

Wilson Disease in 5 Sibs in a Turkish Family

Wilson Disease in 5 Sibs in a Sibships of 10 Three Unaffected Sibs
Being Abnormal Copper and Ceruloplasmin Levels

10 ÇOCUKTAN 5'İNDE WILSON HASTALIĞI BULUNAN BİR TÜRK AİLESİ

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SUMMARY

Wilson disease of "hepatic" form in 5 sibs of a sibship of ten in a Turkish family of south-east extraction is reported. The diagnosis was confirmed in these 5 sibs, 2 male and 3 females by all means, while the remaining 3 male sibs were accepted manifesting heterozygotes. The concentration is due to the founder effect.

Key Words: Wilson disease, Hepatolenticular degeneration, Autosomal recessive, Founder effect

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ÖZET

On çocuktan 5'inde fatal seyidi "hepatik" form Wilson hastalığı olan bir türk ailesi rapor edildi. İki erkek ve 3 kız çocuğunda klinik ve laboratuvar olarak Wilson sirozu tanısı konuldu, diğer kardeşlerden üçü heterozigot olarak kabul edildi.

Anahtar Kelimeler: Wilson hastalığı, Hepato-lentiküler dejenerasyon, Otozomal resesif

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The juvenile form of hepatolenticular degeneration is determined by a pair recessive genes autosomal nature. This type which occurs in Western Europeans and several other ethnic groups, has onset before age of 16 years and is frequently a hepatic disease (1). Heterozygotes have normal levels of ceruloplasmin, although they can be identified by decreased reappearance of radioactive copper into serum and ceruloplasmin. Passwell et al. (2) described this form prevailing among some Arab communities with interethnic differences. In Sardinia the condition is also of high incidence (3). Frydman and colleagues (4) reported a large kindred with affected individuals over two generations. Recent data indicates that the locus of Wilson disease is on a D group chromosome (5,6).

Aksoy and Erdem (7) described 49 cases from different parts of the country, including sibship with multiple affected ships. We here present from central Anatolia another sibship of ten five of whom have juvenile form of Wilson disease while seemingly unaffected 3 sibs together with both parents showed low le-

vels of ceruloplasmin. So far as we know this is another largest example after that of Bramwell (8). Moreover, the K family has attracted public interest because of the dramatic stories of affected individuals.

Case Report: The K. Family

Proposita M.K. (Prot.No. YiH 21234/90; Fig. 1, III-34) is a 15-year old female. She was born in the village Evciler, Bala, Ankara. She is unmarried. Her developmental story was described uneventful until about 2 months ago. At that time she noticed swelling of abdomen. While the swelling was becoming worse she experienced abdominal discomfort, nausea, vomiting and both hematemesis and melena. Her urine got dark. These signs and complaints were indeed not unfamiliar to the parents because of similar picture in their older children, so they immediately referred to our hospital. She further described secondary amenorrhea for about 5 months and frequent urination 2 to 3 times a night for about 2 months and palpitation not related to the exercise.

Height was 154 cm, weight 53 kg, blood pressure 70/110 mmHg and pulse rate 82 in minute. On palpation epigastrium was found tender with free ascites of moderate amount. The spleen was palpable on anterior axillary line and liver 5 cm below the costal margin. There occurred conspicuous collateral veins. Other

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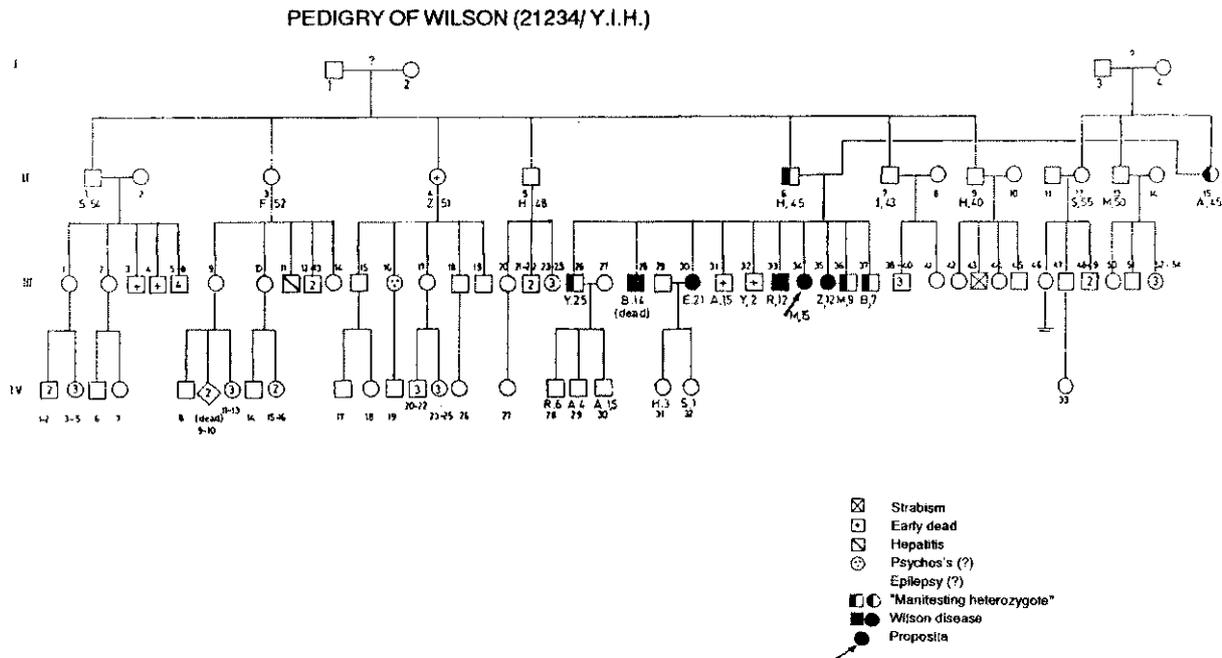


