) 746-8833

Sept. 22-25, 1991: International Conference on Alzheimer's Disease
Amsterdam
Alzheimer Society, Seadwei 8, 9261 XM, Oostermeer, the Netherlands

Sept. 22-27, 1991: Meeting of the International Society for the Study of Vulvar Disease
Oxford, England
Conference Associates and Services Ltd., Congress House, 55 New Cavendish St., London W1M 7RE, England

Sept. 23, 1991: Precongress courses on Cytogenetics, Molecular Genetics and Endoscopy (in conjunction with the 5th International Symposium on Colorectal Cancer)
Turin, Italy
Organizing Secretariat, Francorosso Health Congress, 26 Corso Vittorio Emanuele, 20122 Milano, Italy; telephone 011-39-2-76008561, fax 011-39-2-784967

Sept. 24-26, 1991: 5th International Symposium on Colorectal Cancer — Biology and Management of High Risk Groups
Turin, Italy
Organizing Secretariat, Francorosso Health Congress, 26 Corso Vittorio Emanuele, 20122 Milano, Italy; telephone 011-39-2-76008561, fax 011-39-2-784967

Sept. 25-27, 1991: National Institutes of Health Consensus Development Conference — The Treatment of Panic Disorder
Warren Grant Magnuson Clinical Center, National Institutes of Health, Bethesda, Md.
Conference Registrar, Prospect Associates, 500-1801 Rockville Pike, Rockville, MD 20852; (301) 468-MEET, fax (301) 770-5164

Sept. 25-28, 1991: International Symposium on Pediatric Dermatology
Trapini, Italy
Dr. G. Fabrizi, Department of Dermatology, Catholic University, Largo Gemelli, 8-00168 Rome, Italy

Sept. 26, 1991: Health Care Aides
Baycrest Centre for Geriatric Care, North York, Ont.
Sybil Gilinsky, Education Department, Baycrest Centre for Geriatric Care, 3560 Bathurst St., North York, ON M6A 2E1; (416) 789-5131, ext. 2365, fax (416) 785-2378

Sept. 27-29, 1991: Dermatology '91 Conference
Vancouver
Symposium coordinator, Karyo Communications Inc., 3661 W 4th Ave., Vancouver, BC V6R 1P2; (604) 732-9106

Sept. 27-29, 1991: 4th International Multidisciplinary Conference — The Worker in the Workplace: Rehabilitating Musculoskeletal Injuries
University of Toronto
Marc I. White, executive director, Physical Medicine Research Foundation, 510-207 W Hastings St., Vancouver, BC V6B 1H7; (604) 684-4148, fax (604) 684-6247

Sept. 29-Oct. 1, 1991: Canadian Academy of Child Psychiatry 11th Annual General Meeting
Ramada Renaissance Hotel, Saskatoon
Mrs. Bonnie Rowley, executive assistant, Canadian Academy of Child Psychiatry, Local Arrangements Committee, c/o Youth Services Program, 311-20th St. E, Saskatoon, SK S7K 0A9; (306) 966-2939, fax (306) 652-8848

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