Phenotypes and Chronic Organ Damage May Be Different among Siblings with Wilson’s Disease

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Abstract

Background and Aims: Cloning of ATP7B provided evidence that Wilson’s disease is a hepatic copper toxicosis with a variety of extrahepatic complications. Affected siblings with the same genetic background and exposure to similar environmental factors may be a good model for the study of genotype-phenotype correlation. Methods: Twenty-three affected siblings in 11 families were selected from a database. The first phenotypes were determined according to the international proposal. The final types of chronic organ damage were re-evaluated for life-long management. Results: Phenotypes were identical in 5 of the families and different in 6 of the families. The acute hepatic phenotype H1 was found in 3 younger siblings and 1 older sibling. All survived an acute episode of hemolysis with underlying chronic liver disease. One also presented complication with neurological disease. The neurological phenotype N1 with neuropsychiatric symptoms and hepatic disease was found in 2 aged siblings of 1 family, in an older sibling in 3 families and in the oldest sibling in 1 family. Phenotypes in siblings were mainly split by either H1 occurring in random order or age-dependent N1. Types of chronic organ damage were identical in 8 of the families and different in 3 of the families. The same combination of chronic liver disease was found in 6 families and chronic liver disease complicated with neurological disease in 2 families. Split organ damage in siblings was found when an older sibling was complicated by neurological disease. There was no reverse combination of a younger sibling being complicated by neurological disease in any of the families. Conclusion: Phenotype combinations of siblings were mainly modified by externally-induced hemolytic episodes, while chronic organ damage in siblings was split by age-dependent neurological complications.

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Introduction

The cloning of ATP7B, responsible for Wilson’s disease (WD), provided evidence that WD is a primary hepatic disease caused by toxic copper retained in the liver.¹–³ In addition, various forms of extra-hepatic organ damage occur in patients. They include an acute hemolytic episode of transient jaundice and anemia, neuropsychiatric disorders, and Kayser-Fleischer (KF) rings.⁴–⁷ WD first appears with diverse clinical features, resulting in a delayed diagnosis and poor prognosis. To promote an early diagnosis and consequently improved prognosis, an international study group for WD (ISGW) proposed the first clinical features consisting of acute hepatic (H1), chronic hepatic (H2) and neurological (N1, etc.) phenotypes, and a scoring system for the definite diagnosis of WD.⁸ The phenotyping of ISGW has been proposed to simplify the diverse clinical features for diagnosis at the initial presentation, but it does not describe the chronic organ damage of WD which will require life-long treatment. Chronic liver disease, designated as phenotype H2 in the ISGW proposal, is a fundamental feature of WD.⁹ Neurological disease is a major chronic complication of patients with phenotype N1,¹⁰ and hemolytic episodes are major acute complications of patients with phenotype H1.¹¹

Affected siblings who have the same genetic background and exposure to similar environmental factors, including...
foods and drinking water, during their childhood growth in a familial setting may be a good model for the study of the genotype-phenotype correlation of WD, which has been the main clinical issue since the cloning of ATP7B.12–16 In this retrospective study, we evaluated the clinical features of 23 affected siblings in 11 families using the phenotypes of the ISGW proposal at the first appearance8 and the final diagnosis based on chronic organ damage for the life-long treatment of patients.9,11

Methods

This study was approved by the review boards evaluating research involving human subjects at the Aichi Gakuin University School of Pharmacy (Nagoya, Japan) and participating hospitals. Informed consent for ATP7B analysis was then obtained from each patient according to the study protocols approved.

Two or more siblings with WD found in a family were selected from our database covering the last 20 years. All plural siblings referred to our institutes underwent ATP7B analysis for the final diagnosis of WD.17 Homozygotes or compound heterozygotes of ATP7B responsible for copper toxicity were diagnostically definitive for WD. In the patients for who genetic diagnosis was incomplete, the scoring system proposed by ISGW was applied for the final diagnosis of WD.

According to the ISGW proposal6 the clinical features at the initial manifestation were classified into H1, H2 and N1 phenotypes. Briefly, the phenotype H1 causes acute jaundice due to hepatitis-like illness or Coombs-negative hemolysis in a previously apparently healthy subject, the phenotype H2 is any type of chronic hepatic disease, and the phenotype N1 refers to chronic hepatic disease associated with neuropsychiatric symptoms being present at diagnosis. Information on the chronic liver diseases of our patients was complete at the time of ATP7B examination.

