

**Neurological Wilson Disease in children: a three years
experience from Multan**

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Abstract

Objective: To describe the neurological manifestations, results of investigations and response to treatment in Wilson disease in children from Multan.

Methods: This cross sectional study was conducted at Neurology Department of Children Hospital and Institute of Child Health Multan from June 2005 to May 2008. Fifty children were included in this study. Age at onset of symptoms, sex, duration of symptoms, presenting complaints, consanguinity among parents, family history and response to treatment was noted. Chi square test was used to measure relationship between variables and response to treatment. P value of less than 0.05 was taken as significant.

Results: Of the 50 cases studied, 48 were index cases and two were diagnosed on screening. Male female ratio was 2.1:1. Mean age at onset of symptoms was 9.06 ± 2.65 years. Dystonia, dysarthria and cognitive decline was seen in 92%, drooling in 68%, tremors in 52%, chorea in 24% and seizures in 12% of children. Kayser Fleischer rings and elevated 24 hours urinary copper after penicillamine challenge, 1567 ± 167.35 $\mu\text{g}/\text{day}$ was present in all 50 children. Twenty two (44%) children showed early response, 24 (48%) late response and 4 (8%) children showed no response after one year of treatment. Late, greater than 10 years of age at onset of symptoms, less than 6 months duration of symptoms and urinary copper excretion of less than 1000 $\mu\text{g}/\text{day}$ were found statistically significant factors for early response to treatment.

Conclusion: In the study population, dystonia, dysarthria and cognitive decline were the commonest presentations. Twenty four hour urinary copper was found helpful for diagnosis. Penicillamine was found to be an effective drug for treatment as overall response was noted in 92% of children.

Keywords: Children, Wilson disease, Neurological manifestation, Multan, Pakistan (JPMA 61:743; 2011).

Introduction

Wilson disease (WD), first described by Kinnear Wilson in 1912,¹ is a rare, autosomal recessive disorder of copper accumulation and toxicity. The incidence is 1 in 500,000 births and prevalence is about 1 in 30,000.²

The abnormal gene is located on chromosome 13q. This gene encodes a copper transporting P-type ATPase, ATP7B which is critical for biliary copper excretion and its incorporation into ceruloplasmin. Absence or malfunction of ATP7B results in decreased biliary copper excretion and its accumulation in liver.³

WD can virtually involve any organ of body but brain, liver and eyes are the main targets.⁴ The neurological disease usually presents with movement disorder along with abnormalities of speech.⁵

It can manifest insidiously or precipitously with dystonia, drooling, tremors, dysarthria and lack of motor coordination. Intellectual impairment or emotional disturbances are also frequent. Rare presentations include epileptic seizures and pyramidal signs.⁶ Hemiparesis can be the initial presentation in few cases.⁷

Diagnosis of WD is often difficult and is formulated through clinical, biochemical, imaging, histochemical and genetic evaluations. However, in neurological presentations, usually it is straight forward with presence of Kayser-Fleischer rings and urine copper of more than 100 μ g/day. In doubtful cases serum ceruloplasmin level, copper level and mutation analysis may be helpful.²

Treatment of Wilson disease consists of copper chelating agents such as D-penicillamine, trientine, dimercaprol and tetrathiomolybdate along with zinc and pyridoxine.⁵ Zinc was approved for treatment of WD in 1997.⁸

Neurological manifestations of Wilson disease can vary extremely and often diagnosed with long delay. It is one of the familial degenerative diseases in the field of paediatric neurology where early diagnosis and prompt treatment can avoid permanent neurological disability. This study was planned to see the spectrum of neurological manifestations of Wilson disease in children and response to treatment in our set up.

Patients and Methods

This cross sectional study was conducted at Neurology department of Children Hospital and Institute of Child Health Multan, Pakistan from June 2005 to May 2008. During this period 14,978 children with various neurological diseases were seen in Neurology out patient department. Out of which 50 children (0.33%) of up to 16 years of age were diagnosed as Wilson disease and included

in this study.

Diagnosis of neurological Wilson disease was made on the presence of the following three parameters. Firstly, History of progressive movement disorder and/or cognitive decline. Diagnosis of cognitive decline was made on the basis of history of parental concern of deterioration of higher mental function and was assessed by PEEP (portage early education plan) and Slosson IQ test. PEEP was used for children younger than 5 years or older who do not cooperate for standard IQ test. Slosson IQ test was used for older and cooperative children. Secondly, Presence of Kayser Fleischer rings in eyes; and with Elevated 24 hours urinary copper excretion after pencillamine challenge.

