CASE REPORT

Juvenile fibromyalgia in an adolescent patient with sickle cell disease presenting with chronic pain

Stalin Ramprakash,^{1,2} Daniel Fishman³

¹Department of General Paediatrics, Luton and Dunstable Hospital, Luton, UK

²Department of Paediatric Haematology and Oncology, Great Ormond Street Hospital, London, UK

³Department of Rheumatology, Luton and Dunstable Hospital, Luton, UK

Correspondence to

Dr Stalin Ramprakash, stalinr@hotmail.com

Accepted 16 September 2015

SUMMARY

Juvenile fibromyalgia in children with sickle cell disease has not been reported in the literature. We report an adolescent patient with sickle cell whose pain symptoms progressed from having recurrent acute sickle cell pain crisis episodes to a chronic pain syndrome over several years. He was eventually diagnosed with juvenile fibromyalgia based on the clinical history and myofascial tender points and his pain symptoms responded better to multidisciplinary strategies for chronic fibromyalgia pain. Chronic pain in sickle cell disease is an area of poor research, and in addition there is inconsistency in the definition of chronic pain in sickle cell disease. Central sensitisation to pain is shown to occur after recurrent painful stimuli in a genetically vulnerable individual. In a chronic pain condition such as fibromyalgia central sensitisation is thought to play a key role. Fibromyalgia should be considered as one of the main differential diagnosis in any sickle cell patient with chronic pain.

BACKGROUND

Acute pain crisis is a well-recognised complication of sickle cell disease in children. Chronic pain, which is rare, is often attributed to ongoing vaso-occlusion, avascular necrosis and ankle ulcers even though objective evidence of the cause of chronic pain is not obvious in a significant proportion of patients. Chronic pain can be the main presenting feature of central sensitisation conditions like fibromyalgia. The focus of treatment strategies will vary significantly whether the chronic pain is a direct result of the sickling process or central sensitisation phenomenon. Making an accurate diagnosis of the cause of chronic pain is paramount in delivering appropriate targeted treatment that is most beneficial for the patient. By writing this up, we would like to highlight that fibromyalgia can evolve in children with sickle cell disease and present with chronic ongoing pain, which may be wrongly attributed to sickling pain.

CASE PRESENTATION

Our patient was born at 42 weeks gestation by spontaneous vaginal delivery. He was diagnosed with homozygous sickle cell anaemia (Hb-SS disease) through the National Haemoglobinopathy Screening Programme. He suffered episodes of dactylitis as an infant and toddler. He did reasonably well until the age of 7 years, with only the occasional painful crisis. At 7 years of age, he developed girdle syndrome and required intensive care treatment. He developed further complications at

12 years of age with *Salmonella sepsis*, without any evidence of osteomyelitis. Shortly thereafter, he developed cholecystitis, following which he had a cholecystectomy and an umbilical hernia repair in the same year. From the age of 13 years, he suffered frequent episodes of painful crisis, which progressed to chronic pain, with intermittent exacerbations. The ongoing pain significantly affected his life, with a school attendance of <50%.

INVESTIGATIONS

His sickle cell disease was characterised by a high systemic inflammatory response, as suggested by an elevated total white cell count ($12\text{--}20 \times 10^9/\text{L}$), neutrophil count ($5\text{--}10 \times 10^9/\text{L}$), lymphocyte count ($5\text{--}10 \times 10^9/\text{L}$), eosinophil count ($0.5\text{--}1.0 \times 10^9/\text{L}$) and platelet count ($600\text{--}800 \times 10^9/\text{L}$). His erythrocyte sedimentation rate varied from normal to 20 mm/h and C reactive protein varied from normal to 30 ng/mL. His baseline absolute reticulocyte count ranged from 300 to $400 \times 10^9/\text{L}$, Hb from 70–80 g/L and lactate dehydrogenase levels from 370 to 450 IU/L.

He underwent multiple investigations for his many persistent symptoms, which included ongoing severe body pain, abdominal pain, recurrent headaches, malaise and poor sleep. These investigations included a whole body MRI, an MR cholangiogram, abdominal ultrasound, upper and lower gastrointestinal endoscopy, lung function tests, polysomnography to rule out obstructive sleep apnoea, rheumatoid factor, antinuclear antibodies (ANAs) and an autoimmune tissue panel. None of these investigations revealed any significant abnormality. Since he reported episodes of disabling abdominal pain, a tertiary paediatric gastroenterology opinion was sought. After endoscopy, he was given a diagnosis of irritable bowel syndrome.

