Clinical Reasoning:

A 55-year-old man with rapidly progressive dementia and parkinsonism

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SECTION 1

A 55-year-old right-handed man presented with a history of rapidly progressive apathy and behavior changes, speech loss, bladder and bowel incontinence, and gait loss in the previous month. He had been diagnosed with depression 7 months before and tried to commit suicide with carbon monoxide poisoning 2 months before, needing treatment in a hyperbaric chamber, with a good recovery. He had no history of other comorbidities and an unremarkable family history. At the first neurologic evaluation at our department, he presented with marked apathy and mutism, pseudobulbar affect, marked frontal release signs, generalized rigidity with

hypomimia, global hyperreflexia with a left extensor plantar reflex, infrequent generalized myoclonus, and gait apraxia. Basic laboratory tests including electrolytes, complete blood count, carboxyhemoglobin, and liver function tests and CT scan had normal results. He had been medicated with lorazepam and mirtazapine but abandoned medication 2 weeks after the suicide attempt. He denied drug use or substantial alcohol consumption.

Questions for consideration:

1. What is the differential diagnosis for subacute cognitive and motor changes?
2. What are the initial steps in evaluation?

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SECTION 2

Given the rapid and progressive worsening, both motor and cognitive, prion diseases (either sporadic or familial: Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome, and fatal familial insomnia) would be on top of the differential diagnosis list. However, there is not a pathognomonic biomarker for these conditions (besides, of course, the genetic testing for the familial conditions) and other conditions must be ruled out first. In a subacute presentation of a multidomain decline, encephalitis (either of infectious or inflammatory etiology, namely paraneoplastic) must always be considered, as it is treatable. The presence of seizures, headache, fever, or neck rigidity would argue for these, but they were absent.

Also, an uncommonly rapid progression of the typical degenerative disorders, most of the time a process that had been going unnoticed, must be considered, as these are common final diagnoses of rapidly progressive dementias. Among them, corticobasal degeneration, progressive supranuclear palsy, and Lewy body dementia can account for both parkinsonian and cognitive features, with the latter having frequent rapid declines. The prominent loss of speech could also point out primary progressive aphasia, occurring both in Alzheimer disease and frontotemporal dementia. However, the predominance of frontal lobe dysfunction manifestations makes frontotemporal dementia and progressive supranuclear palsy the most probable of this group. Of note, the precedent history of depression is common in neurodegenerative processes and psychiatric changes can also occur in a prodromal phase of autoimmune or paraneoplastic encephalitis.

Psychiatric disorders should be a diagnosis of exclusion, but, given the recent history of the patient, must be kept in mind. Also, because of the history of recent depression, occult alcohol abuse complicated by

Marchiafava-Bignami or Wernicke syndromes should be taken into account. Some other hypotheses should not be forgotten, although a normal CT scan makes them very unlikely: normal pressure hydrocephalus (due to the presence of the triad of cognitive decline, gait changes, and bladder control loss, this would be a valid hypothesis and may be treatable); CNS neoplasms and vasculitis, leukoencephalopathies, and vascular dementia (multi or strategic infarcts) could also present with a similar history and have specific treatment.

The initial workup would include intracranial imaging to exclude mass lesion or hemorrhagic or ischemic changes. MRI can further support the diagnosis of encephalitis or prion disease or reveal focal atrophic processes, typical of certain degenerative processes. Lumbar puncture should be performed to exclude CNS infection and to search for inflammatory signs. CSF analysis for 14-3-3 protein can support the diagnosis of prion diseases and Alzheimer biomarkers can support the diagnosis of this disorder. EEG could also point to encephalitis or prion diseases. Electrolyte abnormalities, HIV, syphilis, Lyme disease, hyperparathyroidism, and Hashimoto thyroiditis must always be considered.

CSF was normal (proteins: 34 mg/dL; white blood cells: 0/mm³; red blood cells: 0/mm³; glycosis: 51 mg/dL; CSF:blood ratio: 0.67). Alzheimer CSF biomarkers revealed decreased β -amyloid (255.6 pg/L) and increased tau (1198.9 pg/L) and phosphorylated tau (16.3 pg/L). 14-3-3 Protein was negative. EEG showed a general slowing without periodic activity. The MRI (3T) showed diffuse change in the supratentorial white matter signal, not involving the basal ganglia (figure).

Questions for consideration:

1. How can one interpret the CSF and EEG findings?
2. Does MRI change the differential diagnosis?

MRI shows diffuse supratentorial white matter involvement (B), with relatively preserved basal ganglia (A). The diffuse hyperintensity was evident on diffusion-weighted imaging (C) but not on apparent diffusion coefficient map (D).

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SECTION 3

With such rapid progress, one would expect changes in the CSF analysis in a case of infectious or inflammatory encephalitis. 14-3-3 Protein was negative. The absence of EEG findings specific to prion diseases or encephalitis also speaks against these. Alzheimer CSF biomarkers suggest Alzheimer disease, but it is rare to find values of tau and phosphorylated tau so high in that setting and parkinsonian features with such a sudden onset are very atypical. The coexistence of those features with cognitive decline might point to an atypical parkinsonism syndrome. Given the symmetry, corticobasal degeneration is highly unlikely, whereas progressive supranuclear palsy can present with a frontal lobe syndrome and symmetric parkinsonian features. In addition, Lewy body dementia can also manifest with cognitive decline and parkinsonian features, but loss of speech is rare. On the other hand, frontotemporal dementia usually unfolds with language and behavior changes and, in some pathologic subsets, it can also present with parkinsonian features. However, rapid decline is unusual in these disorders.

