Isolated persistent elevation of alanine transaminase for early diagnosis of pre-symptomatic Wilson's disease in Chinese children

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Background: **Recent studies presented a contradictory approach for the investigation of pediatric patients with an isolated increase in alanine transaminase. While classical teaching advised for a thorough investigation, recent studies suggested the yield on further investigation was low and thus not necessary. Yet the approach to the same clinical problem may need to be different due to variable disease prevalence rates among different ethnic populations. For the population with a higher prevalence rate of genetic liver diseases like Wilson's disease, an abnormal liver function may be the first presenting feature for some patients.**

Methods: **We reviewed 10 Chinese children with Wilson's disease who were diagnosed at a presymptomatic stage because of an isolated persistent elevation of alanine transaminase.**

Results: **All 10 patients did not have overt symptoms of liver impairment or neurological deficit. They were picked up incidentally with an abnormal liver function test. All patients were started on treatment shortly after diagnosis, and they remained well and symptom-free on the latest follow-up.**

Conclusions: **This case series illustrated that an isolated persistent elevation of alanine transaminase is an important clue to the early diagnosis of pre-symptomatic Wilson's disease. It is particularly relevant in the Asian population where the disease is more prevalent.**

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Introduction

Isolated elevation of serum alanine transaminase when detected incidentally is a common pediatric management problem that many primary care physicians and pediatricians face in their day to day practice. In many cases, this elevation is transient and resolves itself in a few weeks. However, for those patients with persistently elevated transaminases, the issue of how extensive the subsequent follow up investigations leads to a continuous debate. Although the classical teaching advocates thorough investigations into various causes, including genetic, metabolic, immunologic and drug-related liver diseases,[1,2] some recent studies suggested the contrary. A study[3] on 72 children from Israel concluded that isolated elevation of alanine transaminase in healthy young children indicated a benign condition. If no pathology was found during a routine investigation, the authors of the study recommended that these children be followed up conservatively.

It is well understood that different populations may have different disease prevalence rates based upon different genetic background as well as environmental influences. The prevalence of genetic diseases among different ethnic groups can be very variable indeed. Among the Chinese population, one of more common genetic conditions affecting the liver is Wilson's disease, an inherited disorder of copper metabolism leading to systemic copper accumulation in multiple organs. Early diagnosis is most essential to ensure good treatment outcome in these patients. An isolated persistent elevation of alanine transaminase may be an important early

clue, and a "wait and see" approach while the patient is asymptomatic may have missed the earliest opportunity for the diagnosis and treatment of the patient.

The worldwide prevalence of Wilson's disease was estimated to be 1 in 30 000 by Sternlieb and Scheinberg in 1984.[4,5] While direct comparative studies with similar diagnostic or screening methodology on the prevalence rate among different ethnic groups are lacking, more recent population studies like the following three did suggest a higher prevalence rate especially among the East Asian population. Yamaguchi et al[6] using an immunoassay with monoclonal antibody against holoceruloplasmin identified three cases out of 24 165 (estimated prevalence of 1 in 8000) Japanese children with Wilson's disease from late infancy to preschool age. In Korea, Hahn et al[7] using a sandwich ELISA method for ceruloplasmin in dried blood spots reported one case in 3667 (estimated prevalence of 1 in 3600) children with Wilson's disease aged three months to 15 years. Among the southern Han Chinese population, a prevalence rate of 1 in 5400 was suggested by Mak et al[8] who detected 3 carriers of the East Asian specific founder mutation p.R778L among 660 unrelated Hong Kong Chinese adults using a novel genetic approach. While a genuine difference due to the genetic make-up between the Caucasian and East Asian population is a highly plausible explanation, this observed great difference in prevalence rate may also be partly explained by the different methods used in ascertaining the prevalence. The more recent studies tended to be population based screening studies. Thus, more pre-symptomatic/asymptomatic individuals may have been identified. Overall, it does appear that Wilson's disease may be more prevalent than the previously widely quoted figure of 1 in 30 000, and this disease may indeed be more prevalent in East Asia where it is considered one of the most common inherited diseases affecting the liver.[9]

The classic symptomatic presentation of Wilson's disease comprises of the trio of liver disease plus neurological and ophthalmological involvement. Hepatic manifestation is the earliest manifestation for pre-symptomatic pediatric patients. They commonly present with abnormal alanine transaminase which is often found incidentally as shown in the series studied. Without treatment, Wilson's disease causes progressive liver disease, neurological deterioration and death. When diagnosed early, it is a highly treatable condition with good outcome. Furthermore, patients who are diagnosed early may not require traditional treatment with D-penicillamine or trientine. Over the last four decades, less toxic zinc therapy has been used as the mainstay of treatment for pediatric patients especially those with mild disease and low body copper load.[10-14]

Early diagnosis of Wilson's disease is an important step for good therapeutic outcome as well as prevention or amelioration of potential lethal complications. Primary care physicians and pediatricians, particularly those who practice in Wilson's disease prevalent regions, should be alerted to the diagnosis of the disease and its early manifestations like asymptomatic elevation of alanine transaminase.