During the 24 hr urine collection, patients were given two 500 mg oral doses of D-penicillamine 12 hour apart and urinary copper excretion of more than 500 μ g/24 hrs was considered diagnostic. Children having Wilson disease without neurological manifestations were excluded from this study.

A performa was used to record demographic data (age and sex) and the details of history including age at onset of symptoms, duration of symptoms, presenting complaints (progressive dystonia, tremors, chorea, gait problems, cognitive decline, seizures, slurring of speech, dysphagia and drooling of saliva), history of consanguinity among parents (first cousins) and positive family history.

Following investigations were performed in all patients: Slit lamp examination for Kayser Fleischer (K-F) rings (K-F rings were checked by two experienced consultant ophthalmologists on different occasions to minimize the error of examination), twenty four hours urine for copper after penicillamine challenge, total and differential leukocyte count, platelet count, liver function tests, urine analysis and abdominal ultrasonography. Neuroimaging studies (CT/MRI brain) were not performed in any of the study participants. EEG was performed only in those children having history of seizures.

After making the diagnosis, treatment was started with penicillamine, zinc sulphate and pyridoxine (50 mg/day) along with dietary advice (prohibition of nuts, chocolates and fish intake). Penicillamine was started with 10 mg/kg/day in three divided doses one hour before meal and gradually increased up to 30 mg/kg/day over a period of one month. Zinc (elemental) was given 25 mg 12 hourly in < 10 years old and 50 mg 12 hourly in >10 years old children. Children were monitored monthly for response of therapy and for any side effects of treatment.

For measurement of response all children were categorized in 1 to 3 grades (Box-1). This categorization was based on functional ability to perform daily activities. Children were categorized before and after six months of

BOX-1:

Grade 1: Unable to perform daily activities like feeding, bathing, dressing, unable to speak, walk and presence of severe cognitive decline.

Grade 2: Able to feed, dress, bath and walk but with assistance, speech started but with slurring, presence of drooling and moderate cognitive decline.

Grade 3: Able to feed, bath, dress and walk independently, able to speak clear sentences, no drooling, able to write independently and mild cognitive decline.

initiation of treatment.

Response meant shifting from grade 1 to 2 or from 2 to 3. Response was also divided into early (within six months of treatment) and late (after six months of treatment). Cognitive assessment was performed at the start of treatment and then after every six months.

If the difference between chronological age and mental age was less than one year then it was labeled as mild cognitive decline, between 1-2 years as moderate and if this difference was more than two years then called as severe. This assessment may not be correct as cognitive level before symptoms was not known.

Children were monitored for the following side effects: hypersensitivity reactions, neutropenia, thrombocytopenia, pancytopenia, proteinuria, fanconi syndrome and nephrosis. For these side effects complete blood count including platelets, urine analysis and serum creatinine were performed monthly for initial three months and then after every three months for one year. After one year these tests were performed after every 6 months. Abdominal ultrasound was performed after every three months.

Family members (siblings and parents) of index cases were also screened. Screening was done through slit lamp for presence of Kayser Fleischer rings, 24 hours urine for copper and serum ceruloplasmin level.

Data was analyzed statistically by SPSS 10. Descriptive statistics (Mean and standard deviation) was used to describe the numeric variables like age at onset of symptoms, duration of symptoms and urinary copper excretion while frequencies are used to describe the string variables like sex, clinical features, family history, consanguinity and response to treatment. Chi square test was applied to measure the relationship between variables (age at onset of symptoms, male sex, duration of symptoms, urinary copper excretion and grade of disease) and response to treatment. P value of less than 0.05 was taken as significant.

Results

Out of fifty children, 48 were index cases and two

cases were diagnosed on screening. Thirty four children (68%) were males while sixteen (32%) were females. Mean age at onset of symptoms was 9.06 ± 2.65 years (range 4 -16 years). Mean duration of symptoms before presentation was 10.16 ± 20.67 months (range one month to 9 years). Consanguinity among parents was present in 46 (92%) children. Family history of neurological disease was noted in 34 (76%) children and history of death of sibling with neurological disease was present in 12 (24%) children.

Clinical manifestations are shown in Table-1.

Table-1: Neurological manifestations of Wilson disease (n= 50).

Clinical feature	Number of patients (%)
Chorea	12 (24%)
Cognitive decline	46 (92%)
Dystonia	46 (92%)
Drooling	34 (68%)
Dysarthria	46 (92%)
Risus sardonicus	20 (40%)
Swallowing problem	44 (88%)
Seizures	06 (12%)
Tremors	26 (52%)
Walking difficulty	42 (84%)

Dystonia, dysarthria and cognitive decline were the most common clinical presentations. Dystonia was generalized in 32 (64%) children while 14 (28%) children were having hemidystonia.

