SHORT REPORT

Wilson's disease: diagnostic errors and clinical implications

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Background: Therapeutic outcome of Wilson's disease (WD) significantly depends upon its early recognition. However, because of its rarity in community and protean manifestations, the diagnosis and treatment are often delayed.

Aim: To ascertain diagnostic errors at initial evaluation in these patients.

Methods: Analysis of medical records of 307 patients of WD registered over 30 years was done regarding presenting manifestations, initial diagnostic omissions, and interval between onset of symptoms to diagnosis and treatment.

Results: Of the 307 patients of WD diagnostic errors by referring doctors from different specialties of health care were detected in 192 patients. These were diverse and multiple and included schizophrenia, juvenile polyarthritis, rheumatic chorea, nephrotic syndrome, metachromatic leucodystrophy, congenital myopathies, subacute sclerosing panencephalitis, neurodegenerative disease among others. The mean (SD) delay was two (three) years (range: 0.08–30 years). Some of the interventions before establishment of correct diagnosis were electroconvulsive therapy, thalamotomy, antipsychotics, and surgical correction for bony deformity. While 98 patients were referred with correct diagnosis, only 16 were given specific treatment.

Conclusion: Awareness among health professionals about varied presenting features of WD and high index of suspicion may have prognostic implications.

W ilson's disease (WD) is a rare inherited disorder of copper metabolism with broad clinical spectrum and often requires a high index of suspicion for correct diagnosis. Studies in Europe have estimated the prevalence rate to be 12–29 cases per million population.[1] The increase in prevalence is probably attributable to improved diagnostic techniques, better ascertainment, and prolonged survival. It is extremely important for physicians and health professionals at primary care level to recognise and diagnose this treatable disease at an early stage. The authors in this study discuss various aspects of clinical presentation, initial, diagnostic omissions, and delay in the diagnosis of WD at all levels of health care.

METHODS

A large cohort of patients with WD has been followed up over the past three decades (1970–2003), at the Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, a university teaching hospital in south India. These patients have been diagnosed based on the clinical manifestations, low serum copper and ceruloplasmin concentrations, increased 24 hour urinary copper excretion, and presence of KF ring by slit lamp examination.

The information related to early stages of the illness, initial diagnosis, delay in diagnosis and treatment by the referring physicians or at NIMHANS, were obtained from case records of 307 patients (M:F = 211:96). Ninety eight patients (31.9%) with correct referral diagnosis and 17 pre-symptomatic people (5.5%) diagnosed during screening of family members of index patients were excluded. Thus data from case records of 192 patients of WD were analysed.

RESULTS

Diagnostic errors or no diagnosis by referring doctors were detected in 192 (62.5%) of 307 patients. Professionals from all specialties of the healthcare system—that is, general practitioners, physicians, orthopaedicians, paediatricians, nephrologists, psychiatrists, and neurophysicians—initially evaluated patients. Some of them were also evaluated at teaching or non-teaching hospitals before referral. Initial diagnosis involved many systems of the body and often included multiple diagnoses in several patients (table 1). Of the 98 patients with correct referral diagnosis, only 16 patients (16.3%) were receiving de-coppering treatment at the time of referral.

Initial diagnoses in patients with neurological presentations were diverse and ranged from ''no diagnosis'' to non-committal diagnosis as ''neurological problem'' and specific diseases like stroke in young, cerebral venous thrombosis, seizures, epileptia partialis continua, action myoclonus, essential tremors, mental retardation, neuromuscular disorder, tetanus, congenital myopathies, dystonia, post-encephalitic parkinsonism, progressive myoclonic epilepsies, poliomyelitis, subacute sclerosisng panencephalitis, cerebellar degeneration, brain tumours, Hallervorden Spatz disease, Kuf's disease, adrenoleucodystrophy, metachromatic leucodystrophy, among others (fig 1).

The mean (SD) age at onset of symptoms in these patients was 13.5 (6.9) years (range: 3–44 years) and the mean age at presentation at NIMHANS was 15.6 (7.3) years (range: 3–45 years). The mean delay in diagnosis was 2.0 (3.0) years (range: 0.08–30 years). Of these 38.7% (n = 118) had more than one year delay in diagnosis, whereas only 15.1% (n = 46) were diagnosed within one month of onset. The common presenting symptoms were: tremors 97, dysarthria 48, jaundice 38, abnormal gait 27 and abdominal distension 24, musculoskeletal complaints 16, seizures 15, behavioural problems 14, dystonia 11, clumsiness 8, drooling 8, decreased activity/generalised weakness 7, decreased scholastic performance 6, changed sensorium 4, bleeding symptoms 4, dysphagia 3, chorea and poor vision one each.