Methods

This retrospective study enrolled 10 pediatric patients with Wilson's disease who had been diagnosed at an early asymptomatic stage at the Prince of Wales Hospital, the teaching hospital of the Chinese University of Hong Kong from 1984 to 2011.

All patients were younger than 18 years at diagnosis. Demographic, clinical and laboratory data at diagnosis and latest follow-up were retrieved from patients' medical records. The variables studied were age at diagnosis, gender, forms of clinical presentation and laboratory results at diagnosis as well as latest follow-up and abdominal ultrasound findings. The diagnosis of Wilson's disease was confirmed by liver biopsy in three patients, and molecular genetic analysis was performed in all patients. The treatment prescribed for these patients and their side-effects were also reviewed.

Results

The clinical and laboratory characteristics of the 10 patients (5 males and 5 females) are shown in Table. All patients were of Chinese ethnic background. The mean age (mean±stand deviation) of the patients at diagnosis was 7.3±4.5 years (range: 2-17 years). All patients were asymptomatic of the disease at presentation. They were incidentally detected to have abnormal serum alanine transaminase level when liver functions were checked for the following reasons: routine health check, febrile illness, acute gastritis, abdominal pain and epilepsy. Kayser-Fleischer rings were not present and no patients had neurological signs or symptoms attributable to Wilson's disease. None of the patients had hemolytic anaemia.

The mean level of alanine transaminase was 228±118 IU/L (range: 86-419 IU/L; normal: <58 IU/L) at diagnosis. It represented a mean elevation of 3.9 folds above the reference limit with the lowest elevation being 1.5 folds. Bilirubin, albumin and alkaline phosphatase levels were within normal limits. On further investigations, all patients had biochemical features of Wilson's disease. The mean serum levels of copper and ceruloplasmin were 4.2±2.1 μmol/L (normal: 10.0-25.2 μmol/L) and <0.1 g/L (normal:

Table. Clinical and laboratory characteristics of 10 pediatric patients with Wilson's disease

Patients	Age at diagnosis (y/sex)	At diagnosis				Genotype*		Latest follow up	
		ALT (<58 IU/L)	Serum ceruloplasmin (0.21-0.59 g/L)	Serum copper (10.0-25.2 μmol/L)	Urinary copper (<1.00 μmol/d)	Allele 1	Allele 2	ALT (<58 IU/L)	Urinary copper (<1.00 μmol/d)
1	6/M	104	<0.1	7.7	2.43	c.525dupA	IVS4-1G>C	55	1.30
2	5/M	145	<0.1	3.9	1.70	c.3443T>C	c.1543+1G>T	24	0.88
3	9/F	397	<0.1	4.5	3.00	c.2975C>T	c.525dupA	51	1.93
4	8/F	241	<0.1	4.3	2.70	c.2975C>T	c 525dupA	39	1.78
5	3/M	419	<0.1	3.6	1.76	c.2333G>T	c.2662A>C	29	0.39
6	7/M	86	<0.1	1.1	1.20	c.3053C>T	c 2939G>A	28	0.52
7	2/M	140	<0.1	1.1	2.43	c.2333G>T	c.2810delT	50	0.69
8	17/F	179	<0.1	5.5	8.03	c.3443T>C	c.3443T>C	102	2.80
9	12/F	296	0.10	6.3	2.68	c.2755C>G	c.3443T>C	45	1.99
10	4/F	275	<0.1	4.2	1.13	c.2755C>G	c.2604delC	75	0.39

ALT: alanine transaminase; M: male; F: female. *: NCBI RefSeq NM_000053.2.

0.21-0.59 g/L), respectively. The mean 24-hour urinary copper excretion without penicillamine loading was 2.70±1.98 μmol/day (range: 1.13-8.03; normal: <1.00 μmol/day). Serum ceruloplasmin was assayed by a standard laboratory method using immunoturbidimetry. The concentrations of serum and urine copper were measured by inductively coupled plasma mass spectrometry.

Abdominal ultrasound revealed mild hepatomegaly and increased hepatic echogenicity with fatty liver appearance in 7 of the 10 patients. Diagnostic liver biopsy was performed in 3 patients when molecular genetic testing was not widely available. These patients showed minimal portal fibrosis with lymphocytic infiltrate. There was macro and microvesicular fatty change. Staining of orcein and rhodanine was negative. Hepatic copper content was elevated at 10.5, 14.9 and 20.8 μmol/g dry weight liver tissue (normal liver: 0.3-0.8 μmol/g).