For cognitive assessment PEEP was used in 42 (84%) children while IQ test was performed in 08 (16%) children. Cognitive decline was mild in 6 (12%) children, moderate in 29 (58%) and severe in 15 (30%) children.

Tremors were noted in 26 (52%) children. Out of these, 21 children were having intention tremors and only 5 were having characteristic wing beating tremors.

Seizures were noted in 06 (12%) children. Out of these six children, four were having generalized tonic clonic seizures while complex partial seizures were seen in two children. EEG was normal in two children, generalized epileptiform discharges were seen in one child while rest of three children were having focal interictal epileptiform discharges (IEDs). Valproic acid (40 mg/kg/day) was used for generalized tonic clonic seizures and carbamazepine (15mg/kg/day) for complex partial seizures. Seizures were well controlled with single antiepileptic drug.

In this study concomitant hepatic manifestations were noted in 4 (8%) children while in 46 (92%) children liver disease was not associated with neurological disease. Among these four children, three were having clinical as well as biochemical evidence of chronic liver disease while one child developed fulminant hepatic failure. Transaminases and abdominal ultrasound was normal in rest of 46 (92%) children.

Table-2: Distribution of children before and after treatment (no 50).

Before treatment (no. of pts/ %)			After treatment (no. of pts/ %)		
Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
18 (36%)	32(64%)	0 (0%)	01 (2%)	20 (40%)	2 9

Kayser Fleischer rings and elevated 24 hours urinary copper after penicillamine challenge was present in all 50 children. Mean urinary copper excretion was $1567 \pm 167.35 \mu\text{g/day}$. EEG was performed in 06 children in this study. Eighteen (36%) patients were in grade 1 disease while 32 (64%) were in grade 2 according to categories designed for response of treatment.

Overall response of treatment was observed in 46 (92%) children. Twenty two (44%) children showed early response while 24 (48%) were late responders. Among early responders 13 were in grade 2 while 09 children were in grade 1 disease. Twenty four children showed late response. Out of these, 16 children were in grade 2 while 08 were in grade 1 disease.

Distribution of patients before and after treatment is shown in Table-2.

Compliance was good in 46 children while 04 children were having poor compliance. No serious side effect was observed in this study. Initial deterioration of neurological symptoms was observed in 34 (68%) children but was transient in majority (30/34) of patients.

The deterioration was noted after three months of treatment in 28 children while 6 children deteriorated after one month of therapy. Deterioration of cognitive level was the commonest observation noted in 26 children while worsening of dystonia and dysarthria was noted in 8 children. This worsening of initial symptoms was resolved after six months of treatment. Two children (4%) showed thrombocytopenia and 3 (6%) developed neutropenia.

Different factors (age > 10 yrs at onset of symptoms, male gender, duration of symptoms, urinary copper excretion <1000 μg and grade 2 disease) were analyzed statistically for early response and are shown in Table-3.

Table-3: Factors associated with early response (no. 22).

Factors	Number of patients (%)	Chi-square value	P-value
Age (>10yrs) at onset of symptoms	17(77.2%)	14.48	0.005
Male gender	16(72.7%)	0.403	0.525
Duration of symptoms (<6mo)	22(100%)	50.00	0.002
Urinary copper (<1000 $\mu\text{g/day}$)	13(59%)	22.35	0.002
Grade 2 disease	13(59.09%)	0.411	0.522

Late (>10 years) age at onset of symptoms, short (less than 6 months) duration of symptoms and urinary copper excretion of <1000 $\mu\text{g/day}$ were found statistically significant factors for early response.

Discussion

Wilson disease was seen more frequently in males in this study. This finding correlates with other studies mentioning high incidence of Wilson disease in males.⁹⁻¹¹

Majority of children (66%) were less than 10 years old in this study. This finding does not correlate with Western literature mentioning that neurological manifestations usually occur after first decade of life. However mean age at onset of symptoms of neurological disease was eight years in Kalra and colleagues study.¹² In Wilson disease age of onset of symptoms is determined by the severity of gene mutations. Some mutations are also population specific. Mutations that completely block the gene function can present as early as 2-3 years of age. Milder mutations are associated with symptoms as late as 70 years of age.² Children born of consanguineous parents had early age of onset and short duration of illness before presentation.¹⁰ These may be the reasons for early onset of symptoms in Asian population. Early presentation usually manifests with hepatic failure but we have noted early presentation with neurological disease. This variation of presentation can not be explained, however, the youngest reported child with cerebral manifestation was four years old.²

In this study positive family history of disease was noted at much higher frequency than mentioned in other studies. It was noted in 25% of index cases by Kalra and 47% by Taly and colleagues.^{9,12}

History of death of a sibling was also noted in 12 (24%) children and in two of the children, three expired siblings had clinical features consistent with Wilson disease. This shows under diagnosis of the disease in our society.