DIFFERENTIAL DIAGNOSIS

We considered the possibility of various organic causes contributing to chronic pain in our patient including avascular necrosis, ongoing sickle vaso-occlusion, ankle ulcers and infections. No definitive cause was found.

TREATMENT

He was started on hydroxyurea at the age of 13 years, with a gradual dose escalation, but he demonstrated no clinical improvement, despite a rise in his fetal Hb level. He was then considered for a transfusion programme, in order to remove

CrossMark

To cite: Ramprakash S, Fishman D. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-211850

any contribution of the sickling process to his pain. Unfortunately, following an exchange transfusion, before he could be started on a regular transfusion programme, he developed a severe delayed transfusion reaction and his Hb fell to below its pretransfusion level. No further transfusions were given, but the dose of hydroxyurea was increased gradually to its maximum, again without any significant clinical improvement. It was discontinued after 1 year as there was no improvement in his pain symptoms.

OUTCOME AND FOLLOW-UP

Owing to the ongoing pain and other somatic symptoms, he was referred to a rheumatologist (DF) who diagnosed juvenile fibromyalgia, based on the clinical history and multiple myofascial tender points. He was then referred to a clinical psychologist to teach him coping mechanisms to manage his ongoing pain and develop strategies to help him function effectively in normal day-to-day life.

Since the diagnosis of fibromyalgia, his quality of life has improved significantly because of the clear explanation for his hitherto unexplained symptoms. He was able to deal with his symptoms in a positive manner with the right support and education about fibromyalgia, with clinical psychology input, adjuvant medical treatment such as amitriptyline and tailored exercise with physiotherapy input. We were able to withdraw all the opioid analgesia he had been taking for the previous few years. He was able to manage his overall condition and pain much better to the extent that he was able to go to university.

DISCUSSION

Although several classification criteria have been proposed, currently the most widely accepted is the 1990 American College of Rheumatology criteria.¹ An adult patient is diagnosed as having fibromyalgia if he or she has widespread pain for at least 3 months in combination with tenderness in at least 11 of 18 tender points.¹ The more recent 2010 American College of Rheumatology Preliminary Diagnostic Criteria for fibromyalgia rely more heavily on reported pain and symptom severity, than tender point counts, as these are unreliable.² A 2011 modification has been proposed. The application of these diagnostic criteria to children has not been validated, as children tend to have fewer tender points. Hence, alternate criteria, based on a study of 33 children by Yunus *et al*, have been proposed. This is generally used in diagnosing children with fibromyalgia, requiring only 5 tender points, compared to the 11 for adult disease.³ The preliminary American College of Rheumatology 2010 criteria require that the fibromyalgia diagnosis should not be made in the presence of a somatic disease which could sufficiently explain the symptoms.² However, fibromyalgia can be diagnosed with confidence even in the presence of other medical conditions.¹

There is an increasing evidence base for central sensitisation in many of the chronic pain syndromes, including fibromyalgia. Central sensitisation is a complex phenomenon in which there is hyperexcitability of central nociceptive circuits brought on by activity dependent changes in synaptic transmission. This increased sensitisation involves changes in receptors, neurotransmitters, ion channels and signalling pathways in the central nervous system to such an extent that even innocuous non-nociceptive stimuli are perceived as painful and the perception of noxious stimuli is exaggerated, prolonged and widespread.⁴ There is evidence to suggest that tender points in fibromyalgia represent hyperalgesia due to central sensitisation.⁵ Recent studies looking at functional activity in the brain have also suggested that acute pain seems to activate somatosensory, insular

and cingulate cortical areas, whereas chronic pain preferentially activates prefrontal and limbic cortical areas. Areas of the brain which are active in chronic pain seem to be those areas which are less involved in acute nociception but more involved in emotions and self-evaluation. In addition, there is evidence of anatomical changes such as regional decrease in grey matter density, volume or thickness in various regions of the brain not limited to nociceptive areas, with varying patterns in different chronic pain conditions, presumably due to anatomical and functional connectivity changes.⁶ It has also been shown that treating chronic pain effectively can reverse these structural and functional abnormalities and restore normal brain function in humans.⁷

It appears that in a genetically susceptible individual, certain environmental factors may bring out the clinical phenotype of fibromyalgia. Peripheral pain generators set up the central sensitisation that is characteristic of fibromyalgia in genetically vulnerable individuals.⁸ Fibromyalgia is known to associate within families. A genetic predisposition to fibromyalgia has been demonstrated in epidemiological studies linking certain genes to fibromyalgia, such as: the SS genotype polymorphism in the promoter region of the serotonin transporter gene (5-HTT)⁹; LL and LH genotype polymorphisms in the gene encoding the COMT (catechol-O-methyltransferase) enzyme¹⁰; a possible gene for fibromyalgia linked to the human leucocyte antigen region has been suggested by the study of muticase families.¹¹ Studies on potential environmental risk factors have shown associations with physical trauma, psychological factors (such as pre-existing somatisation, health-seeking behaviour and poor sleep) and biological factors (abnormalities in the hypothalamic-pituitary-adrenal (HPA) stress-response system).¹²

