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IM - CASE RECORD

The clinical eye

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Initial presentation

Dr. Elia

In September 2011, a 35-year-old woman was admitted to our hospital with abdominal pain, nausea and vomiting. She reported a history of chronic weight loss, vomiting and diarrhea since adolescence. Her symptoms had been worsening over the past few months, with the onset of leg swelling and intermittent paresthesia affecting both feet. The patient denied other symptoms such as fever, shortness of breath, night sweats or joint pain. She was not on any medication and her family history was unremarkable. She did not report any recent travels. She had recently undergone psychiatric consultation on the suspicion of anorexia nervosa.

On arrival the patient appeared cachectic (body mass index: 14 kg/m^2). All vital signs were normal. On examination, the abdomen was distended and mildly tender with reduced bowel sounds. Moderate swelling of both ankles was observed. Neurological examination showed generalized muscle weakness. Psychiatric assessment was normal. No rash, lymphadenopathy or joint swelling was detected. Routine blood tests revealed mild microcytic anemia and low albumin levels.

Further work-up

Dr. Elia

In consideration of the abdominal pain, an abdominal CT scan (Fig. 1) was performed showing distended bowel loops without signs of occlusion, massive gastric dilatation and urinary retention with a markedly enlarged bladder.

Our initial work-up included a wide range of diagnostic tests aiming at investigating the cause of the GI symptoms. On stool examination, undigested meat fibers along with high levels of fat and sugars were detected, confirming malabsorption. Search for ova and parasites, stool culture, Clostridium difficile toxin screen, calprotectin and fecal elastase determinations were all negative.

Esophagogastroduodenoscopy was performed, revealing edema of the gastric mucosa and a hypotonic and dilated stomach. Small-bowel biopsy specimens were negative for Whipple and celiac disease, showing only signs of chronic inflammation.

Vitamin B12, thyroid-stimulating hormone (TSH), antigliadin antibodies, human immunodeficiency virus (HIV) antibodies, the quantiferon test and screening for autoimmunity were all normal.

Due to the complaint of paresthesia, an electroneuronography (ENG) was ordered, showing bilateral sensorimotor demyelinating polyneuropathy in both the lower and upper extremities.

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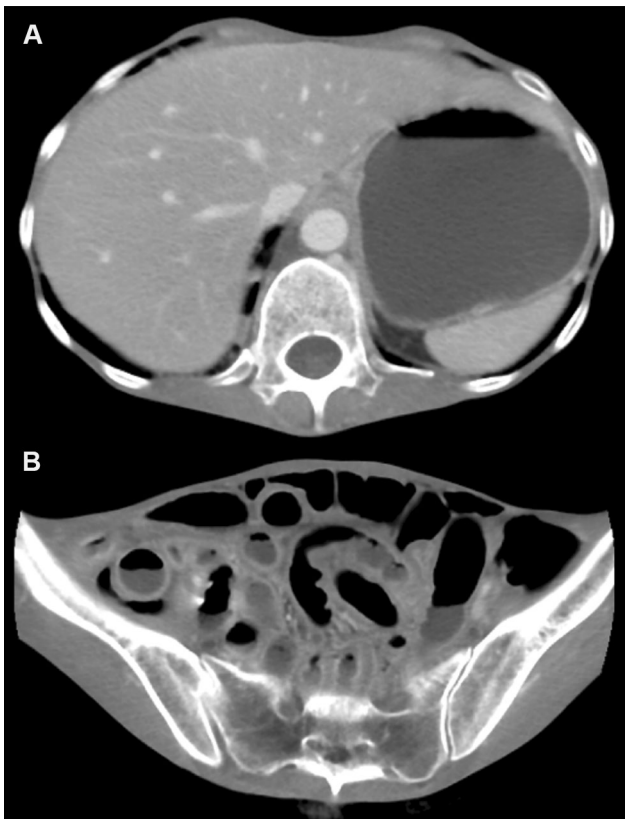

Fig. 1 Abdominal CT scan showing massive gastric dilatation (**a**) and distended bowel loops (**b**)

Differential diagnosis

Dr. Covella, Dr. Aprà

The main complaints of the patient were non-specific long-standing gastrointestinal symptoms, specifically abdominal pain, severe weight loss and chronic diarrhea. The results of our initial work-up were consistent with severe malnutrition secondary to malabsorption, in the absence of a clear cause. At this stage of the diagnostic process, dysmotility was not considered. Gastroparesis and diffuse dilatation of the small bowel, as shown by the CT scan, were initially interpreted as a result of malabsorption and malnutrition. In hindsight, both of these should have raised the suspicion of dysmotility as the primary cause of the abdominal symptoms and malabsorption.

Sensorimotor polyneuropathy in this setting was interpreted as secondary to the severe malnutrition. In this case, some clinical signs had not been given due weight. When neuropathy is due to nutritional deficiencies, axonal involvement is more typically observed rather than demyelination as in this patient. Most commonly, chronic demyelinating neuropathies are either hereditary, inflammatory (i.e., Chronic Inflammatory Demyelinating Polyneuropathy CIDP) or secondary to paraproteinemia [1, 2].