It is noteworthy that there were 37 patients misdiagnosed during first evaluation in our institute at various levels, with a mean delay in diagnosis being 10 days (range: 0–1278 days). Correct diagnosis was established during inter-departmental referral, radiological or copper profile review, reassessment for poor therapeutic response, and progression of disease.

The following two cases illustrate diagnostic diversions and therapeutic implications of delayed diagnosis.

Table 1 Initial diagnosis in patients not involving nervous system

System* (134)†	Different diagnosis
Hepatic (29)	Jaundice, portal hypertension, cirrhosis, infective hepatitis, chronic liver disease
Psychiatric (12)	Schizophrenia, bipolar disorder, depression, mania, anxiety disorder, paranoid psychosis
Orthopaedic (10)	Rickets, juvenile polyarthritis, genu valgum, recurrent fractures, recurrent dislocation of patella ?cause, sequelae of head injury,
Cardiovascular (5)	Rheumatic fever sequelae, vasculitis
Haematological (2)	Idiopathic epistaxis, haemolytic anaemia
Renal (4)	Nephritis, nephrotic syndrome
Others (8)	Malaria, fever ?cause, post-traumatic sequelae, leprosy

*No specific referral diagnosis was available in 91 patients and in 43 patients, some diagnosis was made. Many patients had multiple diagnoses. †Values in parentheses show number of patients.

Case 1

This 29 year old woman was well until the age of 25 years, when she had tremors of upper limbs, progressing over four months to involve all four limbs. She later developed mania. A psychiatrist at another institution started haloperidol, chlorpromazine, and propranolol. Levodopa and carbidopa was then added by a neurophysician for parkinsonism. She did not improve and was advised stereotactic surgery. She under went thalamotomy, four years after the onset of symptom. After this, the tremors had decreased, but one month later she again developed severe mania. She was referred to our institute and a diagnosis of unspecified organic psychosis was considered. Presence of KF rings, low serum ceruloplasmin of 40 mg/l (normal: 150−350 mg/l), and copper of 480 µg/l (normal: 750−1600 µg/l) clinched the diagnosis of WD, five years after the onset. With treatment, she started improving.

Case 2

This 12 year old girl developed pain in both lower limbs when she was seven. She received symptomatic treatment under care of a general practitioner without any relief. Soon deformity of the lower limbs followed the pain. A corrective surgery for genu valgum was done at the age of 10 years without significant functional improvement. At 11.5 years of age, she developed dystonia of hands and a month before consultation at NIMHANS, she sustained fracture of left leg. She was referred to us as "progressive muscular weakness due to degenerative disorder". Diagnosis of WD was confirmed by KF rings, low ceruloplasmin (40 mg/l) and serum copper (260 µg/l) concentrations, and increased 24 hour urinary copper (107 µg/day). She has improved significantly and after nine months of treatment she is independent for activities of daily living and mobility.
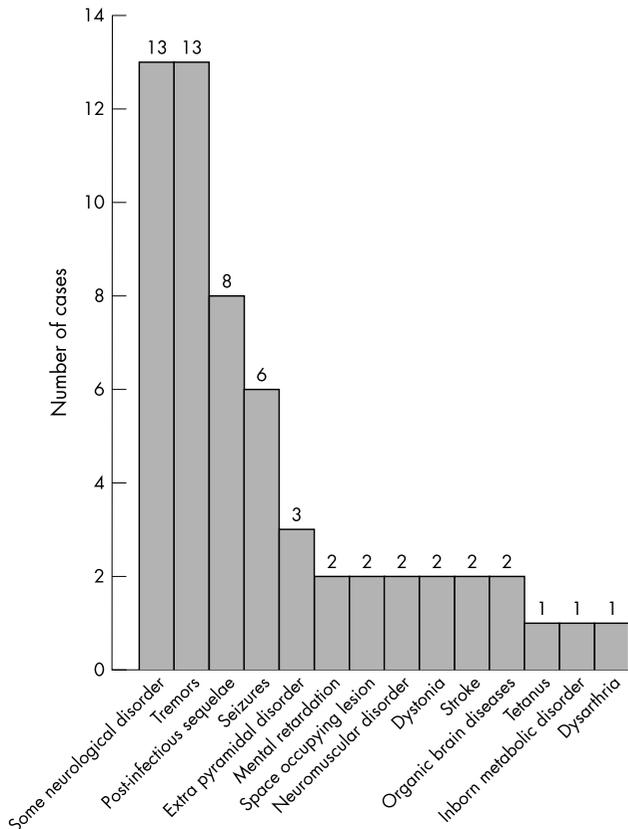
DISCUSSION