Molecular genetic test was performed in all patients (Table). The *ATP7B* gene (all coding exons plus flanking introns, RefSeq accession number NG_008806.1) was sequenced using a standard dideoxy-terminator sequencing method. Nucleotide 1 is A of the ATG-translation initiation codon. Nine patients were compound heterozygotes with two different mutations identified. One patient was homozygous for c.3443T>C mutation. This mutation was identified in two other patients.

All patients were subjected to treatment shortly after diagnosis, and referred for dietetic consultation. Eight patients were given and maintained on monotherapy with zinc. Both zinc acetate and zinc sulphate effervescent capsules were used. Dosage of zinc in terms of elemental zinc was in accordance with Brewer's recommendation.[15] No side-effects from zinc treatment were reported. The oldest patient was started on D-penicillamine in 1984 at five years of age. He continued on penicillamine for the next 15 years and was later switched over to zinc therapy. At age of 33 years, he was entirely symptom-free with normal liver functions. Another patient was started on trientine as the initial therapy. She was switched over to zinc therapy nine months later.

All patients were followed up at regular intervals with clinical and biochemical monitoring and remained well and symptom-free at the latest follow-up. Serial liver function tests showed normal results except mild fluctuations in alanine transaminase level (Table). Most of the patients maintained normal levels except mild elevations of alanine transaminase in two patients (75 IU/L and 102 IU/L; normal <58 IU/L). None of the patients developed anemia during the treatment.

Family screening by molecular testing identified an additional presymptomatic sibling at one year of age. As her liver function tests were entirely normal, she was not included for further analysis.

Discussion

Bugeac et al[3] studied 72 pediatric patients with isolated elevation of alanine transaminase at least 1.5 times above the reference value for three months or longer. They did not find any patients with significant underlying disease and all patients showed the normalized value after a median duration of 11.5 months. Thus, they advocated that isolated elevation of alanine transaminase in healthy thriving children is a benign condition and concluded that "the yield of broad investigation is low". However, a study[2] on 425 Italian children with isolated hypertransaminasemia from a tertiary pediatric center concluded differently. They identified 12% of such cases as having an underlying genetic disorder. They recommended a high level of suspicion for the disorder which may only present with isolated hypertransaminasemia. This difference in clinical approaches between the two papers highlights the fact that clinical practice guidelines developed in one part of the world should not be generalized to other parts of the world without thorough evaluation of disease prevalence or case mix of genetic disorders in

different ethnic populations.

When diagnosed early, Wilson's disease is a highly treatable condition with good outcome. Yet there is no one single test for its diagnosis. Previous diagnostic criteria were mainly based on clinical and biochemical features. With the Sternlieb criteria,[4] the diagnosis of Wilson's disease was established when at least two of the following three criteria were present: 1) serum ceruloplasmin level <0.2 g/L; 2) presence of Kayser-Fleischer rings by slit-lamp examination, or 3) hepatic copper content >250 mg/g dry weight liver tissue in the presence of hepatic and/or neurological manifestations consistent with Wilson's disease. However, for the application of these diagnostic criteria, patients have to have accumulated a substantial amount of tissue copper. For patients who have not had such substantial copper accumulation like pre-symptomatic and pediatric patients, these diagnostic criteria would not be applicable. Indeed, in the present molecular genomic era, a number of genetic diseases can often be diagnosed by identifying disease causing mutations. Ferenci et al[16] in 2003 proposed a scoring system for clinical, biochemical, histological features and mutation analysis. The total accumulated score indicated the possibility that the patient suffers from Wilson's disease. Although it is clinically helpful, this scoring system has not been assessed prospectively.

The availability of better and relative side-effect-free zinc therapy has made treatment of this lifelong disease more tolerable. Treatment outcome of Wilson's disease should be improved, provided that these patients are diagnosed early before the occurrence of irreversible damages. Not until the availability of universal screening, a high degree of clinical suspicion and vigilance remains the most important step in the early pre-symptomatic diagnosis of these patients.

In conclusion, our series represented a group of symptom-free pediatric Wilson's disease patients who had been diagnosed very early with 8 of the 10 patients less than 10 years of age at the diagnosis. Since the publication of our second patient's case report,[17] local pediatricians are more alerted to follow-up tests for abnormal liver function. This leads to the early diagnosis of the subsequent cases. It is crucial for pediatricians and primary care physicians to recognize that a persistently isolated elevation of alanine transaminase in an otherwise normal and asymptomatic child may be the first clue to the diagnosis of Wilson's disease. In parts of the world, where Wilson's disease is more prevalent, for instance, East Asia, this abnormal result should not be left alone without further investigations along the line of Wilson's disease. A follow-up prospective study is highly recommended to help assess the detection rate of asymptomatic Wilson's disease in our locality.

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