MRI did not show atrophy (focal or generalized) or mesial temporal lobe (suggestive of limbic encephalitis) or other gray matter enhancement (suggestive of prion disease, in which changes are best seen in diffusion-weighted imaging sequences). Yet it revealed white matter changes, not usual in those pure

degenerative diseases. Cerebral amyloid angiopathy is improbable as signs of hemorrhage, like cortical superficial siderosis or microbleeds, are absent. Leukodystrophies, such as adult-onset leukoencephalopathy with axonal spheroids, are at this point a possibility. An MRI-based approach¹ would prioritize L-2-hydroxyglutaric aciduria, Kearns-Sayre syndrome, propionic acidemia, Canavan disease, and urea cycle defects based on the white matter involvement pattern. However, the rapidly progressive presentation, the age of the patient, the absence of involvement of brainstem, cerebellum, and basal ganglia, and the absence of involvement of other organs or of family history make leukodystrophies highly unlikely. Progressive multifocal encephalopathy was not considered as the patient was HIV-negative and there were no other risk factors. Although infectious processes are not probable, Whipple disease can present as a rapidly progressive dementia and CSF can be normal. Other toxic leukoencephalopathies were excluded by the absence of exposure (namely, cocaine or other drugs of abuse, immunosuppressive, antineoplastic, or antimicrobial drugs). Also, the presentation and MRI pattern were not suggestive of posterior reversible encephalopathy syndrome and the patient had no history of precipitating factors.

Question for consideration:

1. How can we get to a final diagnosis?

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SECTION 4

A neurodegenerative disorder in a 55-year-old working man going unnoticed seems unlikely. Family history could give additional data to achieve a diagnosis and genetic testing could go a long way. In the absence of an answer and continued worsening, brain biopsy can be enlightening. PET imaging, either DaTSCAN for the atypical parkinsonian syndromes or with amyloid tracers for Alzheimer disease, could also support these diagnoses.

Also, evolution of the clinical picture can give additional information to get to a final diagnosis. If a prion disease was the cause of the clinical picture, the condition would keep worsening and the MRI, CSF, or EEG would reveal specific changes, as would happen in infectious or paraneoplastic encephalitis. Improvement with treatment could also give further clues. Response to thiamin reposition or corticosteroids can point to thiamine deficiency or inflammatory processes. Alzheimer disease, frontotemporal dementia, Lewy body dementia, or progressive supranuclear palsy presenting as a rapidly progressive dementia may have secondary contributing factors to this decline, and patients may stabilize or improve after treatment of that insult.

In the end, we came to the diagnosis of delayed encephalopathy after carbon monoxide poisoning. This was based on the clinical history, presentation, neuroimaging findings, and evolution. The patient recovered well, having a Montreal Cognitive Assessment score of 26 at 6 months after discharge and no relevant motor changes.

DISCUSSION Carbon monoxide poisoning is a frequent cause of intoxication² and one of the most frequent suicide methods.³ Acute poisoning can present with headache, nausea and vomiting, transitory loss of consciousness, altered mental status, and coma.^{4,5} If treated with hyperbaric oxygen therapy, mortality is low.⁵

Delayed sequelae happen in 3%–40% of the intoxicated patients 2 days to 4 weeks after the exposition.^{6,7} Diverse manifestations can occur: gait and motor disturbances, Parkinson-like syndromes, myoclonus, ataxia, chorea, fecal and urinary incontinence, peripheral neuropathies, recurrent headache, epilepsy, and cognitive impairment (involving memory, language, and praxis).^{6,7} Psychiatric sequelae can also occur.^{6,7} MRI can show hyperintensities in globus pallidus in half of the patients and in the white matter in most patients.⁸ There is no approved treatment for the delayed sequelae.⁴ Symptomatic treatment with dopaminergic drugs helps with the parkinsonian symptoms.

The underlying mechanism is unclear. In the acute phase, the damage occurs mostly in the iron-

rich basal nuclei, while in delayed toxicity, the damage occurs mainly in the white matter. The hypothesis of damage being caused by free oxygen radicals has been gaining some consistency.⁹ Lipid peroxidation seems the underlying mechanism of this syndrome.^{5,10}

A good outcome is a possibility: 60%–75% of patients recover during the first year.⁶ Twenty-five percent can remain with persistent dementia or parkinsonism.⁴ Cardiorespiratory arrest and persistent white matter or globus pallidus hyperintensities have been associated with worse prognosis.¹¹

The present case highlights the importance of thinking of other diagnoses when approaching a patient with a rapidly progressing dementia. Some treatable conditions exist and outcome may not always be disastrous. Delayed sequelae following carbon monoxide poisoning should be considered whenever a history of exposure to the gas is a possibility.

AUTHOR CONTRIBUTIONS

Miguel Tábuas-Pereira: study concept and design, acquisition of data, analysis and interpretation, drafting/revising the manuscript for content. Isabel Santana: revising the manuscript for content. Gustavo Cordeiro Santo: acquisition of data, analysis and interpretation of data, revising the manuscript for content.

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