Figure 1

systems were found to be normal excluding Kaiser-Fleischer ring.

Laboratory examinations revealed Hb 10.1 gr/dl, Hot 30.6%, RBC 3.0 millions/ml, WBC 4900/ml, sedimentation rate 23 mm/hour, urea 9 mg/dl, serum creatinine 0.7 mg/dl, total bilirubin 2.9 mg/dl, direct bilirubin 1.5 mg/dl, AP 113 u/dl, globulin 5.8 gr/dl, prothrombin time 23.5", prothrombin activity 19%. Urine analysis reported to be normal except bilirubinuria. Serum copper level was reported 52 u/dl (70-140), serum ceruloplasmin 100 u/dl (250-570) and urinary copper level 2250 jigr/24 hours (50-90).

Chest roentgenogram showed fibrotic changes of lower zone and both diaphragmatic domes were high. On ultrasonographic examination liver surface was found irregular, heterogenous in echogenity and the wall of gall-bladder was edematous. Portal vein was open and the spleen homogeneously enlarged. Signs of ascites were present. Endoscopy exhibited erosive bulbittis.

These findings were compatible with the diagnosis of hepatolenticular degeneration and the patient was put on an adequate diet and therapy. After few months she died because of hepatic coma.

Other Sibs

As it can be seen from the pedigree chart in Fig. 1, proposita is the seventh sib of a sibship of 10, 7 males 3 females. The first male sib Y. (III-26), 25 years of age, is clinically normal but his serum ceruloplasmin level was decreased. He has three children without any health problems. Second sib B. (III-28), also a male, died at 14 years of age because of a liver

disease as diagnosed upon hospital admission. The third sib E. (III-30) is female and 21-year old. She is married and has two female children. Her third pregnancy was terminated due to her liver disease making her pregnancy worse. Although she did not exhibit stigmata typical for Wilson disease or any other physical abnormality at all; liver function tests as well as copper and ceruloplasmin levels were disturbed so that they considered as expression of the same gene. Further more ultrasonographic examination revealed evidence of chronic liver disease.

The fourth and fifth male sibs (11-31, -32) died at one and a half and two years of ages, respectively. No relevant causes were discovered for their early deaths.

The sixth sib R. (III-33) died at 12 years of age. He exhibited a profound icterus and died from esophageal varices bleeding. There were no laboratory details related to this condition, but the history of his illness was characteristic of a chronic liver disease, most probably of wilson type.

Proposita's younger sister Z. (III-35) also died when she was 12. She too had typical findings of Wilson disease and all laboratory tests supported the diagnosis. She was admitted in the same hospital as proposita and showed no associated features.

Last two male sibs Y. and B. (III-35 and -37) are 9 and 7 years old, respectively. Their serum and ceruloplasmin levels were found lower than those of controls. Ultrasonographic examinations were also interpreted normal.

In summary, It was accepted that 8 sibs, 5 definitely and 3 being asymptomatic carriers out of 10 were

affected with hepatolenticular degeneration. We have no sufficient information about two other sibs died at early ages.

Father H., 45, was from the same village Evciler and his wife F., 45, from a nearby village (Fig 1, II-6 and -15). They are from an area where consanguineous marriages are rather prevalent (9). The likelihood is that they share the same autosomal recessive gene so that to consider both parents are manifesting heterozygotes is justified. No any other case with a similar condition is known in the kindred. Sib concentration is probably due to the disturbance of the meiotic division, resulting in differential behavior of both gametes.