Wilson's disease, with its varied clinical manifestations, often poses a diagnostic and therapeutic challenge.[2] Scheinberg et al[3] reported that early manifestations of WD are generally hepatic or neurological (40% each) while remainders present with psychiatric, haematological, renal, or osteochondrotic symptoms.

Various studies on diagnostic errors with specific clinical syndromes show that clinical diagnoses are incorrect at variable frequency.[4–6] Walshe and Yealland[7] analysed initial diagnosis of 136 patients of WD and observed that it fell into four groups—that is, organic disorder other than WD 25.7%, psychiatric illness 23.5%, seizure disorder 19.1%, and WD 31.6%. Incorrect diagnoses were as diverse as flat feet, myxoedema, myasthenia gravis, encephalitis, multiple sclerosis, Parkinson's disease, schizophrenia, depression, anxiety state, etc. They concluded, "no two patients are ever the same, even in a sibship and there is no such thing as typical picture of Wilson's disease". Hu et al[8] noted that among 1011 cases of hepatolenticular degeneration, 516 cases were initially misdiagnosed, 193 cases failed to be diagnosed as a specific disease, and only 302 cases were correctly diagnosed within three months after the onset. Misdiagnoses included more than 100 different diseases like hepatitis, cirrhosis, splenomegaly, arthritis, nephritis, encephalitis, encephalopathy, psychosis, and anaemia. The experience from this study is similar.

Delay in diagnosis and the start of chelation treatment adversely affect the prospects for better outcome. Walshe and Yealland[7] reported a mean delay in diagnosis of 12.8 months. Hu et al[8] observed that the curative effect was better in the group with early diagnosis than in the groups with misdiagnosis and without a precise diagnosis (p<0.01). In our series mean (SD) delay was two (three) years (range:

Figure 1 Initial neurological diagnosis in patients with neurological presentation (n=58).

0.08–30 years) and many of them were severely affected and a few failed to respond to adequate treatment.

The causes for delay in diagnosis are varied. Walshe and Yealland[7] attributed these to underestimation and lack of awareness among treating physicians and laboratory errors in estimation of copper and ceruloplasmin concentrations. They emphasised that evaluation for KF rings should be done by an experienced ophthalmologist, using a slit lamp. Furthermore, KF rings may not be present when illness manifests with non-neuropsychiatric features. In this series the possible causes were: lack of awareness, low prevalence of disease in the community, absence of family history or history of liver disorders, comparatively late age of onset, and absence of clinical markers like KF ring. Patients presenting with behavioural problems often receive antipsychotic agents. With evolution of extrapyramidal symptoms, the hallmark of WD, they are diagnosed as having drug related adverse event. In one patient despite documentation of low concentrations of serum ceruloplasmin and copper, the diagnosis of WD was overlooked and treatment was delayed by over a decade.

It is noteworthy that 83.7% (82 of 98) patients, after being diagnosed as WD by referring physicians, were not given de-coppering treatment. This may be attributed to lack of familiarity about long term management, non-availability of drugs in peripheral centres, cost of the drug, and improper counselling of patients regarding the disease and need for treatment.

We believe that diagnostic possibility of WD should be considered in all young patients presenting with family history of jaundice, neuropsychiatric disorder and childhood deaths in other sibs, undiagnosed bleeding symptoms, recurrent or pathological fractures, recent onset behavioural and personality changes, and extrapyramidal features. Screening tests for all suspected patients should include slit lamp examination for KF ring by an experienced ophthalmologist, abdominal ultrasound for architectural changes in liver, serum copper and ceruloplasmin, and 24 hour urinary copper from a reliable laboratory. It may be noted that we could establish the diagnosis of WD in 17 asymptomatic sibs of index patients during routine screening.

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