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CLINICAL, NEUROLOGICAL, AND LABORATORY FEATURES OF WILSON–KONOVALOV DISEASE IN CHILDREN

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Abstract: Wilson–Konovalov disease (WCD) is a rare hereditary disorder of copper metabolism caused by mutations in the ATP7B gene. Early diagnosis in children is crucial to prevent irreversible organ damage. To investigate the clinical, neurological, and laboratory characteristics of WCD in pediatric patients.
A total of 60 children aged 5–14 years were enrolled: 30 patients with WCD (main group) and 30 healthy children (control group). Family history, cognitive functions (Wechsler scale), ophthalmological findings, biochemical parameters (serum ceruloplasmin and copper, daily urinary copper excretion), and abdominal ultrasound were assessed.
In the main group, the initial complaints were fatigue, weakness, and recurrent epistaxis. Neurological symptoms (dysarthria, dysphagia, hypomimia, affective disorders) were observed in 33.3% of children older than 10 years. Cognitive decline was identified in 13.3% of patients. Kayser–Fleischer rings were detected in 26.7% of cases. Daily urinary copper excretion exceeded 90 µg/day in 40% of affected children. Mean serum ceruloplasmin was 0.9±0.2 g/L (normal: 0.2–0.4 g/L), and total serum copper was 9.8±1.1 µmol/L (normal: 12.56–24.34 µmol/L). Abdominal ultrasound revealed hepatomegaly and gallbladder enlargement of varying degrees.

Keywords: Wilson–Konovalov disease, ATP7B, copper metabolism, pediatrics, neurology, ceruloplasmin, Kayser–Fleischer ring

Introduction

Wilson–Konovalov disease (WCD) is a genetic disorder characterized by impaired copper metabolism due to mutations in the ATP7B gene. The defect leads to abnormal copper accumulation in the liver, brain, and other organs, causing progressive hepatic, neurological, and psychiatric manifestations. The prevalence of WCD is estimated at 1 in 30,000 to 1 in 40,000 worldwide, with significant variation depending on consanguinity rates in different populations. Early diagnosis and treatment are essential, as delayed recognition may lead to irreversible neurological damage and hepatic failure.

While WCD has been extensively studied in adults, data on its pediatric presentation, especially in populations with a high rate of consanguinity, remain limited. This study aims to describe the clinical, neurological, and laboratory features of WCD in children aged 5–14 years, emphasizing diagnostic markers relevant for early recognition.

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Materials and Methods

Study population

A total of 60 children aged 5–14 years were examined. The study cohort was divided into two groups:

- **Main group:** 30 children diagnosed with Wilson–Konovalov disease, all from consanguineous marriages.
- **Control group:** 30 age- and sex-matched healthy children.

Clinical and neurological assessment

Family history and clinical complaints were recorded. Neurological examination included assessment of motor, speech, and cognitive functions. Cognitive function was evaluated using the Wechsler Intelligence Scale for Children (WISC).

Ophthalmological assessment

All patients underwent two ophthalmological examinations, including slit-lamp biomicroscopy, to detect Kayser–Fleischer rings.

Laboratory assessment

- **Biochemical tests:** Serum ceruloplasmin, total copper concentration, and daily urinary copper excretion were measured. Normal values: serum ceruloplasmin 0.2–0.4 g/L; serum copper 12.56–24.34 µmol/L; urinary copper <40 µg/day.
- **Instrumental tests:** Abdominal ultrasound to evaluate liver and gallbladder size.

Statistical analysis

Descriptive statistics were applied. Results are presented as mean ± standard deviation (SD) or percentages.

Results

Clinical features

In the main group, all patients reported nonspecific early symptoms: fatigue, weakness, and recurrent epistaxis. Neurological symptoms appeared later, typically after 8–10 years of age. Dysarthria, dysphagia, hypomimia, and affective disorders were found in 7 patients (33.3%).

Cognitive assessment

Wechsler scale evaluation revealed moderate intellectual decline in 2 children (13.3%).

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Ophthalmological findings

Kayser–Fleischer rings were identified in 4 children (26.7%) using slit-lamp examination.

Laboratory findings

- Daily urinary copper excretion exceeded 90 µg/day in 6 children (40%).
- Mean serum ceruloplasmin was 0.9 ± 0.2 g/L, above the normal upper limit.
- Mean total serum copper was 9.8 ± 1.1 µmol/L, below the normal range.
- Moderately decreased ceruloplasmin levels were found in 5 children (33.3%).

Instrumental findings

Abdominal ultrasound revealed hepatomegaly and variable gallbladder enlargement in all patients of the main group.

Discussion

Our study demonstrates that the first symptoms of WCD in children are nonspecific and may resemble common pediatric complaints such as fatigue and weakness. Neurological symptoms, including dysarthria, dysphagia, and hypomimia, typically emerged after the age of 8–10 years. This aligns with previous reports indicating that neurological involvement in WCD often manifests later than hepatic symptoms.

The presence of Kayser–Fleischer rings in 26.7% of cases confirms their diagnostic significance, although absence does not rule out the disease, particularly in early stages. Elevated urinary copper excretion and reduced serum copper levels were consistent with impaired copper metabolism and remain key laboratory markers for diagnosis. Interestingly, ceruloplasmin levels were not uniformly decreased; while 33.3% of children showed reduced levels, the group mean was elevated. This variability highlights the need to interpret ceruloplasmin in conjunction with other biochemical and clinical findings.

Ultrasound findings of hepatomegaly and gallbladder changes reflect hepatic involvement, which is typically the earliest site of copper accumulation in WCD.

Conclusions

1. Early symptoms of WCD in children are nonspecific (fatigue, weakness, recurrent epistaxis) and may delay diagnosis.
2. Neurological manifestations usually appear after 8–10 years of age, including dysarthria, dysphagia, hypomimia, and affective disorders.
3. Key laboratory markers include decreased serum copper, increased urinary copper excretion, and variable ceruloplasmin levels.
4. Kayser–Fleischer rings were present in approximately one-quarter of patients and remain an important, but not universal, diagnostic sign.

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5. Abdominal ultrasound frequently revealed hepatomegaly, underscoring the importance of hepatic monitoring in pediatric WCD.

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(to be formatted according to the journal's style guide – sample sources below)

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