DISCUSSION

Cox et al. (1) divide Wilson disease into 3 categories, one being atypical and two others typical. These latter are further divided into Slavic and juvenile forms. Some authors 4 and even 5 subtypes of the disease on clinical grounds (10). It is clear that the K. sibs presented here has juvenile form of the condition. So far as clinical examination is concerned the K. sibs showed no signs of neurological deficit. We believe that Wilson disease affecting K. children is a hepatic early onset variety with rapid progression to the death (11). In this fatal progression no sex difference is apparent. The conventional therapy did not alter the course, most probably they were rather late for a controlled treatment.

It seems that the onset of the disease is sudden, although it must be insidious prior to this last period. Despite parents are aware of the condition running among their children they were still late to refer to our hospital. This type seems contrasting to the type associated with neurological signs and symptoms (12).

The cases presented here homozygous individuals for a rare recessive autosomal gene. The absence of parenteral consanguinity did not alter this hypothesis. The parents are in fact south-easterners in origin. Their parents were from southeast Turkey so that it is almost certain they share one or two common ancestors. The concentration of the disease is thus represents a founder effect.

The heterozygotes are of interest because they are clinically normal and ultrasonographic examination revealed normal livers. They have no complaints at all. Nevertheless, serum ceruloplasmin levels were decreased half the normal values whereas copper levels were normal or lowered. The fact that both parents have comparable levels not only between them but also with respect to their offspring, suggest these are asymptomatic cases or manifesting heterozygotes.

This differs from hypoceruloplasminemia which is a dominant trait (13). The decrease of ceruloplasmin level however did not contribute too much to detect the carrier status (6).

REFERENCES

1. Cox DW, Fraser FC, Saas-Kortsak A. A genetic study of Wilson's disease. Evidence for heterogeneity. *Am J Hum Genet* 1972; 24:646-66.2.
2. Passwell JA, Adam A, Garfinkel D, Streifler M, Cohen BE. Heterogeneity of Wilson's disease in Israel. *Isr J Med Sci* 1977; 13:15-9.
3. Giagheddu A, Denelia L, Puggioni G, Nurchi AM, Condu L, Deplano A, Rachele M. Epidemiologic study of hepatolenticular degeneration (Wilson's disease) in Sardinia. *Acta Neurol Scand* 1902-1983; 72(1):43-55.
4. Frydman M, Bonne-Tamir B, Farrer LA, Connealy PM, Magazanik A, Ashbel S, Goldwhich Z. Assignment of the gene for Wilson's disease to chromosome 13:linkage to esterase D locus. *Proc Natl Acad Sci USA* 1985; 82:1819-21.
5. Bonne-Tamir B, Farrer LA, Frydman M, et al. Evidence for linkage between Wilson's disease and esterase D in three kindred. Detection of linkage for an autosomal recessive disorder by the family study method. *Genet Epidemiol* 1986; 3:201-9.
6. Figus A, Lampis R, Devoto M, et al. Carrier detection and early diagnosis of Wilson's disease by restriction fragment length polymorphism analysis. *J Med Genet* 1989; 26:78-82.
7. Aksoy M, Erdem S. Wilson's disease in Turkey, a review of 49 cases in 41 families. *New Istanbul Contrib Clin Sci* 1975; 11(2):92-7.
8. Bramwell B. Familial cirrhosis of the liver. Four case of acute fatal cirrhosis of the liver in the same family, the patients being respectively nine, ten, fourteen and fifteen years of age: suggested relationship of Wilson's progressive degeneration of the lenticular nucleus. *Eding Med J* 1916; 17:90-9 (As mentioned by Walshe JM).
9. Şaylı BS. Anadolu'nun genetik yapısı üzerinde araştırmalar. XXVI Akraba evliliklerine ilişkin ek bulgular. *AÜTF Mecmuası* 1990;43:831-40.
10. Scheinberg JH, Sternlieb I. *Wilson's disease*. Philadelphia, WB Saunders Comp 1984; 78-86.
11. Walshe JM. Wilson's disease presenting with features of hepatic dysfunction. A clinical analysis eighty seven patients. *Quart J Med* 1989; 70(263):253-63.
12. Lingam S, Wilson J, Nazar H, et al. Neurological abnormalities in Wilson's disease are reversible. *Neuropediatrics* 18(1):11-2.
13. Edwards CQ, Williams DN, Cartwright GE. Hereditary hypoceruloplasminemia. *Clin Genet* 1979; 15:311-16.