Eur J Pediatr (1987) 146:261–265

European Journal of
Pediatrics

Presenting symptoms and natural history of Wilson disease

T. Saito

Department of Public Health, School of Nursing and Medical Technology, University of Occupational and Environmental Health, 1-1, Iseigaoka, Yahatanishi-ku, Kitakyushu, 807 Japan

Abstract. The presenting symptoms of Wilson disease and its natural history as related to age are described based on 283 cases collected in Japan. The disease presented with a variety of signs and symptoms; the most frequent were in order of frequency jaundice, dysarthria, clumsiness, tremor, drooling, gait disturbance, malaise and arthralgia. The mean age at onset of the disease was 12.0 years. Hepatic and osteoarthral symptoms developed early and neurological symptoms late. Fifty-eight cases develolped neurological symptoms only, 28 cases had hepatic symptoms only, and in 26 cases hepatic symptoms were followed by neurological symptoms. A higher mortality rate was observed in hepatic, hepato-haematological and hepato-renal cases mainly due to acute hepatic failure resulting in death only a few weeks after onset. Cases having only neurological symptoms showed a more favourable prognosis with a longer survival.

Key words: Hepatolenticular degeneration – Wilson disease

Introduction

Wilson disease (hepatolenticular degeneration) can present with a variety of hepatic, neurological, psychiatric, renal, haematological, ocular, dermatological and osteoarthral signs and symptoms [7, 17, 23]. The great variety of signs and symptoms (referred mostly to symptoms hereafter) sometimes results in diagnostic delay and errors, thus missing a considerable proportion of the patients [19, 24]. The clinical spectrum of Wilson disease is well known [14, 20, 23], but less so its natural history. The purpose of this paper is to present disease patterns and the natural history as related to age.

The frequency of the disease in Japan [18] and in East Germany [5] seems to be relatively high. A higher frequency of the disease than was previously estimated was suggested in countries where the disease had been thought to be rare [19, 25]. The natural history based on a large number of cases in this paper should be helpful to clinicians in making a prompt diagnosis and in recognizing otherwise unsuspected patients.

Materials

All articles from 1965–1977 describing cases of Wilson disease were traced through the Japana Centra Revuo Medicina (Igaku Chuo Zasshi) which records short summaries of all articles in medical journals published in Japan including case presentations at national and local meetings. Fifty-three departments of university hospitals and 44 non-university hospitals had reported Wilson disease cases during this period. A standard questionnaire was sent to each hospital involved in the original collection of data requesting further details of each patient and family members. For cases whose questionnaires were not returned, data were extracted from the original articles and summaries of case presentations.

Such details were also requested of the remaining 154 medical school hospital departments of medicine, paediatrics and psychiatry from which cases had neither been reported in medical journals nor at medical meetings. Eighty-nine departments (58%) of those approached responded to the questionnaires and 43 departments had cases during the same period.

The possibility of duplicated registration of cases was eliminated by a thorough checking of all data. Though all the cases were reported as definite cases of Wilson disease by attending doctors, only those cases which were confirmed to have had, in addition to other manifestations and laboratory results, one or more of the following diagnostic signs were included in the analysis; a Kayser-Fleischer ring, a low serum caeruloplasmin concentration, an increased copper deposition in the liver, and an increased 24-h urine copper level. Cases in which presence or absence of these signs was implicit were excluded. Thus, a total of 283 cases in 264 families was used. Forty-three percent of the cases were reported from departments of paediatrics, 25% from internal medicine, 23% from psychiatry and the rest were from pathology, ophthalmology, surgery and orthopaedics.

Results

Sex

There were 158 male patients (55.8%) and 125 female patients (44.2%). The difference was statistically significant ($0.02 < P < 0.05$).

Age at onset

Age at onset of the disease is shown in Fig. 1. Excluded from 283 cases were 4 asymptomatic cases and 5 cases without this information. The mean age at onset and the standard deviation were 12.0 and 5.5 years respectively. The youngest age at onset was 4 years and the oldest was 30 years. No difference in age at onset between male and female patients was noted.

