

Axonal neuropathy with prolonged sulphasalazine use

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ABSTRACT

Sulphasalazine, one of the 5-amino-salicylates, is widely used for the treatment of inflammatory bowel diseases and arthritis. Among the reported adverse effects are blood dyscrasias and hepatic failure. Peripheral neuropathy has been reported as a rare adverse drug reaction to sulphasalazine. Most reported patients developed symptoms several weeks after onset of treatment. We describe a patient with an axonal polyneuropathy that occurred after two years of treatment with sulphasalazine.

Introduction

Sulphasalazine (sulphasalazopyrine) is prescribed for the treatment of inflammatory bowel diseases and rheumatoid arthritis. Its immunomodulatory action is thought to be multifactorial. It is metabolized by intestinal flora to 5-aminosalicylic acid (5-ASA) and sulphapyridine (1). Reported serious adverse reactions include blood dyscrasias, hepatitis and hepatic failure (2). Peripheral neuropathy has been reported as a rare, dose-related adverse reaction to sulphasalazine. The interval between onset of treatment and symptoms is reported to be several weeks (3; 4) to one year (5). We report a patient with an axonal polyneuropathy that occurred after two years of treatment with sulphasalazine.

Case report

A 21-year-old woman had a 4-year history of progressive destructive changes in the metatarsophalangeal joints of both feet and the proximal interphalangeal joint of the left hand. She was HLA-B27 positive and had a family history of spondylarthropathy. There was no history of diabetes, alcohol or hereditary neuropathy. The cause of this erosive oligoarthritis was thought to be either spondylarthropathy or rheumatoid factor negative rheumatoid arthritis. Because of progressing pain and erosive disease of the feet, we started sulphasalazine one gram twice daily as a disease-modifying antirheumatic agent. This resulted in clinical remission and no progressive erosions, and the medication was subsequently discontinued by the patient. However,

after 6 months, arthritis of the feet re-occurred and sulphasalazine was resumed. Again, a significant improvement of the symptoms was observed. One year after sulphasalazine was resumed, increasing pain and increasing hallux valgus of both feet occurred and progressive destruction of the feet was observed. Apart from various non-steroidal anti-inflammatory drugs to treat the pain in her feet, she did not use any other drugs. The patient presented at our neurologic outpatient clinic with numbness and minor paresthesias of both feet of five months duration. She had difficulty controlling the accelerator pedal of her car and lifting objects with her arms. On examination, her feet showed hallux valgus and deformity of the other toes as well. Her left foot was warm and oedematous. On the sole it had a painless ulceration, which had been there for more than eight weeks. Other joints showed no abnormalities. Neurological examination revealed no abnormalities of cranial nerves and motor function. Achilles tendon reflexes were absent, plantar responses were normal. There was bilateral stocking-type hypaesthesia in the legs with decreased vibration sensation. Laboratory investigations were normal for erythrocyte sedimentation rate, haemoglobin, trombocytes, glucose, liver enzymes, creatinin, thyroid function, vitamin B1, vitamin B12, paraprotein and Borrelia serology. Immunologic parameters revealed a borderline positive antinuclear antibody but antibodies against DNA and extractable nuclear antigens (anti-ENA) were negative as were anti-cyclic citrullinated peptide (anti-CCP) antibodies and rheumatoid factor. Electrophysiological studies demonstrated slowing of the left sural nerve and sensory ulnar nerve action potential with low amplitude on both sides. Motor tibial and peroneal nerve action potentials were slow and of low amplitude. Electromyography revealed polyphasic motor unit action potentials in the right biceps brachii and right tibial anterior muscles. We concluded that the patient was suffering from an axonal polyneuropathy due to sulphasalazine, which we discontinued. We started methotrexate the following month, which

Competing interests: none declared.

was discontinued by the patient after one month. She wore a cast of the left lower leg to stabilise her foot. During the next four months there was complete recovery of sensation in the feet. She noticed the warmth of her cast and later felt the shoes she wore. Nerve conduction studies were unchanged when compared to 7 months earlier. No rechallenge of sulphasalazine was performed for ethical reasons.

Discussion

We diagnosed the neuropathy in our patient as toxic, due to sulphasalazine. We think that other possible causes, including an extra-articular manifestation of rheumatoid arthritis, infective polyneuritis or vasculitic neuropathy are unlikely because of the absence of other positive signs for such diagnoses and the resolution of symptoms after withdrawal of sulphasalazine. We do not think that the absence of recovery of electrophysiological measures of nerve conduction after sulphasalazine discontinuation argues against our conclusion, since it is well known from other toxic neuropathies that electrophysiological recovery may lag behind clinical recovery or will not appear at all (6).

Reports of peripheral neurotoxicity secondary to sulphasalazine are scarce. One reported patient developed a neurotoxic reaction that consisted of confusion, hallucinations and impaired sensation in the legs, which improved in several weeks after discontinuation of sulphasalazine (3). A severe sensorimotor neuropathy with incomplete recovery has been reported in another patient treated with sulphasalazine one gram four times daily because of extensive colitis (4).

The above mentioned patients developed symptoms several weeks after institution of therapy. We found one reported case with delayed neurotoxicity of sulphasalazine. A 52-year-old woman, who had been treated with sulphasalazine because of colitis ulcerosa

for one year, began to experience pain and dysesthesias in the legs. She was diagnosed with toxic sensory neuropathy. Sulphasalazine was discontinued and her symptoms resolved. The dysesthesias reappeared two years after she had restarted sulphasalazine (5).

Toxicity of the central nervous system related to sulphasalazine has also been described. Besides common side effects such as headache and dizziness, there are various reports of encephalopathy, seizures, dysphasia and ototoxicity. Often, this toxicity concurs with hepatotoxicity (7-12).

How sulphasalazine affects the nervous system is unknown. Most authors hypothesize that an accumulation of the metabolite sulphapyridine in the serum is involved in creating toxicity (4, 5). Various adverse effects have been associated with a "slow acetylator" phenotype, meaning they have low activity of the enzyme n-acetyl transferase that acetylates sulphapyridine so it can be excreted in the urine (12-14).

However, one patient was described with a sensorimotor neuropathy due to mesalazine treatment, indicating a toxic effect dependent of the 5-ASA moiety (15). The elimination half-life of the acetylated 5-ASA is comparable to that of sulphapyridine in fast-acetylators (16).

The long time interval between onset of therapy and symptoms of neurotoxicity in the patient described in the literature (5) and our patient suggests a different mechanism than the patients with toxic effects after several weeks. Most neurotoxic effects of the central nervous system also occur after several weeks, with the exception of one reported case. After treatment with sulphasalazine 2 grams daily for two years, this patient developed headaches, seizures and confusion (8). Which component of sulphasalazine is responsible for this late neurotoxicity, remains controversial.

We have described a patient with an axonal neuropathy two years after treatment with sulphasalazine. We want to

emphasize that neurotoxicity can also develop after prolonged use.

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