A Genetic Aspect of Wilson’s Disease in Japan

By

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As sibling cases of one and the same family showed almost complete similarities in their clinical and pathological findings with uniform biochemical disturbances, it may safely be asserted that the disease is inherited in a single factor. As for the genetic ratio, the difference between the value calculated from the Haldane’s formula and the theoretical value 0.25 proved statistically insignificant. So Wilson’s disease is inherited in an autosomal single recessive pattern. Multiple factors, for example, three complicated factors may be excluded.

In our country the gene frequency is estimated at 0.003 by applying the Dahlberg’s formula, so the expected incidences of patients and heterozygous carriers are about three in a hundred thousand and about six in a thousand, respectively. The extraordinarily high incidence of the disease in our country may be due to the strikingly high frequency of cousin marriages and our diet.

André and van Bogaert\(^1\) brought forward evidence to show that Wilson’s disease is inherited in a recessive manner, moreover they considered that the disease affects the families which show disturbances of digestive organ and of nervous system at once, then the disease is inherited probably from two genes. Recently Beam,\(^2\) an authority on Wilson’s disease, has conceived that the disease is possibly determined by a single abnormal allele, but he has also considered a suppressor gene or more than two alleles. In our country, Yamauchi\(^3\) was of the opinion that liver and metal factors are inherited in a dominant manner, while nerve factor is inherited in a recessive manner on the basis of the former two factors. Investigating children with Wilson’s disease, Arima \textit{et al.}\(^4\) had concluded that the disease is probably inherited in an autosomal single recessive mode.

The author’s study\(^5\) revealed that three sister cases of one and the same family showed almost complete similarities in their clinical and pathological findings with uniform biochemical disturbances. Also the author’s report\(^6\) on sibling cases of separated families showed that the affected siblings in one and the same family bear wonderful similarities in their clinical features. According
to the above-mentioned results, in other words, considering the almost uniform process of the disease in sibling cases, it may safely be asserted that the disease is inherited in a single factor. To study the genetical aspect of the disease a statistical analysis should also be made.

**MATERIALS AND METHODS**

Forty-four families, comprising eighty-four patients with two hundred and eight separated siblings were gathered from the author’s own cases and the Japanese literature which had been reported by 1963, under the conditions that at least a patient of family was surely affected from Wilson’s disease and that the pedigrees were clear and siblings were more than two. In the Japanese literature the earliest onset of the disease was at the age of five and therefore unaffected siblings who have not yet reached the age of five or who died before reaching this age have been ruled out. The families of patients were divided into four groups: A) families whose parents were mostly first cousins with more than two affected siblings, but of whom a pair of parents were second cousins and another pair of parents were of a distant consanguineous marriage, B) those whose parents were first cousins with only one propositus, C) those whose parents were not of consanguineous marriage with more than two affected siblings, and D) those whose parents were not of consanguineous marriage with only one propositus (Table I).

<table>
<thead>
<tr>
<th>Table I</th>
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<tr>
<td><strong>GENETIC FINDINGS</strong></td>
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</tbody>
</table>

**Sex ratio:** According to that classification, ratios of male or female patients to the same sex siblings were calculated. In groups A and C, the ratio of male patients to male siblings was 48\%, the ratio of female patients to female siblings was 54\%, so there was slight predominance of female sex in the calculated sex ratio, but almost no significant difference between them. The sex incidence of
Wilson’s disease has been uncertain, although the disease has often been considered to occur more commonly in males and Sano et al.\textsuperscript{7} and Arima et al.\textsuperscript{4} reported that hepatic type was very often seen in female patients. According to the above calculation, it may be said that a 1: 1 sex ratio is observed.

**Genetic ratio:** A roughly calculated ratio of patients to all siblings was 43\% in groups A and B and 36\% in groups C and D, then there was no great difference between the former and the latter groups. It is very interesting that in groups B and D the ratios of patients to siblings were both 24\%, which were very coincident with an expected value in a single recessive inheritance.

Neither parents of patients with Wilson’s disease themselves were found to be affected by the disease nor any biochemical abnormality suggestive of Wilson’s disease detected. As the adequate genetic explanation for all these observations above stated, it can be considered that the condition is very probably inherited in an autosomal single recessive mode. If the allele responsible for Wilson’s disease is recessive, the parents of the affected individuals are heterozygous for the abnormal allele. The genetic ratio is expected to be 0.25 if the recessive hypothesis is correct.

