CASE REPORT

Pure motor axonal neuropathy triggered by antituberculous therapy in an undiagnosed case of acute intermittent porphyria

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SUMMARY

A man aged 22 years misdiagnosed as suffering from recurrent abdominal tuberculosis, in view of recurrent abdominal pain was treated for abdominal tuberculosis in the past. The patient was prescribed antituberculous therapy. 2 months after starting treatment, he developed progressive weakness of all 4 limbs. Electrodiagnostic examination revealed an acute severe motor axonal neuropathy. Further workup revealed elevated porphyrin precursors in urine.

BACKGROUND

Acute intermittent porphyria (AIP) presents with a diverse group of symptoms including neurological complications. Early recognition demands a high index of clinical suspicion as delayed diagnosis and treatment can result in a poor neurological outcome.¹

Porphyrias are a group of rare hereditary disorders caused by defects in haem synthesis.² AIP is one of eight types of porphyrias. This is an autosomal dominant disorder with a defect in the enzyme *ALA deaminase*, which is involved in metabolism of haem.³ The attacks of AIP are often precipitated by prolonged fasting or low caloric intake, alcoholic binge, nicotine abuse, stress secondary to concurrent infections, surgery, psychological factors and myriad of prescription drugs including antituberculosis therapy (ATT).⁴ Early diagnosis and treatment is critical for a good clinical outcome.¹ Some of the first-line ATT drugs are known to cause direct peripheral neuropathy as well as precipitate AIP.^{5,6} The incidence of ATT triggering 'porphyric neuropathy' is unknown. Therefore, the development of neuropathy in a patient taking ATT should be worked up for potentially treatable aetiologies, especially in atypical cases.

CASE PRESENTATION

A man aged 22 years presented to us with symptoms of bilateral progressive limb weakness for 6 weeks and shortness of breath for 10 days. Weakness started with difficulty in lifting his arms to wear his shirt, followed by difficulty gripping things with his hands after 1 week. Later, he developed difficulty standing up from a sitting position and subsequently was unable to walk within 4 weeks of symptom onset. There were no visual, sensory or bladder symptoms.

The patient was treated for presumed abdominal tuberculosis 12 years ago. Rationale behind that diagnosis, details of workup performed and treatment provided were not known to the patient. Over the past 3–4 years, he started reporting of episodic abdominal pain. There was no history of associated fever, vomiting, loose stools, night sweats and weight loss. The patient was investigated for his symptoms elsewhere. Work up included CT scan of the abdomen showing borderline enlarged mesenteric lymph nodes and ileal loop thickening, and oesophagogastrroduodenoscopy with laparoscopic biopsy of the mesenteric lymph nodes, revealing non-specific inflammatory changes. The patient was presumed to have recurrence of abdominal tuberculosis and subsequently first-line antituberculous therapy (ATT) was started 2 months prior to presentation to our hospital.

The examination revealed a young man with average height and built who had difficulty breathing. He had generalised muscle wasting and hypotonia. Power was 0/5 proximally and 1/5 distally in all four limbs, according to medical research council (MRC) grading. Muscle stretch reflexes were absent in all limbs with bilateral downgoing plantar responses. The sensory examination was normal. Over the course of the next few days, the patient had progressive respiratory distress requiring mechanical ventilation.

INVESTIGATIONS

MRI of the brain and cervical spine were unremarkable. Nerve conduction studies (NCS) and electromyography (EMG) revealed normal sensory responses. There was severe symmetric reduction of all motor amplitudes in the upper and lower extremities. Complete absence of recruitment of voluntary motor unit action potentials was seen in most proximal and distal muscles with recruitment of large amplitude/broad duration motor units in some distal lower extremity muscles. Severe active denervation was seen in all muscles examined, affecting proximal and distal muscles equally, including the diaphragm. Keeping in mind, the differentials for pure motor axonal neuropathy, further workup was recommended. Twenty-four-hour urinary porphobilinogen and amino-levulinic acid (ALA) were found to be high, 5.9 mg/24 hours (range 0–3.4 mg/24 hours) and 22 mg/24 hours (range 1.5–7.5 mg/24 hours), respectively. Serum lead levels were within normal limits. Hence, the diagnosis of AIP was made.

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TREATMENT

Owing to non-availability of haematin, the patient was managed with intravenous glucose with subsequent improvement in episodic abdominal pain.

