Axonal Neuropathy as a Rare Side Effect of Sulfasalazine
Jamila Essouri*, Amina Mounir, Fatima Ezzahra Abourazzak and Taoufik Harzy
Rheumatology Department, Medical School, Sidi Mohammed Ibn Abdellah University, Hassan II University Hospital, Fez, Morocco

Abstract
Sulfasalazine, one of the 5-aminosalicylates, is widely used for the treatment of inflammatory bowel diseases and arthritis. Beside its classic adverse effects like blood dyscrasias and hepatic failure, peripheral neuropathy has been reported as a rare adverse drug reaction to sulfasalazine. The mechanism of this neurotoxicity is unknown tell nowadays. We report a case of neurotoxicity that occurs after prolonged use of sulfasalazine. Previously, reported cases of neurotoxicity have not shown improvement of electric signs in nerve conduction study after stopping treatment.

Keywords: Sulfasalazine; Neurotoxicity; Crohn's disease; Polyneuropathy

Introduction
The sulfasalazine (SSZ) is principally administered against inflammatory mediated disorders such as Crohn’s disease and ulcerative colitis; moreover, it is indicated in peripheral spondyloarthritides and Rheumatoid arthritis, thanks to its immunomodulator effect. Among the reported adverse effects of SSZ we find blood dyscrasias and hepatic failure. Peripheral neuropathy has been reported as rare adverse drug reaction [1,2]. This paper describes a patient with an axonal polyneuropathy due to prolonged SSZ use.

Case Report
A 53 year old woman had a 7-year clinical history of psoriatic arthritis, she has never suffered from diabetes, alcohol, exposure to toxic or hereditary neuropathy. We started methotrexate early in the disease, but after 2 months it was discontinued because of gastrointestinal side-effects; then we introduced SSZ one gram twice daily; This resulted in clinical remission. For three years she complained of hands and feet tingling (after 4 years of use of SSZ). Rheumatologic exam found a deformity of hands and feet related to joint destruction.

Neurological examination, that included exam of sensory and motor system, of deep tendon reflexes and exam of cerebellum, was normal. Routine laboratory investigations were normal: haemoglobin=11 g/L, trombocytes=217000/mm³, leukocytes=4870/mm³, glucose=0.89 mg/l, liver enzymes GOT=14 GPT=11, creatinin=8, TSHus=0.41 µU/ml, vitamin B1, vitamin B12, hepatic viral serology (HVB, HVC, HIV), antinuclear antibody, antibodies anti DNA and extractable nuclear antigens (anti-ENA) were negative as were anticyclic citrullinated peptide (anti-CCP) antibodies, anti neutrophil cytoplasmatic antibodies (ANCA) and rheumatoid factor. Nerve conduction studies and electromyography objectified lower motor amplitudes at four members and low amplitude of sensory ulnar nerve on both sides and abolition of the sensory response to the lower limbs ; it was an axonal sensitivomotor polyneuropathy (Table 1). Sulfasalazine was stopped; then, it has been a gradual improvement of tingling. Electromyography, after 6 months, objectified axonal sensitivomotor polyneuropathy slightly asymmetrical at upper limbs and improvement of sensory impairment at lower limbs (Table 2).

Discussion
We diagnosed the neuropathy in our patient as toxic due to sulfasalazine. We think that other possible causes, including an extra-articular manifestation of psoriatic arthritis, infective polyneuritis or vasculitic neuropathy are unlikely because of the absence of other positive signs for such diagnoses and the clinical and electrophysiological improvement after withdrawal of sulfasalazine, even if the reintroduction test was not done for ethical reason. The cases reported in the literature of peripheral neurotoxicity due to sulfasalazine are rare, the percentage of such complication is unknown. A patient developed neurotoxic reaction that included confusion, hallucination and paresthesias of legs with improvement a few weeks after withdraw of SSZ [3]. A severe sensitivomotor neuropathy with incomplete recovery was reported in an other patient treated by SSZ four grams per day for extensive colitis [4]. A recurrence of paresthesia of legs was reported after reintroduction of SSZ in 52-year-old man who was treated for ulcerative colitis [5]. The central neurotoxicity due to sulfasalazine was also reported. Furthermore headache and dizziness, aseptic meningitidis, convulsion, encephalopathy and transverse myelitis were reported [6]. The sulfasalazine is metabolized by intestinal flora to 5-aminosalicylic acid (5-ASA) excreted in the feces and sulphapyridine absorbed by the intestines [1]. How sulfasalazine affects the nervous system is unknown. some authors suggest 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 [7,8]. However, one patient was described with a sensorimotor neuropathy due to mesalazine treatment, indicating a toxic effect dependent of the 5-ASA moiety [9]. The onset delay of symptoms after the beginning of treatment varies from one case to another as described in the literature, indicating a different mechanism of neurotoxicity associated with sulfasalazine [5]. The exact prevalence of drug-induced neuropathies is difficult to determine (about 5%), it is usually a distal axonal neuropathy and often have a favorable prognosis with a gradual recovery after treatment discontinuation, the only therapeutic management [10].