After a thorough initial assessment, the clinical picture, according to our interpretation, was consistent with cachexia due to malabsorption associated with severe gastrointestinal dysmotility and demyelinating polyneuropathy, in the absence of an identifiable cause.

Disease progression and final diagnosis

Dr. Aprà, Dr. Perna

During hospitalization, the clinical condition remained mostly unchanged. Because of the severely compromised nutritional status, supportive treatment with parenteral nutrition was started.

During the 3rd week of hospitalization, one of the physicians noted a facial similarity between the patient and another woman recently admitted for myasthenic crisis, namely, a drooping upper eyelid. When queried, the patient and relatives reported that the suspected eyelid ptosis had been present since adolescence. However, this clinical sign had never been reported in her previous medical records.

A revision of the entire case was made in light of this finding, with a stronger emphasis on neurological signs and on the hypothesis that malabsorption might be due to gastrointestinal dysmotility. A PubMed search with keys "gastrointestinal dysmotility" and "ptosis" revealed 30 entries, all but one referring to a single clinical entity: mitochondrial neuro-gastrointestinal encephalomyopathy (MNGIE).

Based on the combination of malabsorption caused by gastrointestinal dysmotility, neurological abnormalities such as ptosis, and peripheral neuropathy, MNGIE was then hypothesized. An MRI study of the brain was obtained with evidence of diffuse white matter disease compatible with MNGIE-related leukoencephalopathy (Fig. 2). Eventually, direct sequencing of the thymidine phosphorylase gene (TYMP) confirmed the diagnosis.

Our patient has been followed by the nutrition service, and chronically supported by parenteral nutrition. Stem cell transplantation was not considered a viable option in consideration of her general conditions. Three years later the patient died of pneumonia and respiratory failure.

Discussion

Dr. Covella

The severe form of malabsorption with gastrointestinal dysmotility encountered in this patient can be described as

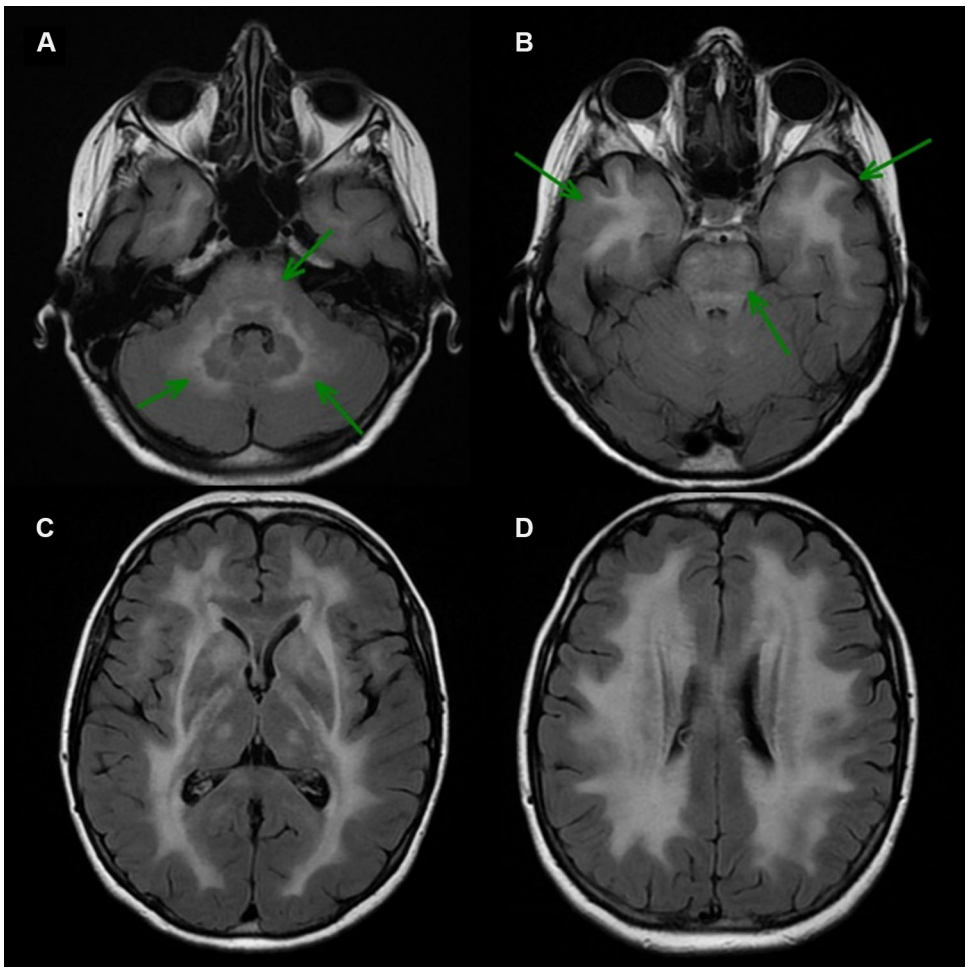

Fig. 2 MRI FLAIR sequences showing symmetric changes in white matter signal affecting the cerebellum (**a**), pons (**b**) and supratentorial regions (**c**, **d**)