The chronic organ damage of patients for their life-long management was classified into two types: uncomplicated chronic liver disease of Wilson (WD) and chronic liver disease complicated with neurological disease of Wilson (WD with N).5,6,9 Phenotype combinations at the first appearance and final combinations of chronic organ damage renewed for life-long management were investigated in the 23 affected siblings of the 11 unrelated families.

Results

The clinical features, ATP7B mutations, first phenotypes and final diagnoses of the 23 siblings affected with WD in the 11 families are summarized in Table 1. Twenty-one affected siblings of 10 families were either homozygous or compound heterozygous for the ATP7B mutation responsible for WD. The diagnosis of WD in the 2 heterozygous siblings was confirmed by the clinical characteristics of hypoceruloplasminemia, KF rings and copper contents in the liver and urine.8

According to the phenotypes of ISGW, the identical combination of H2/H2 was found in 4 families and N1/N1 in 1 family, while the different combination of H1/H2 was found in 2 families, H1/N1 in 2 families, H2/N1 in 1 family, and H2/H2/N1 in 1 family.

There were 4 siblings affected by phenotype H1. They comprised 2 each of the phenotype combinations H1/H2 and H1/N1. All the patients survived their acute episodes with conservative treatment and short-term anti-copper regimens.

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The phenotype H1 first appeared in a younger sibling in 3 of the families, and in 1 older sibling in 1 family. Re-evaluation of the H1 phenotypes at the recovery stage showed that WD remained in 3 of the survivors and WD with N in 1 survivor. The phenotype H2 or WD was incidentally found in 4 unrelated patients during the investigation of their biochemical liver damage of unknown etiology. Subsequent family studies identified another sibling with phenotype H2, being affected with WD. There were 6 siblings affected by phenotype N1, and they comprised H1/N1 in 2 families, H2/H2/N1 in 1 family, H2/N1 in 1 family, and N1/N1 in 1 family.

The final organ damage combinations of siblings renewed for their life-long management were WD/WD in 6 families, WD/WD with N in 2 families, WD/WD/WD with N in 1 family, and WD with N/WD with N in 2 families. In the 3 families with split organ damage combination, neuropsychiatric symptoms appeared age-dependently in the older sibling in 2 of the families and in the oldest sibling in 1 family. The identical organ damage of WD with N was found in the relatively aged siblings after ATP7B study of family members. The probands were both younger siblings because the genetic study was the first for the older siblings with neuropsychiatric symptoms.

Discussion

The study results obtained from the plural siblings with the same genetic backgrounds and exposure to similar environmental factors before their late teens provided important information regarding the genotype-phenotype correlation of WD. Different from other genetic diseases, the phenotype combinations of the affected siblings with WD were significantly modified by the phenotype H1 complicated with self-limiting hemolysis. The phenotypes at the first manifestation and chronic organ damage requiring lifelong anti-copper management were different in 6/11 and 3/11 family members, respectively.

Physiologically, the liver takes up dietary copper from the portal blood, synthesizes cuproproteins in hepatocytes, and secretes excess copper into the bile via the essential role of the hepatic copper transporter ATP7B.5 Dysfunction of ATP7B causes a sequence of the copper-induced chronic liver diseases of steatohepatitis, chronic hepatitis and cirrhosis in patients.5,6 Therefore, the liver disease stages may be age-dependent in most siblings with the same genetic background and similar environmental factors.

Copper is a hemolytic agent.18 The hemolytic episode of phenotype H1 may occur in WD patients with excess copper stored in the liver and other organs when these organs are incidentally damaged, releasing the toxic copper into the systemic circulation.4–6 Triggers inducing copper overflow may include infectious agents, toxins and drugs. It may be incidental to whether or not either a younger or older sibling is affected by such an external agent. Therefore, the phenotype H1 in a sibling with WD could be determined by an environmental factor rather than the age and genetic background.9,11

When the uncomplicated liver disease of Wilson is designated WD, the neurological disease designated N is a major extra-hepatic complication of WD.6,10 Non-ceruloplasmin-bound copper accumulates increasingly in the brain of WD patients along with the progression of copper-induced liver disease.4–6 This process may also be age-dependent in affected siblings. In fact, in our family studies, an older sibling with WD was the first to be complicated by N, followed by the identification of WD in a younger sibling. When WD with
In an older sibling had been missed due to various reasons, a younger sibling presented with Wilson’s disease (WD) with neurologic manifestations. However, the reverse split combination of a younger sibling with WD with neurologic involvement and an older sibling with WD was not found in our case study. Such reverse split, suggesting involvements of the genes other than ATP7B, epigenetic factors and environmental agents, was reported in neuropsychiatric disorders of relatively aged patients. A male patient with digenic mutations in PRNP and ATP7B presented with a severe neuropsychiatric disorder, while his older sister with ATP7B mutations alone had asymptomatic liver disease of WD.16 Two females from two monozygotic twins were first complicated by neurological disease at the ages of 26 and 36 years respectively; yet, their siblings remained asymptomatic for more than 2 and 3 years respectively.14 Two male siblings, at the ages of 16 and 28 in a single family, and a male patient, at the age of 32 in another family, first presented with neurological symptoms, followed by the identification of older female siblings with asymptomatic WD.12 Backgrounds other than ATP7B may cause a reverse split of the neurological complications in relatively aged pairs of affected siblings, probably because of the prolonged period of exposure to these factors.