OUTCOME AND FOLLOW-UP

The patient was gradually weaned off from mechanical ventilation over a period of 17 days. His limb weakness did not improve during hospitalisation and he went home with a modified Rankin scale score of 4 after an almost month long hospital stay. On telephonic follow-up at 6 months, the patient was able to ambulate with help of two family members.

DISCUSSION

The prevalence of symptomatic AIP is 2–3 cases per 100 000 persons per year.⁴ The most common presenting features include intermittent episodes of abdominal pain followed by nausea, vomiting and severe constipation with minimal objective findings.³ The observed precipitants of AIP, either directly or indirectly via induction of cytochrome p450 or haem oxygenase, stimulate D-amino-levulinic acid (dALA) synthetase activity which subsequently results in an increased biosynthesis of haem and various intermediate porphyrins.³

The patient's long-standing history of episodic abdominal pain was likely a manifestation of underlying AIP, which was overlooked. The previous attack which precipitated severe pure motor axonopathy was presumed to be triggered by the use of first-line antituberculous treatment. All of the first-line ATT drugs are known precipitants of AIP except ethambutol. Rifampicin is a cytochrome p450 inducer, hence depletes haem in the liver, which can potentially trigger attacks of AIP.⁶ Isoniazid, on the contrary, may trigger AIP by irreversible inactivation of cytochrome p450 and resultant increase in haem biosynthesis through a complex mechanism.⁷ The porphyrogenicity of pyrazinamide has been attributed to its ability of inducing ALA synthetase activity.^{6, 8} Lists of potentially safe and unsafe drugs are available over the internet (eg, <http://www.porphyrria-europe.com> and <http://www.uct.ac.za/depts/porphyria>) and it is important to consult references before initiating any treatment.⁹ Peripheral neuropathy in AIP is usually triggered by the use of porphyrogenic drugs during attacks.³ Motor nerves are affected more severely than sensory nerves. Differentials for acute, motor predominant, axonal neuropathies include acute motor axonal variant of Guillain-Barre syndrome, vasculitis, toxicity (eg, lead, amiodarone) and porphyria.¹⁰ In the latter, characteristically, weakness starts in proximal musculature and usually involves upper limbs first followed by the lower limbs.³ The patient also showed this typical pattern of muscular weakness. Causes for proximal more than distal neuropathies are limited, including porphyria, diabetic plexopathy and sometimes polyradiculopathies. In severe porphyria cases, facial paralysis, dysphagia and ocular palsies may be encountered.¹⁰ Tendon reflexes are diminished or absent, but in some patients, ankle jerks may be retained;¹¹ however, this was not seen in our case likely due to the severity of nerve damage. Patients in whom diagnosis and treatment is delayed, respiratory failure may ensue.¹² Other neurological manifestations of AIP include autonomic dysfunction, neuropsychiatric manifestations and rarely seizures.³

NCS in patients of AIP with neuropathy reveals low motor amplitudes with relatively preserved conduction velocities. Sensory amplitudes may be normal or slightly reduced. EMG obtained early on in the course of neuropathy secondary to AIP

reveals poor recruitment of motor units with denervation changes appearing later on in the disease course.¹⁰ Our patient's electrodiagnostic examination was consistent with these findings. Histopathological studies have shown axonal degeneration and preferential loss of large myelinated axons in these patients¹⁰ likely due to neurotoxic effects of elevated levels of one or more haem pathway intermediates, ALA being the most probable candidate.³ Recovery from AIP neuropathy depends on degree of axonal degeneration. It occurs slowly over several months and is often incomplete.¹⁰ Close follow-up is important to avoid or promptly treat recurrent attacks because these are detrimental for chances of a good functional outcome. Moreover, once the diagnosis is made, DNA analysis and genetic counselling should be offered to screen family members in order to prevent acute attacks in those with latent disease.²

Learning points

- ▶ Early diagnosis of acute intermittent porphyria warrants a high index of clinical suspicion.
- ▶ Most common neurological complication is pure motor axonopathy causing symmetrical muscular weakness starting from upper limbs followed by lower limbs and involvement of proximal muscle groups preceding that of distal musculature.
- ▶ Prompt diagnosis and treatment is critical for a good neurological outcome.

Contributors Case was seen by MUZB and SK. The idea to report this case was put forward by MUZB and was discussed with SK who gave design for the case report. Then, HH and MUZB reviewed literature and wrote the initial draft. This was reviewed by SK and advised suggestions and correction which were performed by MUZB and HH. This was repeated at least three times and this case report was completed. All of us participated in case writing.

Competing interests None declared.

Patient consent Obtained.

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