In addition to widespread pain and tender points, other common features of fibromyalgia are fatigue, headache, depressed mood and disturbed sleep. Although juvenile fibromyalgia has been less well studied than adult fibromyalgia, it is apparent that the clinical features are similar, but with some important differences.^{13 14} For instance, in addition to diffuse widespread pain (93%), which is the hallmark of fibromyalgia, sleep disturbance (96%) is a highly prevalent symptom in juvenile fibromyalgia in comparison with that in adults. The next most commonly reported symptoms were headaches (71%), general fatigue (62%) and morning stiffness (53%).¹⁵ Another study comparing fibromyalgia in children who had disease onset before 10 years of age with those above 10 years found that the clinical features were similar, but stiffness, subjective joint swelling, abdominal pain and initial presentation in a wheelchair were found more frequently in the younger children, who also had more tender points. The mean length to onset of symptoms to diagnosis was much longer in younger children presumably due to under-recognition.¹⁶ Juvenile fibromyalgia carries a better prognosis than adult fibromyalgia. In a 30-month follow-up period, 73% of children no longer fulfilled the criteria for fibromyalgia.¹⁷ Another follow-up study by Siegel *et al*¹⁵ reported that the majority of children with fibromyalgia improved over 2–3 years follow-up. Low mood in adolescents was reactive (to the pain-associated disability) rather than a primary depression.¹⁸ This is in contrast to that in adults with fibromyalgia where primary depression is frequently seen.¹⁷

There is a significant overlap in the clinical features of fibromyalgia and chronic fatigue syndrome (CFS) in children. However, there is a suggestion of immunological differences, such as high ANA titres and a high prevalence of anti-Sa antibody in CFS, suggesting that immunologically they are different in children.¹⁹

Sickle cell disease is well known to cause recurrent vaso-occlusive pain crisis episodes. The frequency of painful episodes increases as children mature from childhood into adolescence.²⁰ In a small proportion of adolescents and adults, the pain becomes more chronic in nature. Some of the known causes of chronic pain in sickle cell disease are: avascular necrosis, ankle ulcers and acute crisis superimposed on chronic pain. There are no studies specifically addressing chronic pain in sickle cell disease.²¹ There are inconsistencies in the definition of chronic pain in sickle cell disease, as recurrent vaso-occlusive crisis can present as chronic pain. Even those studies that reported chronic pain in sickle cell disease often studied recurrent vaso-occlusive crisis, rather than other dimensions of chronic pain or causes of chronic pain. There is a lack of definition as to what constitutes chronic sickle cell pain.²² A study which reviewed 19 studies that investigated chronic pain in adults with sickle cell disease reported that none of those studies defined chronic pain.²² There is no clear agreement on when the pain should be considered chronic pain even with other medical conditions, though it is generally considered as pain that persists or recurs for more than 3 months. The International Association for the Study of Pain has introduced a coding system to study chronic pain in a research setting because it was felt that defining chronic pain as persistent pain more than 3 months is too simplistic and does not take into consideration pathological and healing processes involved under different medical conditions.

Chronic pain was reported in at least 29% of adults with sickle cell disease and most frequently in those 25–44 years of age. In a review of four studies of adult patients with sickle cell and chronic pain that reported employment status, the majority of patients with sickle cell with chronic pain (61%) were either unemployed and/or disabled.²² There are no published estimates of the incidence of chronic pain in children with sickle cell disease.

If it is assumed that any condition which causes recurrent pain is likely to promote central sensitisation in a genetically vulnerable individual, this may progress on to generalised widespread pain fulfilling the criteria for fibromyalgia syndrome. In the absence of large-scale studies, the treating physicians may wrongly attribute chronic pain in patients with sickle cell to an ongoing sickling process, rather than to a chronic pain condition such as fibromyalgia. A study that looked for evidence of central sensitisation in a subgroup of adult patients with sickle cell disease experiencing only episodic pain concluded that, especially in the older patients, there were early signs of disturbed processing of painful stimuli and the patients were transitioning into a state of chronic pain.²³