WD can mimic many neurological disorders and is often diagnosed with long delays.¹³ The manifestations of WD are so protean and the disease masquerades so well that recognition of the possibility of Wilson disease is a major problem.¹⁴

The areas of the brain involved in Wilson disease are those that coordinate movement.¹⁵ Therefore, it presents with movement disorders. The most common clinical presentations were progressive dystonia leading to dysarthria, difficulty in walking and abnormal posturing. This finding can be correlated with Sinha and colleagues study mentioning dystonia in 96% of cases while Machado and Soltanazdeh

noted dystonia in 69% and 42% of children respectively.^{10,15,16}

Tremors were noted in 26 (52%) children. The frequency of tremors noted in this study can be correlated with other studies mentioning tremors in 40%-60% of cases.^{9,15} Chorea was also noted in 12 (24%) children in this study. It was noted in 16% by Machado and colleagues.¹⁵

In addition to movement disorder, dysarthria was also seen frequently in WD. It was noted in 46 (92%) of our children and 80% by Sinha and Soltanazdeh while Machado observed dysarthria in 91% of patients.^{10,15,16} Drooling was seen in 68% of patients in this study. It was seen in 48% of patients by Soltanazdeh.¹⁶

Cognitive decline was also noted at much higher frequency (92%) in this study. It was seen in 71% of patients by Sinha.¹⁰ Epilepsy was noted in 06 (12%) children in this study while it was observed in 4.2% of patients by Machado.¹⁵

Majority of children presented with combination of above mentioned clinical features. WD must be considered in differential diagnosis of any child with progressive deterioration of neurological function. Neurological WD has heterogeneous manifestations and should be considered in patients presenting with dysarthria, drooling, psychiatric symptoms or any kind of movement disorder.^{10,16}

In this study presence of K-F rings and elevated urinary copper was found very helpful for diagnosis. This finding is supported by other studies.^{2,9,13}

We used penicillamine along with zinc and pyridoxine for the treatment of two presymptomatic children. There is controversy regarding treatment of presymptomatic patients in WD. Some are in favour of penicillamine and zinc^{17,18} while others recommend only zinc therapy for treatment of presymptomatic patients.^{4,14,19} However, the most appropriate therapy for treatment of Wilson disease remains controversial.^{20,21}

Penicillamine was found effective drug in this study as only 8% of children showed no response. Among non responders, one was presymptomatic child and despite repeated counseling, parents were reluctant to give regular medicines in apparently healthy child. This child became symptomatic after two years and treatment was restarted. Rest of the three non-responders were the index cases and poor compliance was the probable reason for treatment failure.

We have not observed any acute hypersensitivity reaction in this study which is mentioned in about 25%-30% of patients in literature.¹⁶

Major side effect of treatment was the initial

deterioration of neurological symptoms observed in 34 (68%) patients in this study but was transient in majority of children (30/34). This was noted in 50% of patients by Sinha and colleagues.¹⁰

The mechanism of this initial worsening may be the aggressive mobilization of copper by penicillamine leading to further elevation of the brain copper temporarily.¹⁷

Treatment of neurological Wilson disease has changed in developed countries from penicillamine to tetrathiomolybdate and trientine because of the risk of serious neurological worsening with penicillamine.^{17,18} In our set up it is difficult to start treatment with tetrathiomolybdate or trientine because of cost and problems of availability (Both of these medicines are still not registered in Pakistan).

Neutropenia and thrombocytopenia noted in few cases were corrected with reduction of dose of penicillamine.

Children were followed for two years but 2 (4%) children were lost to follow up after one year of treatment.

Positive prognostic factors for early response were calculated and it was found that late onset of symptoms, short (less than 6 months) duration of symptoms before start of treatment and 24 hours urinary copper excretion of <1000 µg were associated with early response.

The degree of recovery in a newly diagnosed patient depends on severity of disease and appropriate and early management. Severe abnormality at the start of treatment results in greater eventual disability. That is why early diagnosis and treatment are so vital in Wilson disease.^{22,23}

Few limitations of this study were unavailability of neuroimaging of our patients and short duration of follow ups.

Conclusion

Dystonia, dysarthria and cognitive decline were the common presentations. Twenty four hour urinary copper after penicillamine challenge was found helpful for diagnosis. Penicillamine was found effective drug for treatment.

Since large number of children had positive family history and even death of sibling, a high index of suspicion should be kept in any child presenting with progressive deterioration of neurological functions. Screening for K-F rings and urinary copper is suggested as a simple and cost effective way of detecting a curable disease at an early stage.

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