

# Putamina Involvement in Wernicke Encephalopathy Induced by Janus Kinase 2 Inhibitor

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**Objective:** The aim of the study was to report a case of Wernicke encephalopathy (WE) due to fedratinib (Janus Kinase 2 inhibitor) treatment with atypical neuroimaging findings.

**Methods:** We present a detailed report of the case and literature review.

**Results:** A 68-year-old woman under treatment with fedratinib (investigational JAK2 inhibitor) developed memory impairment, diplopia, and ataxia compatible with WE. Brain magnetic resonance imaging showed extensive lesions involving medial thalami, periaqueductal gray, caudate nuclei, and putamina. Thiamine supplementation provided clinical recovery and radiological improvement of the lesions described. Basal ganglia lesions have been previously described in children with this disease, but this is rarely found in adults. Clinical trials including fedratinib have been recently discontinued, and its involvement in pathogenesis of WE may be related to thiamine-transporter inhibition.

**Conclusions:** Our case represents an example of drug-related WE, with a rare radiological pattern. Precocious diagnosis and treatment are essential to prevent irreversible brain injury.

**Key Words:** Wernicke encephalopathy, putamen, thiamine, magnetic resonance imaging

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A 67-year-old woman was admitted to our hospital for evaluation of rapidly progressive symptoms including diplopia, repetitive speech, short-term memory impairment, and difficulty to carry out everyday tasks such as cooking, for the last month.

Her medical history consisted of essential thrombocythemia under treatment with investigational JAK2 inhibitor fedratinib (SAR302503, end-stage clinical trial), which caused nausea and vomiting as adverse effects for the last 6 months. No other previous medical condition or treatment was reported.

On admission, the patient was drowsy, oriented for place but not for time, with decreased speech fluency, impaired fixation memory, and dyscalculia (mini mental status examination, 19/30 points). On examination, pupil reflexes and visual field were intact, but presented continuous gaze-evoked nystagmus to both right and left side, and restricted upward gaze with “setting-sun” sign. There was neither facial palsy nor other cranial nerve dysfunction. Examination of strength, deep tendon reflexes, and sensitivity was normal. A subtle finger-to-nose dysmetria was noted, along with wide-based gait ataxia. Vital signs and general examination were normal.

Due to presence of neurological symptoms, an urgent computed tomography scan was performed revealing hypodense changes in basal ganglia, midbrain, and thalamus bilaterally (Fig. 1A). Because clinical presentation and long history of vomiting were consistent with Wernicke encephalopathy (WE), the patient was promptly treated with B<sub>1</sub>-B<sub>6</sub>-B<sub>12</sub> complex and admitted to neurology ward. A complete blood count showed macrocytic anemia, thrombocytosis, and high erythrocyte sedimentation rate as reasonable for the patient's medical history. Tumor markers, kidney, and liver function tests were normal. A lumbar puncture was performed, and analysis of the cerebrospinal fluid was noteworthy for a slightly elevated protein (0.56 g/L).

Brain magnetic resonance imaging (MRI) showed bilateral hyperintense T2/FLAIR (fluid attenuated inversion recovery) signals in both medial thalami, rostral midbrain, and periaqueductal gray (Figs. 1B, C). Similar lesions were found in both heads of caudate nuclei, putamina, and globi pallida. These were hypointense in T1 and exhibited slight gadolinium contrast enhancement. Diffusion-weighted imaging and apparent diffusion constant images showed hyperintense and slightly increased signals on basal ganglia, respectively.

During the first week of B complex treatment, the patient showed significant clinical improvement, disappearing nystagmus, upward gaze restriction, gait ataxia, and dysmetria. Cognitive dysfunction also improved, but short-term memory deficits still remained. Vitamin B was continued orally, and the patient was discharged 2 weeks after admission, almost completely restituted.

Three months after discharge, the patient was reevaluated, complaining some memory impairment, but completely recovered from the rest of the symptoms.

A new brain MRI was performed 6 months after discharge (Figs. 1D, E), showing minimal signal alterations at structures mentioned previously, compared with the previous MRI.

## DISCUSSION

Wernicke encephalopathy is a serious neurological syndrome caused by thiamine (B<sub>1</sub>) deficiency, characterized by ataxia, impaired eye movements, and altered mental status. Most frequent etiologies are alcoholism,<sup>1</sup> bariatric surgery,<sup>2</sup> prolonged fasting or unbalanced intravenous feeding,<sup>3</sup> and hyperemesis gravidarum.<sup>4</sup> However, drug-related WE is extremely rare.