Chronic Intestinal Pseudo-Obstruction (CIPO), a severe functional digestive syndrome characterized by persistent inability of the bowel to propel luminal contents, in the absence of mechanical obstruction [3]. Both clinical and radiological presentations mimic mechanical ileus: abdominal pain and distension during sub-occlusive episodes, with dilated bowel loops and air-fluid levels; either paradoxical or bacterial overgrowth diarrhea, and chronically inadequate oral intake leading to frank malnutrition. CIPO can occur secondary to several systemic conditions including neurological, endocrine, autoimmune, infectious and neoplastic disorders; primary forms of CIPO can be sporadic or familial [4].

In this patient, CIPO co-existed with demyelinating neuropathy and blepharoptosis, raising the hypothesis of MNGIE. MNGIE, although a mitochondrial disease, is characterized by nuclear inheritance with an autosomal recessive transmission. A loss-of-function mutation in the thymidine phosphorylase gene (*TYMP*) results in abnormally high thymidine and deoxyuridine plasma and tissue levels causing instability of mitochondrial DNA and dysfunction of the mitochondrial respiratory chain [5]. Gastrointestinal and neurological symptoms dominate the clinical picture of MNGIE, with the most frequent features being severe gastrointestinal dysmotility eventually leading to malnutrition, leukoencephalopathy (shown on MRI in all cases and often asymptomatic), progressive external ophthalmoplegia, ptosis, and polyneuropathy [6, 7]. MNGIE shows a slowly progressive evolution, with onset typically occurring during the first three decades of life, and leading to death in most patients by the age of 40. Infections—most commonly aspiration pneumonia—represent the most frequent cause of death [7]. The original clinical diagnostic criteria [2] and common additional features of MNGIE are reported in Table 1.

Diagnostic tests for MNGIE include urine thymidine and deoxyuridine assays, which show abnormally high values of these metabolites and quantitative measurement of thymidine phosphorylase activity in the buffy coat [8]. Definitive diagnosis can be obtained by sequencing the *TYMP* gene on peripheral blood-extracted nuclear DNA.

No effective pharmacological treatment is currently available for the management of patients with MNGIE [9]. Replacement of thymidine phosphorylase activity by

Table 1 Clinical diagnostic criteria and common features of MNGIE [2]

Clinical diagnostic criteria of MNGIE
Low body weight
Extraocular muscle involvement: ptosis and/or ophthalmoparesis
Gastrointestinal dysmotility (chronic diarrhea and/or pseudo obstruction)
Sensorimotor peripheral neuropathy
Additional common findings
Leukoencephalopathy
Early onset sensorineural hearing loss
Hepatic cirrhosis
Hypogonadism
Anemia

means of allogeneic stem cell transplantation or liver transplantation has shown promising results in a small number of selected patients, despite several challenges and high mortality rates [10, 11].

The very low prevalence of MNGIE, the lack of familiarity with this condition, and the possibility of atypical presentations account for the reported delay in the diagnosis [12]. More frequent causes of malnutrition or chronic diarrhea, such as anorexia nervosa and irritable bowel syndrome, represent common misdiagnoses for MNGIE [7]. In cases where gastrointestinal involvement is less prominent, MNGIE-associated polyneuropathy can mimic other forms of neuropathy such as Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) [13].

In this case we described, a correct diagnosis was obtained only several years after the onset of MNGIE, and it was in part serendipitous, thanks to the recent hospitalization of another patient with blepharoptosis that allowed the clinicians to focus on this important clinical sign.

This diagnostic delay represents a major issue, because novel therapeutic options such as liver transplantation and allogenic hematopoietic stem cell transplantation can correct the biochemical imbalance, but do not target irreversible tissue damage when this has already occurred.

Conclusion

Dr. Elia, Dr. Aprà, Prof. Crupi

This clinical case offers a number of interesting features, and at the same time, it raises important questions concerning clinical reasoning and the modalities used by physicians to reach (or miss) a diagnosis. We report the case of a patient with long-standing, chronic malabsorption that was left with no diagnostic explanation for approximately 20 years. The final diagnosis is an extremely rare genetic disorder carrying a dismal prognosis. Is the rarity of this condition enough to explain the diagnostic delay? What type of clinical reasoning was used by the physicians who were involved in the patient's care during all these years, and what prevented them from reaching the correct diagnosis? These questions are further discussed in a Clinical Note in this Journal [14].

Compliance with ethical standards

Conflict of interest Authors declare that they have no conflict of interests.

Statement of human and animal rights All procedures performed in the present study involving human being were in accordance with the ethical standards of the institutional and national research committee and with 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

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