Presenting signs and symptoms

Table 1 shows the proportion of various signs and symptoms described as the presenting symptoms by attending doctors. Of the 283 cases 4 cases were asymptomatic and 3 cases were without this information. Each percentage gives the proportion of cases which had that symptom as a presenting one among the 276 cases. Most cases presented with more than one symptom, thus addition of all the percentages exceeds 100%.

Among the 28% (77 cases) presenting with jaundice, 19 cases were confirmed by laboratory tests on admission to have haemolytic anaemia. An additional nine cases developed haemolytic episodes several weeks after the onset of hepatic symptoms. Acute hepatic failure followed haemolytic episodes in most of the cases in both groups.

Tremor was commonest in the hands (82%). Gait disturbance in osteoarthral symptoms was due to abnormalities in the knee joint, and this is differentiated from gait disturbance due to neurological symptoms accompanying other neurological symptoms.

Of the 8% who presented with oedema, half developed it with hepatic symptoms and the remaining half with renal signs and symptoms including proteinuria detected at onset. Other unspecific symptoms in Table 1 appeared mostly with hepatic symptoms.

Twenty-one cases among the 276 were reported to have a history of renal diseases such as nephritis, glomerulonephritis or nephrotic syndrome. In retrospect it is very likely that they were diagnosed erroneously. However, those symptoms were not included in Table 1. Other erroneous diagnoses included Parkinsonism, neurosis, schizophrenia, epilepsy, infectious hepatitis, hypersplenism, rheumatic fever, and familial haemolytic anaemia. Splenectomy was performed in ten cases under the diagnosis of hypersplenism.

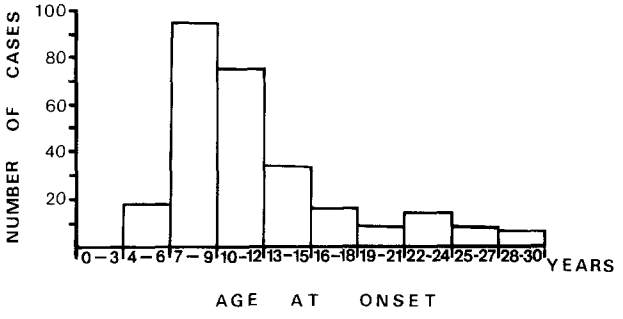

Fig. 1. Age at onset of the disease in 274 patients

Natural history of the disease

The natural history of the disease has been shown in Fig. 2 by plotting the clinical course collectively as disease patterns against age. The patterns in the figure were formed as follows.

First, each case was classified into a disease pattern according to the sequence of age at onset of organic signs and symptoms. For example, a case in which hepatic symptoms first appeared and then neurological symptoms followed was classified as an HP→NR pattern. (HP stands for hepatic and NR for neurological. The arrow indicates the chronological sequence.) An HP→NR→RN pattern consists of cases in which hepatic symptoms developed first, and neurological symptoms second, renal symptoms coming third. Cases in which more than one category of symptoms developed simultaneously were classified separately from those in which symptoms developed sequentially. An example of this onset is an HP-HM/RN pattern in which hepatic, haematological and renal symptoms developed simultaneously. (HM stands for haematological and the hyphen indicates simultaneous onset.) All the cases were classified in this way resulting in 14 patterns which consisted of more than 3 cases and 58 patterns with less than 4 cases.

