CASE REPORT

Use of gabapentin in the treatment of chronic pain in an adolescent with sickle cell disease

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SUMMARY

Vaso-occlusive crises are the most common manifestation of sickle cell disease (SCD) and the main cause of hospital admission in these patients. There is emerging evidence that vaso-occlusive pain has both nociceptive and neuropathic components. However, the treatment of SCD-related pain with neuropathic drugs has not yet been systematically studied, particularly in children. We describe a 14-year-old girl with SCD and multiple hospital admissions for pain management for severe acute vaso-occlusive pain episodes. The patient was evaluated by a multidisciplinary team of specialists which considered that the chronic, refractory pain she was experiencing for years was probably neuropathic in origin and it was decided to start oral gabapentin (300 mg/day). At 10 months follow-up, the patient reported remarkable improvement in her quality of life with a significant decrease in the number of hospital admissions (three admissions for acute vaso-occlusive pain episodes in 10 months versus the previously monthly recurrences).

BACKGROUND

Vaso-occlusive crises are the most common manifestation of sickle cell disease (SCD) and the main cause of hospital admission in these patients.^{1,2} Local vaso-occlusion causes episodes of severe pain, leading to bone infarction and inflammatory mediators' release.³ Pain is associated with significant morbidity and presents great variability among patients, being influenced by biological and psychological factors.⁴

There is emerging evidence that vaso-occlusive pain has both nociceptive and neuropathic components.⁵ Neuropathic pain occurs as a result of peripheral or central nervous system injury and is shown to be associated with higher pain intensity, longer duration of symptoms and refractoriness to conventional analgesics.³

The management of neuropathic pain includes anticonvulsants, gabapentin being the most used and also acknowledged as the most effective.⁶

In this article, the authors draw attention to the benefit of using anticonvulsants, such as gabapentin, as adjuvants in the management of patients with SCD with frequent pain crises and difficult pain management.

CASE PRESENTATION

We describe a 14-year-old adolescent girl diagnosed with SCD at the age of 8 months, followed in the paediatric haematology unit of a tertiary hospital. The patient was homozygous for haemoglobin

S (haplotype β S Bantu/Bantu). Since the age of 9 years, the patient had multiple hospital admissions for pain management in the setting of severe acute vaso-occlusive pain episodes. In this context, at the age of 11 years, she was started on hydroxyurea (15 mg/kg/day), which was progressively titrated until 25 mg/kg/day due to an insufficient response (maximum increase in fetal haemoglobin of 35%). In spite of a good adherence to treatment, acute vaso-occlusive pain episodes were increasingly more frequent (with a monthly recurrence) and long-standing (pain lasting for a week) with the need for hospital admission. Pain management required intravenous acetaminophen, ketorolac and opioids (morphine via both infusion and patient-controlled analgesia) at escalating doses. In the setting of chronic pain with multiple and prolonged hospital admissions, the patient showed progressively lower educational achievements and presented with symptoms suggestive of depression. She was submitted to psychiatric evaluation, which didn't show any other psychological comorbidity, and was medicated with sertraline. Additionally, during these hospital stays it was observed that the patient experienced pain from non-painful stimuli and sensitivity to cold and heat, with overlap between neuropathic and nociceptive descriptors of pain in the same admission.

At this point, the patient was evaluated by a multidisciplinary team of specialists (paediatric haematologist, anesthesiologist, child psychiatrist and psychologist), which considered that the chronic, refractory pain the patient was experiencing for years was probably neuropathic in origin. Therefore, the decision was to start treatment with oral gabapentin (100 mg twice a day, 4 mg/kg/day). The dose was increased until 7 mg/kg/day divided into three doses (300 mg/day). Treatment with hydroxyurea was maintained.

OUTCOME AND FOLLOW-UP

At 10 months follow-up, the patient reported a remarkable improvement in her quality of life, well-being and pain control. Furthermore, the number of hospital admissions decreased to just three admissions for acute vaso-occlusive pain episodes in 10 months. No significant side effects have been reported with gabapentin (current maintenance dose 7 mg/kg/day). The patient maintains regular multidisciplinary follow-up.

DISCUSSION

Gabapentin has been used with success in the treatment of neuropathic pain in various clinical

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settings, such as cancer, painful diabetic neuropathy, postherpetic neuralgia and a variety of other complex regional pain syndromes.⁵⁻⁷ However, the treatment of SCD-related pain with neuropathic drugs, as the gabapentin, has not yet been systematically studied, particularly in children.^{3,5} To our knowledge, this is the first report describing the use of gabapentin in an adolescent with SCD.

Gabapentin is structurally similar to γ -aminobutyric acid (GABA), but it does not bind to GABA receptors or interferes with its metabolism.^{7,8} Gabapentin is thought to exert its analgesic effect through a mechanism of antagonism of N-methyl-D-aspartate receptors; additionally, injured peripheral nerves' ectopic discharges are inhibited by gabapentin.

Gabapentin binds to $\alpha 2\delta$ subunits of Ca^{2+} channels at the post-synaptic dorsal horns, subsequently inhibiting high-threshold neuronal Ca^{2+} currents. This reduces the release of the excitatory amino acid glutamate with a consequent disruption of neuropathic pain perception.^{7,8}

There are few side effects associated with gabapentin, the most frequent being somnolence, dizziness, headache, diarrhoea, ataxia and fatigue.^{7,9} In our case, no significant side effects have been reported.

In addition to showing significant evidence of effectiveness in the management of neuropathic pain, gabapentin has demonstrated opioid-sparing effects in acute postoperative pain in both adults and children, believed to be due to the prevention of opioid tolerance development.⁵ It is plausible that, if treatment with gabapentin is proven effective, it could be prescribed for outpatient administration in conjunction with oral opioids and non-steroids at the time of pain onset with the goal of reducing the need for acute visits and hospitalisations for vaso-occlusive crisis.⁵

In fact, since our patient was started on gabapentin, a remarkable improvement in quality of life has been reported with a significant decrease in the number of hospital admissions (three admissions for acute vaso-occlusive pain episodes in 10 months, instead of the previous monthly recurrences).

Published data have revealed that, although patients with SCD frequently experience neuropathic pain, only a small percentage of them is prescribed with specific neuropathic pain medications.¹⁰ Brandow *et al*¹⁰ suggested that the absence of a systematic screening for the manifestation of neuropathic pain in patients with SCD could be the explanation for the uncommon prescription of neuropathic pain drugs in this population.

The commonly accepted definition for neuropathic pain is pain originated by a lesion or dysfunction of the somatosensory system.^{3,4,6,10} Its pathophysiology is still unknown.^{6,10} However, it appears to result from 'central sensitisation': a situation where repeated and frequent pain stimuli may sensitise supraspinal areas responsible for noxious processing, leading them to be more active in upcoming events of pain stimulation, the expression of which being a decrease in the noxious threshold.^{4,6,8,10} Indeed, it seems to be the association of hypoxia/ reperfusion injury, ischaemic tissue damage and inflammation that are in the origin of many features of SCD pain.^{11,12} Recently, special consideration has been given to the transient receptor potential vanilloid type 1 (TRPV1) because its activation is related with the sensation of pain.^{11,12} Studies suggest that the TRPV1 receptor contributes to the mechanical hypersensitivity in SCD at the cellular, primary afferent terminal and behavioural levels.^{11,12}

Neuropathic pain can manifest as hypersensitivity, increased pain from a normally painful stimulus and/or allodynia, pain due to a non-painful stimulus.^{3,6}

Due to the lack of validated scales for neuropathic pain in SCD, diagnosing this disorder with certainty is not easy. We suspected that the pain experienced by our patient probably had a neuropathic origin when the acute vaso-occlusive pain episodes became monthly occurrences, long-standing and requiring intravenous analgesic and opioids at maximum doses. During these hospital stays it was observed that the patient experienced pain from non-painful stimuli and sensitivity to cold and heat, with overlap between neuropathic and nociceptive descriptors of pain in the same admission.

Additionally the psychological component may have influenced pain perception in this clinical case. It is well established that depression is associated with an abnormal pain perception and with an increased incidence of vaso-occlusive episodes in patients with SCD.¹³ In fact the pain aetiology seems to be multifactorial in this case, where the nociceptive and neuropathic components were aggravated by a concomitant mental illness.

In conclusion, we report the successful use of gabapentin in the treatment of chronic pain in an adolescent with SCD. Its effectiveness and the low incidence of side effects encourage a more frequent use of gabapentin in situations where neuropathic pain seems to have a key role. Nevertheless, prospective randomised controlled studies are needed in order to define which patients are experiencing neuropathic pain and to potentially include gabapentin as a first-line therapy for neuropathic pain in those situations.

Learning points

- ▶ There is emerging evidence that vaso-occlusive pain has both nociceptive and neuropathic components.
- ▶ The treatment of sickle cell disease (SCD)-related pain with neuropathic drugs has not yet been systematically studied, particularly in children.
- ▶ We report the successful use of gabapentin in the treatment of chronic pain in an adolescent with SCD.
- ▶ Its effectiveness and the low incidence of side effects encourage a more frequent use of gabapentin in situations where neuropathic pain seems to have a key role.

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