

# Gabapentin Can Improve Dystonia in Confirmed Wilson Disease

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Wilson disease (WD) is an autosomal recessive disease of copper metabolism due to mutations in the ATP7B gene on chromosome 13<sup>1</sup>.

Patients may show a disabling movement disorder characterized by extrapyramidal signs with dystonia and choreoathetosis, associated with psychiatric signs and liver involvement, usually occurring during the first decades of life.

Copper chelation by D-penicillamine represents the main therapy in WD. Those patients who experience severe side-effects due to D-penicillamine may instead be commenced on another chelating agent, such as trientine hydrochloride. Zinc acetate, also accepted for the treatment of WD, especially in pre-symptomatic stages of the disease, stimulates the induction of the intestinal cell metallothionein, which eventually reduces copper absorption from the intestinal tract and its transport to the liver<sup>2</sup>.

The symptomatic treatment of WD is commonly unsatisfactory, however<sup>1,2</sup>.

We observed a case that is of particular interest, since a young patient with WD showed a striking improvement of axial and segmental dystonia on gabapentin at a low dosage.

## CASE REPORT

A 33-year-old Caucasian woman had developed hand tremor, limb rigidity, speaking difficulties and swallowing problems, requiring gastrostomy, over the previous three years. She reported "hepatitis" in her childhood. Her clinical examination showed poker face, severe dysarthria, hypophonia and dysphagia, with marked drooling. She also presented generalized dystonia with episodic opisthotonus and retrocollis, axial and segmental dyskinesias, bradykinesia, rest and action tremor. She could neither walk nor support her trunk when sitting [MMSE 25/30, Barthel Index 18/100, Global Assessment Scale for Wilson's Disease (GAS/WD): Tier1: L1, C4, M4, O1, Tier2: 49; Fahn-Marsden (BFM) scale: 67/120]<sup>3,4</sup>. (see Video 1).

Serum ceruloplasmin level was 0.28g/L (normal values 0.2-0.6g/L). The 24-hour urine copper level was 144µg/day (normal values < 60µg/day). Keyser-Fleischer rings were detected on slit lamp examination. Micronodular cirrhosis and gastro-esophageal varices were also found. T2-weighted magnetic resonance imaging (MRI) sequences detected several hyperintensities in the brainstem, cerebellum and putamen.

The analysis of ATP7B gene showed a homozygous c.3207 C>A (p.H1069Q) mutation.

Diazepam (6mg/day) and trihexyphenidyl (6mg/day) were ineffective. D-penicillamine (750mg/day) did not change the overall clinical situation, but increased the frequency of the dystonic spells. It was discontinued after a few days because of thrombocytopenia. After discontinuation, the dystonic spells quickly decreased, although they still occurred at the same level as before initiating penicillamine. While waiting to start trientine hydrochloride, another drug with potential long-term efficacy in WD, and two weeks after the discontinuation of penicillamine, we introduced gabapentin, which showed potential efficacy in the symptomatic treatment of WD<sup>5</sup>.

After obtaining a written consent from the patient, we started gabapentin at a dosage of 900mg/day. The same day of the administration, the drug induced a striking reduction of the dystonia and a global clinical improvement, especially in walking (Barthel Index 65/100; GAS/WD Tier1: L1, C4, M3, O1; Tier2: 14; BFM scale: 23.5/120). (see Video 2).

The patient resumed oral eating and her speech improved significantly. Attempts to further increase the dose of gabapentin had no significant effect, while the short-term discontinuation of the medication caused a quick worsening of symptoms.

Over the following eight months, she progressively displayed gait instability, modest axial and segmental dystonia.

## DISCUSSION

Dystonia is a disabling condition in WD, observed in 11 to 65% of patients<sup>1</sup>, possibly linked to functional impairment in striato-cortical circuits. Treatment is rarely effective<sup>1,2</sup>.

The anticonvulsant drug gabapentin, interacting with P/Q-type Ca<sup>++</sup> channels, increases glutamate in the neocortex and hippocampus and inhibits excitatory neurotransmitter release in the spinal cord<sup>6</sup>. Gabapentin can show some efficacy in limb dystonia and hemifacial spasms<sup>7</sup>, although occasionally it can induce dystonia<sup>8</sup>.

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Paroxysmal dystonia was previously improved by gabapentin in three young patients with non-genetically confirmed WD. Persistent dystonia was partially improved in only one. None of these patients recovered significantly<sup>6</sup>. In our patient with a homozygous c.3207 C>A (p.H1069Q) mutation in the ATP7B gene, low-dose of gabapentin dramatically reduced sustained and dystonic spasms and strikingly improved her overall condition. She could walk independently once again and attain some improvements in her activities of daily living. The progressive reduction of efficacy of gabapentin in this patient suggests that the action of this drug on the neurotransmitters' release could be time-dependant, but this observation needs corroboration in a longer follow-up.

In conclusion, we suggest that gabapentin may be beneficial to treat the functional impairment in cases of genetically-confirmed WD with extrapyramidal manifestations.

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