Conclusion
The neuropathy due to sulfasalazine is scarce, its mechanism still...
### VC Motrice

| Test | Recueil | Point de stimulation (recueil) | Lat., ms | Ampl., mV | Dur., ms | Surf mVxms | Increm Surf., % | Dist., mm | ∆lat., ms | Vit., m/s |
|------|---------|--------------------------------|----------|-----------|----------|------------|-----------------|-----------|----------|-----------|
| 1 MEDIAN, D | poignet | 2.05 | 4.12 | 15.3 | 15.3 | | | | | |
| | coude | 5.60 | 4.10 | 12.4 | 14.9 | -2.2 | 200 | 3.55 | 56.3 | |
| 3 CUBITAL, D | poignet | 2.20 | 2.59 | 17.4 | 11.1 | | | | | |
| | sous coude | 6.05 | 2.42 | 14.8 | 12.1 | +8.9 | 200 | 3.85 | 51.9 | |
| 7 MEDIAN, G | poignet | 2.10 | 2.49 | 3.50 | 4.7 | | | | | |
| | coude | 5.65 | 2.57 | 4.00 | 5.0 | +5.9 | 200 | 3.55 | 56.3 | |
| 9 CUBITAL, G | poignet | 2.20 | 2.02 | 15.1 | 8.9 | | | | | |
| | sous coude | 6.80 | 1.48 | 17.8 | 7.3 | -18.1 | 200 | 4.60 | 43.5 | |
| 13 SPE, D | cheville | 2.85 | 1.71 | 11.9 | 7.8 | | | | | |
| | sous genou | 8.50 | 1.69 | 13.1 | 8.0 | +2.3 | 320 | 5.65 | 56.6 | |
| 15 SPI, D | cheville | 3.30 | 3.94 | 12.3 | 11.8 | | | | | |
| 18 SPE, G | cheville | 3.65 | 2.16 | 15.3 | 9.1 | | | | | |
| | sous genou | 9.15 | 2.14 | 13.7 | 10.9 | +19.5 | 280 | 5.50 | 50.9 | |
| 20 SPI, G | genou | 4.15 | 2.84 | 13.7 | 11.8 | | | | | |

### VC Sensitive

| Test | Recueil | Point de stimulation (recueil) | Lat., ms | Ampl., mV | Dur., ms | Surf mVxms | Increm Surf., % | Dist., mm | ∆lat., ms | Vit., m/s |
|------|---------|--------------------------------|----------|-----------|----------|------------|-----------------|-----------|----------|-----------|
| 5 N. MEDIAN INDEX, D | poignet | 1.55 | 33.1 | 1.80 | 14.7 | 90 | 1.55 | 58.1 | |
| 11 N. MEDIAN INDEX, G | poignet | 1.50 | 36.9 | 1.50 | 22.6 | 85 | 1.50 | 56.7 | |
| 12 CUBITAL, G | 3.20 | 4.1 | 2.35 | 3.5 | 80 | 3.20 | 42.0 | |
| | | | | | | | | | |

### Parameters onde F

| Test | Recueil | Fmin Lat., ms | F ampl., µV | M lat., ms | M+M fmin lat., ms | Fmoyen/M ampl., % |
|------|---------|--------------|-------------|------------|-------------------|--------------------|
| 2 MEDIAN, D | 23.6 | 194 | 1.50 | 22.1 | 3.5 | 5.4 |
| 4 CUBITAL, D | 27.6 | 221 | 1.90 | 25.7 | 5.6 |
| 8 MEDIAN, G | 22.4 | 162 | 2.20 | 20.2 | 5.6 |
| 10 CUBITAL, G | 20.6 | 220 | 2.35 | 18.3 | 6.8 |
| 14 SPE, D | 18.1 | 167 | 2.95 | 15.1 | 5.7 |
| 16 SPI, D | 45.0 | 174 | 3.40 | 41.6 | 3.1 |
| 19 SPE, G | 48.8 | 744 | 3.20 | 43.8 | 2.7 |
| 21 SPI, G | 48.4 | 54.6 | 4.30 | 44.1 | 2.1 |

Figure 1: Initial nerve conduction study of upper and lower lumbs.
unknown requiring extensive studies. Despite its rarity, and in the absence of specific treatment, we have to discuss the introduction of electrophysiological studies in monitoring patients with sulfasalazine use for early diagnosis.

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