In the second step a mean for age at onset in each symptom category was calculated for each disease pattern. For exam-

Table 1. Presenting signs and symptoms in 276 cases

I. Hepatic				V. Osteoarthral	
Jaundice	28%	Muscle rigidity	3%	Arthralgia (knee)	7%
Hepatomegaly	9	Emotional instability	3	Gait disturbance	3
Abdominal pain	5	Other psychological	4		
Splenomegaly	5	Mask-like face	3	VI. Dermatological	
Ascites	5	Dysphasia	2	Pigmentation	1%
Abdominal distension	3	Falling IQ	1		
Bleeding (nasal, gum)	3	Rush phenomenon	1	VII. Unspecific	
Gynecomastia	1	Others	1	Malaise	9%
Others	1			Oedema	8
				Nausea, vomiting	6
II. Neurological		III. Haematological		Fever	4
Dysarthria	19%	Anaemia	2%	Anorexia	1
Clumsiness	18	Haemolysis	1	Diarrhoea	1
Tremor	13	Others	1		
Drooling	8				
Gait disturbance	8	IV. Renal			
Involuntary movement	4	Haematuria	2		
		Others	1		

Percentage gives the proportion of the cases which had that sign or symptom as a presenting one among the 276 cases

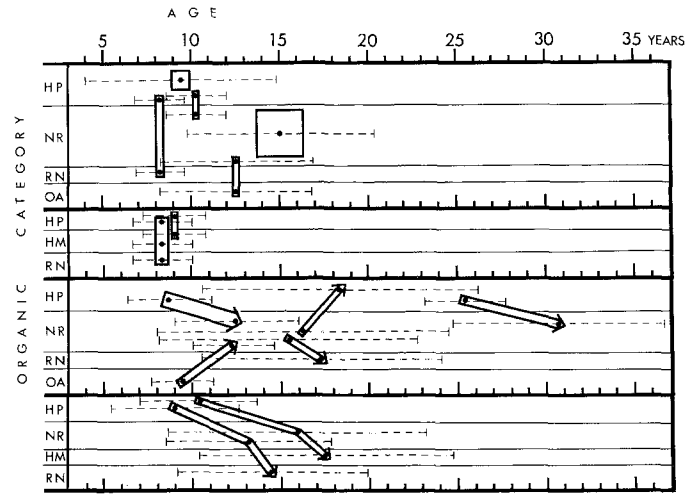

Fig. 2. Natural history of the disease expressed by disease patterns of clinical courses against an age scale. *HP* stands for hepatic, *NR* for neurological, *RN* for renal, *OA* for osteoarthral, and *HM* for haematological. *Dots* represent means, width of *arrows* and horizontal width of *bars* represent numbers of cases, and *dashed lines* represent standard deviations. See text for details

ple, in the HP→NR pattern consisting of 19 cases, a mean of 8.8 years was obtained by dividing the sum of age at onset of hepatic symptoms by 19. A mean of 12.5 years for age at onset of neurological symptoms was obtained in the same way. When different hepatic symptoms developed at different times in a case, the earliest one was taken to mark the age at onset. This was applied to other organic categories. Then each mean, represented by a dot in the figure, was connected by an arrow whose width represents the number of cases, crossing from HP area to NR area to indicate sequential development. A standard deviation for the age at onset is shown by a horizontal dashed line extending from the dot.

Other patterns were formed in the same way. In simultaneous onset patterns the bars are vertical, as shown in the first and second rows in the figure. There were patterns involving more than three organic categories, but they all occurred in less than four cases.

To sum up, Fig. 2 is interpreted as follows. Arrows and bars, summarizing patterns of sequential development of organic symptoms, represent various clinical courses collectively and also indicate age at onset and relative frequency.

