The Occurrence of Multiple Sclerosis in the Hutterites of North America

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ABSTRACT: Objective: To report the occurrence, clinical characteristics and genealogical analysis of multiple sclerosis in the Hutterites of North-Western United States and Western Canada. Background: The incidence of multiple sclerosis is reported to be lower or rare in certain ethnic groups and genetic isolates and was previously observed to be absent in the Hutterite population. Methods: After long-term surveillance, six patients were identified and clinical examinations and laboratory investigations including VER and MRI were completed. Results: The six cases included two brothers, two first cousins, male and female, another male and female, all representing two of the three endogamous groups of Hutterites, are linked to two common ancestors through lines of descent dating to 1723. The individual pedigrees were analyzed from extensive genealogical records covering eight generations. Conclusion: The incidence of multiple sclerosis in Hutterites is low in a high risk area of North America. A specific mode of inheritance pattern has not been established and a common founder effect may play a role in the development of multiple sclerosis. The genetic contribution of the Hutterites seems greater than previously recognized.


THE POPULATION

The Hutterite Brethren constitute a religious and genetic isolate residing on highly mechanized communal farms (colonies) in the four Western Canadian provinces and in the states of North Dakota, South Dakota, Washington, Montana and Minnesota.

The Hutterites, a Swiss Anabaptist movement, originated in the Tyrol region of Austria around 1526. Following numerous migrations an original group of 1,265 Hutterites emigrated to the Dakota territories in the USA from the Ukraine in Russia between 1874-1879. A population of 443 settlers formed three original colonies in South Dakota and the establishment of these colonies formally initiated three endogamous subdivisions, the Dariusleut, Lehrerreut and Schmiedeleut and have maintained their separate identities and endogamous marriage patterns. The remaining two-thirds, the Prairieleut settled on individual homesteads in the same region.

The individual leuts expanded and subdivided into further colonies and eventually moved to the Canadian prairie provinces of Manitoba and Alberta in 1918 and to Saskatchewan in 1952. The Hutterite population is closed to immigration and has been very little intermarriage between the groups since 1918. The three leuts form the legal entity of the Hutterian Brethren Church.

There are 362 colonies in the three Canadian prairie provinces and the North-Western United States with an average of 80 persons per colony and a range of 60-120. The population of Hutterites in Western Canada is 21,495 (Canada census 1991) and 9,848 (estimated 1990) in the North-Western States. There are 17 traditional family names among the colonies.

A base population of 92 people is believed to have given rise to the current population. Because of the small number of immigrant ancestries, it has been estimated that the average relationship among the Hutterites is closer than second-cousins. The Schmiedeleut of South Dakota and Manitoba trace their ancestry to 53 founders, the Dariusleut to 74 founders and the Lehrerreut to 69 founders. Each colony has a council with a head Minister and a secretary (or “BOSS”) who manages the economic affairs.

METHODS

We investigated six cases of MS in the Hutterite population of Saskatchewan and Alberta, Canada, and Montana, United States of America who were ascertained over a five year period. The study was initiated by contacting the neurologists and Neuromuscular Clinics listed in the American Academy of Neurology registry. Contacts were also made with the MS clinics in Western Canada. Information of potential cases was first provided by a colony minister and on follow-up visits to the colonies, these persons had a form of limb-girdle dystrophy that provided by a colony minister and on follow-up visits to the

The study was initiated by contacting the neurologists and Neuromuscular Clinics listed in the American Academy of Neurology registry. Visits were also made to South Dakota and to the first Schmiedeleut colony established in 1874 near Yankton, South Dakota. The local records keeper/historian recalled no cases of MS in this leut.

The medical records for the index and the five other cases were obtained through family physicians and neurologists. The results of previous laboratory investigations and spinal fluid examinations were accepted if available. Five of the six patients had been seen by at least two neurologists and arrangements were made for review of the first four cases at the Calgary MS Clinic by the study neurologist who confirmed the diagnosis based on standard diagnostic criteria. The visual evoked responses (VER) and MRI scanning were done on all six individuals. Urine homocystine and methylmalonic acid, and plasma methionine levels were determined on the first four cases.

CASE HISTORIES

Patient 1

The index case is a 47-year-old female who at age 28 complained of left-sided weakness, incoordination and diplopia which resolved with minimal residual. The incoordination of the left leg and tingeing of the left hand recurred in 1984 and persisted 18 months. There was a complete loss of vision in the left eye, with subsequent recovery of light perception at this time. Six months later weakness and ataxia occurred in both legs and recovery was incomplete. Five years later, in 1991, the gait remained mildly impaired with mild left hemiparesis. Vibration was impaired in the left foot. Left optic disc pallor and papillary afferent defect were present. The course has been relatively quiescent since 1986.

Patient 2

This 36-year-old male, a first cousin of the index case, developed right optic neuritis in 1967 at age 28 with full recovery. Fourteen years later he developed moderately severe quadruparesis with bowel and bladder retention and a sensory level to the shoulders. He was unable to feed himself and had severe difficulty with walking. After six weeks he had slight impairment of tandem gait and was fully recovered in 3 to 4 months.

He experienced similar severe attacks each of the next four years, characterized by diplopia and incoordination of the legs lasting about 4 weeks. In 1990 he developed some stiffness of the right leg with limp, dysarthria and fatigue. Approximately a year later he developed some dragging and stiffness of the left leg which recovered. There has been no recurrence since.