Conclusions
The phenotype combinations of the siblings with WD in our case series were significantly modified by acute hemolytic episodes, and split chronic organ damage was determined by the age-dependent neurological complications.

Conflict of interest
The authors have no conflict of interests related to this publication.

Author contributions
Conception of study objective and design (SK, HH), collection of data (MM, TN, DK, HS, RI, YS, MY, KH, MI), analysis of data (AK, YT, KK), revising the article for important intellectual content (SY, SW, HG).

Table 1. Clinical features, ATP7B mutations, first phenotypes and final diagnoses of the 23 affected siblings in 11 families

| Family | Siblings | Age | Sex | ATP7B-1 | ATP7B-2 | First phenotypes | Final diagnosis |
|--------|----------|-----|-----|---------|---------|------------------|----------------|
| 1 | 1<sup>st</sup> | 6 | F | 2333G>T | 2333G>T | H1 | WD |
| 2 | 10 | M | 2333G>T | 2333G>T | H2 | WD |
| 2<sup>nd</sup> | 6 | M | 2333G>T | 2621C>T | H2 | WD |
| 2 | 17 | M | 2333G>T | 2621C>T | H2 | WD |
| 3 | 10 | F | 2871delC | 2871delC | H2 | WD |
| 2 | 14 | F | 2871delC | 2871delC | H2 | WD |
| 3<sup>rd</sup> | 17 | M | 2871delC | 2871delC | N1 | WD with N |
| 4 | 12 | F | 2871delC | 3809A>G | H2 | WD |
| 2<sup>nd</sup> | 17 | M | 2871delC | 3809A>G | N1 | WD with N |
| 5 | 13 | M | 2871delC | 3643G>T | H2 | WD |
| 2<sup>nd</sup> | 17 | M | 2871delC | 3643G>T | H1 | WD |
| 6 | 16 | M | 1708-5T>G | 3809A>G | H2 | WD |
| 2 | 18 | M | 1708-5T>G | 3809A>G | H2 | WD |
| 7 | 16 | M | 1708-5T>G | 1708-5T>G | H2 | WD |
| 2 | 18 | M | 1708-5T>G | 1708-5T>G | H2 | WD |
| 8 | 31 | M | 2298_2299insC | 2755C>G | N1 | WD with N |
| 2 | 37 | M | 2298_2299insC | 2755C>G | N1 | WD with N |
| 9 | 32 | F | 2871delC | - | H1 | WD |
| 2<sup>nd</sup> | 35 | M | 2871delC | - | N1 | WD with N |
| 10 | 38 | M | 1846C>T | 1846C>T | H2 | WD |
| 2<sup>nd</sup> | 41 | M | 1846C>T | 1846C>T | H2 | WD |
| 11 | 40 | M | 2659delG | 4007T>C | H1 | WD with N |
| 2 | 47 | M | 2659delG | 4007T>C | N1 | WD with N |

<sup>1</sup> A proband in the affected siblings; <sup>2</sup> Both siblings visited a hospital on the same day.

Abbreviations: M, male; F, female; H1, acute hepatic phenotype; H2, chronic hepatic phenotype; N1, neurological phenotype with neuropsychiatric symptoms and chronic hepatic disease; WD, uncomplicated chronic liver disease of Wilson; N, neurological disease of Wilson; WD with N, chronic liver disease complicated with neurological disease of Wilson.

Note: Two siblings were affected in 10 families, and 3 siblings in 1 family. A younger sibling was the proband in 6 families, while either older or the oldest sibling being the proband in 4 families. Two affected siblings with different phenotypes were referred to hospital on the same day. Nine affected siblings of 4 families were homozygous, 12 affected siblings of 6 families were compound heterozygous, and 2 affected siblings of 1 family were heterozygous for the ATP7B mutation responsible for WD. All 4 patients with the phenotype H1 survived their acute episodes with underlying chronic diseases.
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