The most frequent pattern was a neurological-only pattern. There were 58 cases and the mean age at onset of neurological symptoms was 15.0 (SD 5.3) years (expressed as mean [1 SD] hereafter). The distribution of age at onset in this pattern is positively skewed and the majority of cases developed the symptoms between the ages of 9 and 16 years. The next most frequent pattern, that categorized as hepatic-only, comprised 28 cases. The mean age at onset was 9.4 (SD 5.4) years and most cases developed the symptoms between the ages of 5 and 10 years again with a positive skewness. Somewhat similar to the hepatic-only pattern, hepato-haematological, hepato-haematological-renal and hepato-renal patterns developed quite early at around 8 years of age, the number of cases being 10, 12 and 6 respectively. The third most frequent pattern was a hepato→neurological pattern. As cases in this pattern were seen as two separate groups in the original data, they were split into two; an early onset and a late onset pattern. The early onset pattern, in which hepatic symptoms developed before 14 years of age, comprised 19 cases. The mean age at onset of hepatic symptoms in this group was 8.8 (SD 2.4) years and that for neurological symptoms was 12.5 (SD 3.5) years. The average time between hepatic and neurological symptoms was 3.8 (SD 2.9) years. The late onset type, in which hepatic symptoms developed after 22 years of age, consisted of 7 cases with mean age at onset of 25.5 (SD 2.3) years for hepatic and 30.7 (SD 6.0) years for neurological symptoms. The time from the onset of hepatic symptoms to the onset of neurological symptoms was longer in this group, with a mean of 4.8 (SD 3.3) years.

The symptoms described above in the natural history appeared before treatment and therefore, the disease patterns in Fig. 2 represent the natural history without medical intervention.

Kayser-Fleischer rings were reported to have been observed in 233 cases, but the timing of their appearance was not determined. In most cases the rings were already present on the first examination. Twenty-one cases were recognized to have had cataracts of sunflower appearance, again with no information as to onset.

The prognosis in each disease pattern over the observed period was as follows. The mortality rate of the hepatic-only pattern was 62% and almost all of the deaths occurred within a few weeks due to acute hepatic failure. The hepato-haematological, hepato-haematological-renal and hepato-renal patterns followed a similar course and the mortality for the three groups combined was 44%. Twenty-nine percent of the cases with early onset hepato→neurological pattern died with a mean survival time of 18 months. For the late onset pattern the figures were 43% and 30 months. The neurological-only pattern had a favourable prognosis with a mortality of 22% and a longer mean survival of 55 months. In other types the numbers of cases were too small to be included here. It is noted that prognosis does not necessarily reflect the natural history of the disease because of the inevitable alteration of the clinical course by treatment after the last symptoms presented in Fig. 2.

Discussion

The cases collected in this study seem to represent roughly one-third of the cases of Wilson disease in Japan during the study period. When the incidence of the disease in Japan was around 1 in 20,000 during the study period [18], there must have been 70–90 new cases every year, which amounts to between 900 and 1200 cases for that period. In this study 283 cases were used in the analysis. In addition, from the total of 264 families, 55 cases did not have sufficient data and a further 62 siblings were suspected cases without definite diagnosis, thus totalling 400 cases.

Hepatic-only pattern patients were probably under-represented in this study. Among the 62 suspected cases mentioned above, 55 died with symptoms strongly suggestive of Wilson disease, 39 of acute hepatic failure. The possibility is that hepatic type patients must have been lost disproportionately because of missed diagnoses.

The proportion of the disease pattern and the proportion of presenting symptoms depend upon the proportion of medical specialities from which cases are reported. A larger proportion of neurological type in the past reports [6, 12, 15], may have been due to such selection. A paediatric department

reported a high proportion of a hepatic type [11]. In the present study the majority of hepatic cases were reported from departments of paediatrics and more than half of the neurological cases were reported from departments of medicine and psychiatry. Therefore, the selection of cases always needs to be carefully evaluated before analysing the natural history. In addition, geographical differences need to be noted. An epidemiologic study in East Germany [5] gave a much higher proportion of a neurological type than that in this study.

The mean age at onset of the disease is also affected by the proportion of disease patterns, since hepatic type patients were of an earlier age at onset. Therefore, comparison of mean age at onset among various studies should be made with particular attention to this point. A previous study carried out in Japan [4] gave a mean age at onset of 12.2 years, which is very close to that in this study. In that study 50% were hepatic type and 50% were neurological type by their definition.