Patient 3

This 37-year-old left handed male, had developed coldness of the left leg and arm with gradual weakness in 1984 at age 26. He also had fatigue and aching and numbness in the fingers of the right hand. All of these symptoms resolved. Two months later he developed bilateral blurred vision with inability to read followed by recovery in one month. Four years later he developed acute weakness, loss of balance and incoordination, intermittent diplopia and intermittent urgency and frequency of micturition. Three years later the visual acuity in the left eye was 20/60, mild left-sided ataxia was present with impaired vibration and a gait difficulty. This course has been slowly progressive and the patient remains ambulatory without aids.
RESULTS

Six clinical cases of definite multiple sclerosis are reported, with the diagnosis supported by neurological examination and laboratory evidence in each case. Three cases are in the Lehrerleut and three in the Dariusleut subdivisions in this large Hutterite kinship. The female index case and her male first cousin, and a third female live on separate Lehrerleut colonies in Montana. The two brothers on Dariusleut colonies, one in Saskatchewan and one in Alberta, prior to this investigation had no previous contact with the three relatives in Montana. The two brothers had lived together 17 years. Each of the six live and had the onset of the disease in separate rural colonies. The six cases, representing 3 family names, all trace back to two common founders (Figure).

There are a total of 49 siblings in the 5 family branches of the patients. Two brothers have four children each, under age 20. The index case has one child age 20 and the male first cousin has no children. The remaining male has four children, ages 32-39.

The clinical course has been remitting and exacerbating in three cases, primary progressive in one and secondary progressive in two cases (Table). All remain independent in their life skills and ambulatory with very mild to moderate disability. Five cases had abnormal prolonged visual evoked responses and only three had a history of optic neuritis. The MRI reports of white matter abnormalities were consistent with MS in all six patients. Testing for urinary and plasma organic amino acids and serum methionine levels were all within normal limits.2021

DISCUSSION

The six cases of MS occur in two of the three endogamous groups, the Dariusleut and Lehrerleut, representing approximately

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**Figure: PEDIGREE OF MULTIPLE SCLEROSIS CASES IN HUTTERITES.** The condensed pedigrees show affected members of sibships (dark symbols, female (O) and male (O). The arrow indicates the index case. The double lines indicate consanguineous matings. The Roman numerals indicate the generations, and the right hand column the years of birth of successive generations.
Table: Clinical Characteristics of Multiple Sclerosis in Hutterites.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Date of Birth</th>
<th>Place &amp; Year of Onset</th>
<th>Age at Onset</th>
<th>Clinical Course</th>
<th>KEDSS</th>
<th>Visual Evoked Response (MSEC)</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Female</td>
<td>1948</td>
<td>Montana 1976</td>
<td>28</td>
<td>RR</td>
<td>4.5</td>
<td>R-129 L-NIL</td>
<td>+</td>
</tr>
<tr>
<td>2. Male</td>
<td>1939</td>
<td>Montana 1967</td>
<td>28</td>
<td>RR</td>
<td>1.5</td>
<td>R-144 L-121</td>
<td>+</td>
</tr>
<tr>
<td>3. Male</td>
<td>1958</td>
<td>Alberta 1984</td>
<td>26</td>
<td>SP</td>
<td>4.0</td>
<td>R-107 L-132</td>
<td>+</td>
</tr>
<tr>
<td>6. Female</td>
<td>1956</td>
<td>Montana 1990</td>
<td>36</td>
<td>RR</td>
<td>2.5</td>
<td>R-91.5 L-92.5</td>
<td>+</td>
</tr>
</tbody>
</table>

1KEDSS - Kurtzke Expanded Disability Status Scale
2Clinical Course - RR - Relapsing and Remitting
- PP - Primary Progressive
- SP - Secondary Progressive

21,495 individuals. These religious, genetic isolates live in high-risk areas where the prevalence is reported to be between 100-220/100,000.\textsuperscript{7-11} The estimated prevalence rate in these two groups is low at 28/100,000. The expected number of cases was 21-46.

The genealogy records made it possible to trace the ancestry of the parents of the six cases back to a single couple (Figure). The average relationship of spouses is closer than second cousins. Consanguinity increases the likelihood of homozygous expression of a recessive gene in a population.\textsuperscript{22} MS was not reported to be present in the previous or succeeding generations of each of the cases. The small number of cases in this study may reflect the age of the population in which it is estimated that 40% are under the age of 20 years,\textsuperscript{27} and have not reached the average age of onset of 33 years in the Hutterites. Numerous occurrences of rare recessive disorders are found in related Hutterite sibships.\textsuperscript{23-26}

In the Old Order Amish, another genetic isolate, two cases of MS are reported with no immediate genealogical connection between the two families affected.\textsuperscript{28} Three cases of MS are reported in the old colony (Chortitza) Mennonites and multifactorial causation has been proposed.\textsuperscript{29}

An autosomal recessive mode of inheritance with reduced penetrance, first proposed in twin studies,\textsuperscript{30} may be operative in this large isolate of inbred families in the form of a single mutant gene. The founder effect may play an important role in the etiology.\textsuperscript{31} In the general population, however, family studies data excludes simple Mendelian inheritance and the data are best interpreted as support for susceptibility being polygenic.\textsuperscript{32,33}

Evidence from studies in the outbred Canadian population\textsuperscript{34} strongly support the view that MS is a complex trait in which the genetic component comprises the effects of several loci. These findings in the Hutterites suggest that one or more loci may be recessive.

The occurrence of MS in a genetic isolate as restricted as the Hutterites may help to solve the vexing problem of getting from linkage to locus in this complex trait. When linkages are found the presence of linkage disequilibrium in affected individuals may help in defining the susceptibility loci.

There is ongoing surveillance of the Hutterite population for further cases to provide resources for genetic analysis. This genetic isolate offers potential for the study of genetic epidemiology and molecular biology of multiple sclerosis.

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