Thiamine is a cofactor for key enzymes in energy metabolism; therefore, its requirements depend on metabolic demand. Daily thiamine-required intake is approximately 1 to 2 mg. Because the body reserves of thiamine are only 30 to 50 mg, these would be completely depleted in 4 to 6 weeks in the absence of thiamine intake. Neuronal injury has been related to metabolism inhibition in brain regions with high metabolic requirements and high thiamine turnover.<sup>5</sup>

The anatomic regions most frequently involved by MRI in WE are the thalami, mammillary bodies, tectal plate, and periaqueductal area, which usually show symmetric signal

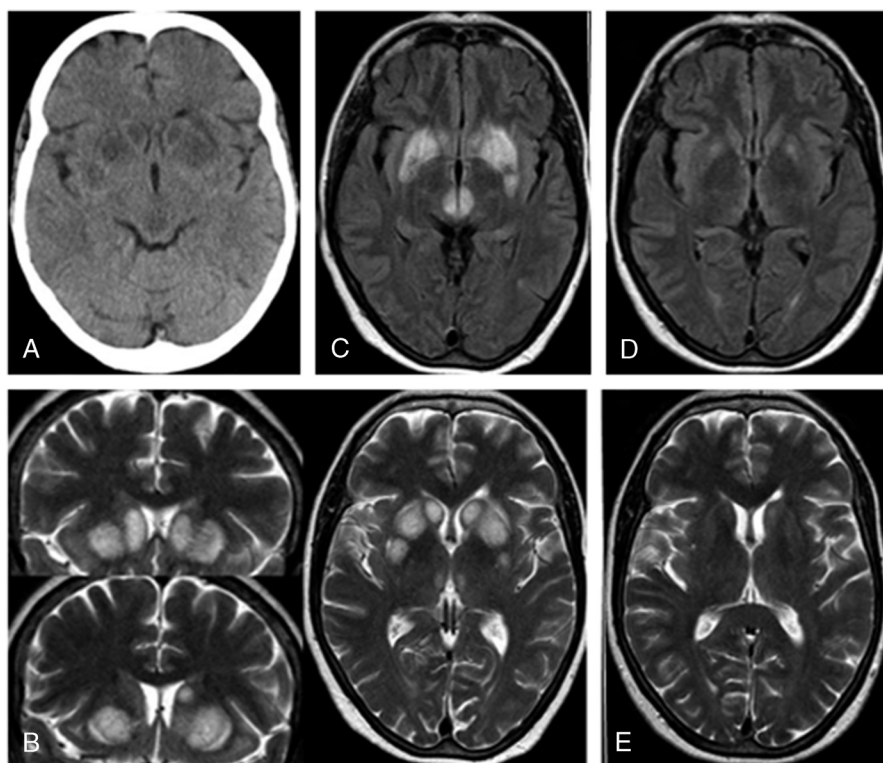
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**FIGURE 1.** A, Urgent brain CT scan showing hypodense changes in caudate, lenticular nuclei, and periaqueductal gray. B, Brain MRI. Coronal and axial T2 sequences showing bilateral hyperintense signal alterations in caudate and lenticular nuclei. C, Brain MRI. FLAIR sequence showing bilateral hyperintense signals in lenticular nuclei and medial thalami. D, Brain MRI 6 months after discharge. FLAIR sequence. E, Brain MRI 6 months after discharge. T2 sequence. Note that previous signal alterations have significantly decreased.

alterations. Similar alterations have also been found in the cerebellum, cerebellar vermis, cranial nerve nuclei, red nuclei, dentate nuclei, caudate nuclei, splenium, and cerebral cortex as atypical MRI findings, always along with typical ones.<sup>5</sup> Putamina involvement has classically been only described in children, in which thiamine-dependent metabolism is increased during development.<sup>6,7</sup>

Fedratinib clinical trials were discontinued worldwide after recent reports of cases consistent with WE among its participants.

Fedratinib is supposed to decrease thiamine absorption by inhibition of human thiamine transporter. This condition seems to be related with the molecular structure of fedratinib and is not shared with others JAK2 inhibitors.<sup>8</sup>

Our case represents an example of extensive lesions caused by a probably long-term thiamine deficiency, which has involved structures rarely affected in adults.<sup>7</sup> It is unknown whether the radiological pattern showed by the patient may be linked to the mechanism of action of fedratinib.

Building knowledge about clinical and radiological manifestation of this reversible as well as fatal condition can help clinicians make quick decisions and improve patient prognosis. Further investigations are needed to define the association between neuroimaging findings and fedratinib treatment in patients with WE.

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