The mean age at onset in other countries tended to be higher than those in Japanese studies. In the epidemiologic study in East Germany [5], in which 14% of the 106 cases were hepatic, the mean age at onset of all the cases was 17.2 years and that for hepatic type was 13.7 years. In the study of European migrants to the USA [6] it was 23.2 years and 22.9% were hepatic type patients. In other studies the mean age at onset was 16.2 years in the USA [21], 12.5 years in India [12], 16.4 years in Taiwan [22], and 16.0 years in England [22]. European and American patients seem to develop the disease later than Asian patients. The content of copper in the diet may play some role in this, but a Japanese diet does not necessarily contain more copper than European or American diets [16]. Indians and Chinese take about half as much copper as Europeans and Americans. Whether this difference in age at onset is due to ascertainment problems or to genetic or environmental factors needs to be studied.

A slight preponderance of male patients was also observed in other studies [1, 5, 10], but whether this is significant is unclear.

Deiss et al. [13], based on their cases and review of the literature, suggested a model for the natural history of the disease proposing five stages in its development. Dobyns et al. [14] proposed that the natural history was in three stages based on their observation of 58 cases and by modifying the model of Deiss. Both models are quite similar and can be summarized as follows. Stage 1: Accumulation of copper in the liver; asymptomatic. Stage 2: Release of copper from the liver and re-distribution to other organs; asymptomatic, mild with hepatic symptoms, or acute and severe with haemolysis or hepatic failure, or death. Stage 3: Chronic accumulation of copper throughout the body and appearance of symptoms; mild with neurological or hepatic symptoms, severe with hepatic failure or with neurological symptoms, or death.

The disease patterns in Fig. 2 agree with the models. Though there were many variations, the most frequent clinical courses were represented by the three patterns; the hepatic and hepato-haematological patterns which coincide with mild or severe cases in stage 2 of the model, hepato→neurological pattern which coincides with the process from stage 2 to stage 3, and the neurological pattern which coincides with stage 3. The two previous studies did not relate stage to age in their models. But in this study their relation was graphically presented. The age at onset and the duration of each stage in the model construed from the main clinical patterns in Fig. 2 are the following. Stage 1; From birth (or even before birth) to 12 years with an average of 9 years. Stage 2; Onset of this stage from 4–12 years with an average of 9 years and the duration of this stage from 1–7 years with an average of 4 years. Stage 3; Onset of the manifestation from 7–16 years with an average of 13 years.

An important finding in this study is the relatively early onset and unexpectedly large proportion of osteoarthral symptoms, particularly arthralgia of the knee. This finding was reported previously [8, 9], but its importance in early diagnosis was not widely recognized. These cases tended to be erroneously diagnosed as rheumatoid arthritis, rachitis and beri-beri when they had not yet developed hepatic or neurological symptoms. The finding calls for more attention to these symptoms in making the diagnosis. As related to bone abnormalities, 11 cases in this study had sustained fractures from minor accidents.

This study found more variability in presenting symptoms and in the natural history than was previously reported. A better understanding of the variability of symptoms and the natural history would lead to earlier diagnosis and hence to better prognosis.

Another contribution of this study would be in understanding the long-term metabolism of copper in humans. Sequential development of organic symptoms in relation to age, particularly the length of time in each stage of the model mentioned previously, would give valuable information on the subject. Though it may not be very helpful for understanding the physiological process of copper metabolism, it is very helpful from the viewpoint of toxicology. If early detection and early treatment of the disease become a common practice in the near future, further opportunity for a similar study on the natural history will not be available. In this sense this study was timely.

The possibility of missing a considerable proportion of patients and high mortality in hepatic type disease at an early age urge us to consider early screening. The disease is preventable [2, 21], a simple method of screening is available [3], and its efficacy established [18]. In the long history of investigation of the cause, treatment and its control [19], we have reached the stage of evaluating the cost and benefit of screening, and working out the best strategy. The better understanding of the natural history provided by this study should give a sound basis for this process.

Acknowledgement. I thank Dr. K. Nomiyama for support, Dr. J. A. H. Waterhouse, Dr. S. Shirahata and Miss R. A. Allcock for valuable suggestions, and most of all the attending doctors at various institutions for their co-operation in providing data for the study.

References

1. Arima M (1974) Genetic aspect of Wilson's disease. Shinkeinaika 1:577–582 (Japanese)
2. Arima M, Komiya K (1970) Prevention of Wilson's disease. Paediatria Universitalis Tokyo 18:22–24
3. Aoki T, Nakahashi M (1977) New screening method for Wilson's disease and Menkes' kinky hair disease. Lancet II:1140
4. Arima M, Sano I (1968) Genetic studies of Wilson's disease in Japan. Birth Defects 4:54–59
5. Bachmann H, Lößner J, Biesold D (1979) Untersuchungen zur Wilsonschen Erkrankung in der DDR. Teil I: Genetik und Epidemiologie. Z Gesamte Inn Med 34:744–748
6. Bearn AG (1960) A genetical analysis of thirty families with Wilson's disease (hepatolenticular degeneration). Ann Hum Genet 24:33–43

7. Bearn AG, Yü TF, Gutman AB (1957) Renal function in Wilson's disease. J Clin Invest 36:1107–1114
8. Boudin G, Pépin B (1961) Osteoarticular changes in hepatolenticular degeneration. In: Walshe JM, Cumings JN (eds) Wilson's disease. Blackwell, Oxford, pp 233–236
9. Canelas HM, Carvalho N, Scaff M, Vitule A, Barbosa ER, Azevedo EM (1978) Osteoarthropathy of hepatolenticular degeneration. Acta Neurol Scand 57:481–487
10. Chiauzzi R, Cunego A, De Luca D (1980) Studio epidemiologico sul morbo di Wilson. G Clin Med 61:284–296
11. Cox DW, Fraser FC, Sass-Kortsak A (1972) A genetic study of Wilson's disease; evidence for heterogeneity. Am J Hum Genet 24:646–666
12. Dastur DK, Manghani DK, Wadia NH (1968) Wilson's disease in India. I. Geographic, genetic and clinical aspects in 16 families. Neurology 18:21–31
13. Deiss A, Lynch RE, Lee GR, Cartwright GE (1971) Long-term therapy of Wilson's disease. Ann Intern Med 75:57–65
14. Dobyns WB, Goldstein NP, Gordon H (1979) Clinical spectrum of Wilson's disease (Hepatolenticular degeneration). Mayo Clin Proc 54:35–42
15. Goldstein NP, Owen CA (1974) Symposium on copper metabolism and Wilson's disease. Mayo Clin Proc 49:363–367
16. Horiguchi S, Teramoto K, Kurono T, Ninomiya K (1978) An attempt at comparative estimate of daily intake of several metals (As, Cu, Pb, Mn, Zn) from foods in thirty countries in the world. Osaka City Med J 24:237–242
17. Leu ML, Strickland T, Wang CC, Chen TSN (1970) Skin pigmentation in Wilson's disease. JAMA 211:1542–1543
18. Saito T (1981) An assessment of efficiency in potential screening for Wilson's disease. J Epidemiol Community Health 35:274–280
19. Scheinberg IH (1983) Investigating diseases no one's got. N Engl J Med 309:918–919
20. Slovis TL, Dubois RS, Rodgerson DO, Silverman A (1971) The varied manifestations of Wilson's disease. J Pediatr 78:578–584
21. Sternlieb I, Scheinberg IH (1968) Prevention of Wilson's disease in asymptomatic patients. N Engl J Med 278:352–359
22. Strickland GT, Frommer D, Leu ML, Pollard R, Sherlock S, Cumings JN (1973) Wilson's disease in the United Kingdom and Taiwan. Q J Med 42:619–638
23. Walshe JM (1962) Wilson's disease – the presenting symptoms. Arch Dis Child 37:253–256
24. Walshe JM (1975) Missed Wilson's disease. Lancet II:405
25. Walshe JM (1984) Wilson's disease. Br Med J 288:1689

Received December 6, 1985 / Accepted November 3, 1986