In a single institution study, 19 children with sickle cell disease were referred to a specialist multidisciplinary pain clinic if they developed a requirement for chronic opioids at home, or had three or more admissions in spite of disease-modifying treatment. Even though avascular necrosis is commonly attributed as a reason for chronic pain in children with sickle cell disease, only a quarter of the cohort had avascular necrosis. Ongoing vaso-occlusion was a possibility, but two-thirds of the study population continued to have pain despite being prescribed hydroxyurea, suggesting that other pain sensitisation and neurobiological mechanisms were involved.²⁴

Differentiating the various causes of chronic pain in patients with sickle cell has treatment implications. In juvenile fibromyalgia, as in any chronic pain syndrome, multidisciplinary care is critical for appropriate assessment and treatment.²⁵ The use of pharmacological agents in isolation has been shown to be ineffective in successfully treating fibromyalgia. Multidisciplinary

treatment as a minimum should involve medication, parent and child education about the condition, individualised graded aerobic exercise, training in pain coping and stress management skills and sleep hygiene education. Prospective studies that looked at long-term opioid use (>3 months) suggest that long-term opioids may not provide sustained analgesia or improve patient function in the majority of cases.²⁶ Some non-randomised prospective studies have suggested that long-term opioid treatment may result in the retardation of functional recovery.^{27–28} The three main drugs licensed for use in the treatment of fibromyalgia in the USA (duloxetine, milnacipran and pregabalin) seem to have the same level of efficacy, both in fibromyalgia and in other chronic pain conditions.^{29–31} Thus, in any chronic pain condition, medication has a role, but other non-pharmacological treatment modalities are as important if not more important.

In patients with sickle cell disease, opioids are commonly prescribed for both acute and recurrent pain crisis episodes. Owing to the persistence of symptoms, they are sometimes prescribed as regular long-term treatment, even though their efficiency is questionable. Disease-modifying treatments such as hydroxyurea and transfusions are often initiated only after significant morbidity and suffering from painful crises. If pain sensitisation and maladaptive cognitive patterns have already set in, and if the major component of pain is due to central mechanisms rather than sickle vaso-occlusion, then sickle-directed management strategies may not be of much benefit. Multidisciplinary pain clinic referral has been shown to reduce the median number of inpatient admissions in patients with sickle cell.²⁴ A recent Cochrane review on the efficacy of psychological management for chronic and recurrent pain in children and adults concluded that for children and adolescents there is evidence that both relaxation and cognitive-behavioural therapy are effective in reducing the intensity of pain in chronic headache, recurrent abdominal pain, fibromyalgia and sickle cell disease (immediately after treatment). Psychological therapies have a lasting effect in reducing pain and disability for chronic headache, but for other mixed pain conditions they had an immediate effect, but this was not sustained. Psychological therapies did not produce changes in depression or anxiety in children with either headache or non-headache conditions.³²

It is not surprising that our patient with sickle cell with juvenile fibromyalgia, who was not improving with disease-modifying treatment or long-term opioids, responded very well to

Learning points

- ▶ Juvenile fibromyalgia should be considered in the differential diagnosis of children with sickle cell disease and chronic pain.
- ▶ In some patients with sickle cell disease the clinical picture can evolve over time from that of acute recurrent pain crisis episodes to chronic continuous ongoing pain.
- ▶ Early rheumatology opinion should be sought in children with sickle cell disease and chronic pain in order to make an early diagnosis of fibromyalgia and appropriate targeted treatment.
- ▶ Large-scale prospective studies are urgently needed to study the prevalence, morbidity and functional impairment imposed by the coexistence of fibromyalgia in sickle cell disease.

multidisciplinary strategies targeting cognitive, behavioural and coping mechanisms, patient and parent education, graded exercise along with the judicious use of pain relief medications including those known to be useful in neuropathic pain. We feel that the most important aspects of treatment of chronic pain in fibromyalgia associated with organic conditions such as sickle cell disease are making the diagnosis, educating the patient and parents about the illness and providing structure for managing life with chronic illness.