Bearn\textsuperscript{8} used the a priori method for calculating genetic ratio. As the data in this paper were obtained not from complete ascertainment but from incomplete one, Haldane’s formula in incomplete ascertainment will enable us to calculate a genetic ratio with higher accuracy.\textsuperscript{9}

\[
\frac{R}{p} = \sum_{s=2}^{S} \frac{1 - (1 - k)p)_{s-1}(1 - k)}{1 - (1 - k)p_{s}} \cdot S \cdot N_s
\]

\[
\frac{1}{\sigma^2} = \frac{\sum_{s=2}^{S} S \cdot N_s}{p \cdot q} + \frac{k (q - p + kp^2)}{p \cdot q} \sum_{s=2}^{S} \frac{(1 - k)p_{s-2}S \cdot N_s}{1 - (1 - k)p_{s}}
\]

\[
-k^2 \frac{\sum_{s=2}^{S-2} (1 - k)p_{s-2}S \cdot N_s}{[1 - (1 - k)p_{s}]^2}
\]

(Haldane’s formula)

where \(k\) is probability that a patient is the propositus, \(p\) genetic ratio=1-q, \(R\) the total number of patients= 84, \(S\) the number of siblings=2 to 9, \(N_s\) the number of families with the number of siblings \(S\) and \(\sigma\) dispersion.

1) Genetic ratio in single ascertainment

In single ascertainment the patient detected originally is only one propositus and other patients are found secondarily on the way of the investigation of the family. When the data are supposed to be obtained from single ascertainment, the coefficient \(k\) in Haldane’s formula becomes negligibly small and the formula is simplified as shown below.

\[
p = \frac{R - N}{T - N}
\]

\[
\sigma^2 = \frac{(T - R)(R - N)}{(T - N)^3}
\]
where \( R \) is the total number of patients=84, \( T \) the total number of siblings=208 and \( N \) the number of families=44. The calculated value of \( p \) from the above formula is 0.244 and that of \( \sigma \) is 0.036. The difference between 0.244 and the expected value 0.25 is one sixth of \( \sigma \), which is statistically insignificant.

2) Genetic ratio in multiple ascertainment

In multiple ascertainment sometimes more than two patients are detected originally as the propositus in the same family, but a part of patients are found secondarily on the way of the investigation of the family with a propositus. In these data the coefficient \( k \) is 44 versus 84=0.524. The value of \( p \) calculated from the Haldane’s formula by putting the value of \( k=0.524 \) and numerals expressed in Table II is 0.297 and the value of \( \sigma \) is 0.0375. The difference between 0.297 and the expected value 0.25 is 0.047, which does not exceed twice the value of \( \sigma \), so it is statistically insignificant.

<table>
<thead>
<tr>
<th>Number of siblings (S)</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of families (N_s)</td>
<td>2</td>
<td>9</td>
<td>11</td>
<td>9</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>S x N_s</td>
<td>4</td>
<td>27</td>
<td>44</td>
<td>45</td>
<td>36</td>
<td>35</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

In either ascertainment, the difference between the calculated values and the theoretical value 0.25 is statistically insignificant. So Wilson’s disease is inherited in an autosomal single recessive pattern. Multiple factors, for example, the three complicated factors which Yamauchi has insisted upon in the genetic mode of the disease may be excluded.

**Gene frequency:** In our country the frequency of cousin marriages in the general population is extraordinarily higher than that expected from random mating. Tanaka’s formula\(^9\) should be used as a substitute for Dahlberg’s formula to estimate the frequency of a very rare recessive allele. Tanaka’s formula is:

\[
q = \frac{c (1 - k)}{16 k - 15 c - c k},
\]

where \( q \) is gene frequency, \( c \) frequency of cousin marriages in the general population in Japan=0.05 and \( k \) observed incidence of cousin marriages in the material to be analyzed=24 versus 44=0.545. Using the numerals expressed above in the foregoing formula,

\[
q = \frac{0.05 (1 - 0.545)}{16 \times 0.545 - 15 \times 0.05 - 0.05 \times 0.545} = 0.003.
\]

In random mating the frequency of a recessive homozygote (patient) equals \( q^2 \), but when an inbreeding coefficient in general population is \( F \), it must be
calculated by applying the formula \( Fq + (1-F)q^2 \). Also the frequency of a heterozygote is given by the formula \( 2pq (1-F) \), where \( p=1-q \). In our country the inbreeding coefficient \( F \) is considered to be about 0.007, so the frequency of a patient is about \( 3 \times 10^{-5} \) and that of a heterozygote is about \( 5.9 \times 10^{-3} \). Subsequently the expected incidences of patients and heterozygous carriers are about three in a hundred thousand and about six in a thousand, respectively. These values are extraordinarily high, as compared with those by Bearn. As one of the reasons for the high incidence of the disease, great importance may be attached to the high frequency of cousin marriages in our country. In addition, however, our mode of living, especially our diet or inner and outer circumstances of families, may play an important role.

Acknowledgment

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References

6) Fukuda, K., Clinical and Biochemical Aspects in Sibling Cases of Separate Families, to be published.