Contributors DF was involved in making the diagnosis of fibromyalgia in this patient. He was also actively involved in reviewing and editing the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Wolfe F, Smythe HA, Yunus MB, *et al*. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990;33:160–72.
- Wolfe F, Clauw DJ, Fitzcharles MA, *et al*. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken)* 2010;62:600–10.
- Yunus MB, Masi AT. Juvenile primary fibromyalgia syndrome. A clinical study of thirty-three patients and matched normal controls. *Arthritis Rheum* 1985;28:138–45.
- Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011;152(3 Suppl):S2–15.
- Sörensen J, Bengtsson A, Bäckman E, *et al*. Pain analysis in patients with fibromyalgia. Effects of intravenous morphine, lidocaine, and ketamine. *Scand J Rheumatol* 1995;24:360–5.
- Apkarian AV. The brain in chronic pain: clinical implications. *Pain Manag* 2011;1:577–86.
- Seminowicz DA, Wideman TH, Naso L, *et al*. Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. *J Neurosci* 2011;31:7540–50.
- Borg-Stein J. Management of peripheral pain generators in fibromyalgia. *Rheum Dis Clin North Am* 2002;28:305–17.
- Cohen H, Buskila D, Neumann L, *et al*. Confirmation of an association between fibromyalgia and serotonin transporter promoter region (5-HTTLPR) polymorphism, and relationship to anxiety-related personality traits. *Arthritis Rheum* 2002;46:845–7.
- Gürsoy S, Erdal E, Herken H, *et al*. Significance of catechol-O-methyltransferase gene polymorphism in fibromyalgia syndrome. *Rheumatol Int* 2003;23:104–7.
- Yunus MB, Khan MA, Rawlings KK, *et al*. Genetic linkage analysis of multicase families with fibromyalgia syndrome. *J Rheumatol* 1999;26:408–12.
- Oliver JE, Silman AJ. What epidemiology has told us about risk factors and aetiopathogenesis in rheumatic diseases. *Arthritis Res Ther* 2009;11:223.
- Buskila D. Pediatric fibromyalgia. *Rheum Dis Clin North Am* 2009;35:253–61.
- Calabro JJ. Fibromyalgia (fibrositis) in children. *Am J Med* 1986;81:57–9.
- Siegel DM, Janeway D, Baum J. Fibromyalgia syndrome in children and adolescents: clinical features at presentation and status at follow-up. *Pediatrics* 1998;101:377–82.
- Eraso RM, Bradford NJ, Fontenot CN, *et al*. Fibromyalgia syndrome in young children: onset at age 10 years and younger. *Clin Exp Rheumatol* 2007;25:639–44.
- Buskila D, Neumann L, Hershman E, *et al*. Fibromyalgia syndrome in children—an outcome study. *J Rheumatol* 1995;22:525–8.
- Buskila D. Fibromyalgia in children—lessons from assessing nonarticular tenderness. *J Rheumatol* 1996;23:2017–19.
- Itoh Y, Shigemori T, Igarashi T, *et al*. Fibromyalgia and chronic fatigue syndrome in children. *Pediatr Int* 2012;54:266–71.
- Panepinto JA, Brousseau DC, Hillery CA, *et al*. Variation in hospitalizations and hospital length of stay in children with vaso-occlusive crises in sickle cell disease. *Pediatr Blood Cancer* 2005;44:182–6.
- Dunlop RJ, Bennett KC. Pain management for sickle cell disease. *Cochrane Database Syst Rev* 2006;(2):CD003350.
- Taylor LE, Stotts NA, Humphreys J, *et al*. A review of the literature on the multiple dimensions of chronic pain in adults with sickle cell disease. *J Pain Symptom Manage* 2010;40:416–35.
- Hollins M, Stonerock GL, Kisaalita NR, *et al*. Detecting the emergence of chronic pain in sickle cell disease. *J Pain Symptom Manage* 2012;43:1082–93.
- Brandow AM, Weisman SJ, Panepinto JA. The impact of a multidisciplinary pain management model on sickle cell disease pain hospitalizations. *Pediatr Blood Cancer* 2011;56:789–93.
- Kashikar-Zuck S. Treatment of children with unexplained chronic pain. *Lancet* 2006;367:380–2.
- Ballantyne JC, Shin NS. Efficacy of opioids for chronic pain: a review of the evidence. *Clin J Pain* 2008;24:469–78.
- Turner JA, Franklin G, Fulton-Kehoe D, *et al*. ISSLS prize winner: early predictors of chronic work disability: a prospective, population-based study of workers with back injuries. *Spine (Phila Pa 1976)* 2008;33:2809–18.
- Braden JB, Young A, Sullivan MD, *et al*. Predictors of change in pain and physical functioning among post-menopausal women with recurrent pain conditions in the women's health initiative observational cohort. *J Pain* 2012;13:64–72.
- Häuser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. *J Pain* 2010;11:505–21.
- Kroenke K, Krebs EE, Bair MJ. Pharmacotherapy of chronic pain: a synthesis of recommendations from systematic reviews. *Gen Hosp Psychiatry* 2009;31:206–19.
- Björkdal JM, Klovning A, Ljunggren AE, *et al*. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: a meta-analysis of randomised placebo-controlled trials. *Eur J Pain* 2007;11:125–38.
- Eccleston C, Palermo TM, Williams AC, *et al*. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. *Cochrane Database Syst Rev* 2014;5:CD003968.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow