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# Behçet's disease in UK children: clinical features and treatment including thalidomide

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## Abstract

*Objective*. To study the clinical spectrum of Behçet's disease (BD) in childhood, and to report our experience of using thalidomide.

*Method*. Ten children, diagnosed with BD, were studied retrospectively.

*Results*. The median (range) age at first presentation was 4 (1.2–12.0) yr, at diagnosis was 11 (3–15) yr and the follow-up period was 4.1 (0.6–6.3) yr. Oral ulcers were present in all patients (100%), genital ulcers were present in six (60%), peri-anal ulcers were present in three (30%), skin manifestations were present in nine (90%), intracranial hypertension was present in two (20%), mild gastrointestinal symptoms were present in five (50%), joint symptoms were present in six (60%), ocular lesions were present in five (50%), but only one child had anterior and posterior uveitis. Therapeutically, a range of drugs was used, including colchicine, that resulted in good responses in five children. Thalidomide (1 mg/kg/week to 1 mg/kg/day) was used in five children who were unresponsive to other immunosuppressive agents. It resulted in complete remission in three children and less frequent milder oral ulcers in two. Neuropathy developed in two children and in one it was irreversible.

*Conclusion*. BD in children is similar to the disease in adults. Thalidomide provided a useful therapeutic option for severe oral and genital ulceration which was unresponsive to other therapies. Awareness of the danger of axonal neuropathy and teratogenesis at all times during thalidomide therapy is crucial. A low dose is probably as effective as higher doses.

KEY WORDS: Behçet's disease, Children, Thalidomide.

Behçet's disease (BD) is a chronic relapsing, inflammatory disorder characterized by recurrent oral aphthae and any of several systemic manifestations. These include genital aphthae, ocular disease, skin lesions, and neurological disease or arthritis [1]. Hulusi Behçet drew attention to the disease in 1937 [2]. Diagnosis of BD can be difficult, as the presentation could be partial [3] or unusual [4, 5]. New international criteria were published in 1990 [6]. They require the presence of recurrent oral aphthae (three times in 1 yr) plus two of the following in the absence of other systemic diseases: recurrent genital aphthae, eye lesions (uveitis or retinal vasculitis), skin lesions (erythema nodosum, pseudovasculitis, papulopustular lesions or acneiform nodules) or a positive pathergy test.

Mundy and Miller [7] reported the first paediatric case in 1978, followed by a few additional reports from different parts of the world [8–10]. Recently, in 1998, an international collaborative study of 86 childhood cases was published [11]. They reported a mortality rate of 3% with a worse prognosis for uveitis in children compared with adults.

Different treatment modalities have been utilized [1], including steroids, colchicine, immunosuppressive medications (azathioprine, cyclosporin, methotrexate and interferon alpha-2b), dapsone and prophylactic penicillin. Another option is thalidomide, which in the 1960s virtually disappeared from clinical use after it was demonstrated to be a causative agent of severe irreversible peripheral neuropathy [12] and a human teratogen [13]. Recently, thalidomide re-emerged as treatment for erythema nodosum leprosum [14] and other serious conditions such as cachexia associated with HIV and cancer, and autoimmune diseases [15]. It is used in severe cases of BD [16] and was shown to be effective for treating the oral and genital ulcers and follicular lesions in adults [17, 18]. Experience of its use in the paediatric population is limited. Only one case is reported of its effectiveness in an infant with BD [19].

We report our experience with 10 children who had signs and symptoms suggestive of BD. We describe the

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patients, their follow-up and report our experience of using thalidomide in five of them.

## Patients and methods (Table 1)

This study was a retrospective review of 10 patients (six females) who presented to Great Ormond Street Hospital for Children between 1971 and 1997. The median (range) age at first presentation was 4 (1.2–12.0) yr, at diagnosis was 11 (3–15) yr and the follow-up period was 4.1 (0.6–6.3) yr; all except one, whose father was Egyptian, were Caucasian in origin (English). There was no family history of BD or recurrent oral aphthosis in any of the children.

## Results

### *Children who fulfilled the international criteria*

Nine children fulfilled the international criteria for diagnosing BD. One child presented with recurrent oral ulcers from the age of 4 yr but did not develop other criteria. He was diagnosed as a partial BD at the age of 13 yr.

### *Clinical features (Table 2)*

*Mucosal lesions.* Buccal aphthosis was present in all the children (100%) and was the presenting symptom of BD in six patients (60%). The median range age at onset was 4 (1.3–12) yr. The number of attacks per year varied from three to ulcers being present almost constantly. The ulcers were very painful and were associated with facial oedema in two patients.

Genital ulceration occurred in six children and usually appeared after the buccal aphthosis, with a median (range) age at onset of 11.4 (5.5–12) yr, and affected the vulva, scrotum and penis.

Peri-anal ulceration occurred in three children at a median (range) age of 4 (3–4) yr and in two children genital ulceration also occurred.

*Skin lesions.* Skin lesions were present in nine children (90%). The cutaneous lesions were variable, including papules, pustules, vesicles, acneiform lesions, pyoderma gangrenosa-type lesions, palpable purpura, hypo-pigmented lesions and purulent bullae. Pustular eruption was the commonest skin lesion, reported in three children. The pathergy test was reported as negative in three patients, but was not undertaken in the other patients. In two children cellulitis was observed.

*Ocular involvement.* Eye lesions were present in five patients (50%). Scleritis and papilloedema due to increased intracranial pressure was the first presentation in one child. Another child was referred at the age of 13.8 yr because of progressive loss of vision secondary to anterior and posterior uveitis. She had a history of recurrent oral ulcers since the age of 2 yr. Her visual acuity was down to 6/24 in the right eye but improved to 6/12 after treatment and in the left eye it was 6/9 which improved to 6/6.

*Joint involvement.* Joint symptoms were reported in six children (60%). Four had arthralgias only. Two children had arthritis; one had swollen ankle joints and the other generalized polyarticular (large and small) arthritis.

*Neurological involvement.* Headache was reported in four patients (40%). Two children had intracranial hypertension with normal cerebrospinal fluid (CSF) protein and sugar. One had a high CSF lymphocyte count of 14/mm$^2$ but his magnetic resonance imaging (MRI) scan was normal. The other child had a considerable abnormality in the EEG, but never had seizures.

*Gastrointestinal involvement.* Five patients (50%) had abdominal pain. In two of them it was associated with constipation. A barium meal was performed in five children to exclude Crohn's disease and was normal in all of them. Colonoscopy and endoscopy were performed in the same children and showed a normal appearance in two children, but one had mild non-specific changes, another had mild duodenitis and oesophagitis and the fifth child had numerous small ulcers in the upper part of the stomach. The two children with abdominal pain, in whom all investigations were normal, were not those with constipation. This indicates that their abdominal pain may not be strictly due to gastrointestinal involvement.

*Systemic presentation.* Two children presented with fever, malaise, anorexia, vomiting, generalized aches, rash and lethargy.

TABLE 1. Course of illness

| Patients | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Sex | F | M | M | M | F | M | F | F | F | F |
| Age at onset (yr) | 4 | 4 | 5.5 | 2 | 1.2 | 12 | 2 | 8 | 11 | 4 |
| Age at diagnosis (yr) | 8 | 13 | 7 | 12 | 3 | 12.3 | 14 | 10 | 15 | 7 |
| Follow-up (yr) | 4.5 | 3 | 3.8 | 4.8 | 1.6 | 2.4 | 5 | 0.6 | 4.4 | 6.3 |
| Steroids | + | + | + | + | + | − | + | + | + | + |
| Immunosuppressives | aza | − | − | aza | aza & MMF | − | cycl | − | − | − |
| Colchicine | + | − | − | + | | + | + | − | − | + |
| Thalidomide (starting age) | 11.1 | 14 | 7 | − | − | − | 16 | − | − | 11.4 |
| Final treatment | thal + pred | thal + pred | thal | colch + aza | MMF | colch | colch | − | − | thal + colch |

+, given; −, not given; aza, azathioprine; pred, prednisolone; colch, colchicine; thal, thalidomide; MMF, mycophenolate mofetil; cycl, cyclosporin.

TABLE 2. Clinical manifestations

| Patients | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Age at appearance of | | | | | | | | | | |
| Oral ulcers | 4 | 4 | 5.5 | 2 | 1.2 | 12 | 2 | 8 | 11 | 4 |
| Genital ulcers | 11 | | 5.5 | 11.5 | | 12 | | 11.5 | | 11.3 |
| Peri-anal ulcers | 4 | | | | 3 | | | | | 4 |
| Ocular | | | | | | | | | | |
| Conjuctivitis | − | − | + | − | − | − | − | − | + | + |
| Episcleritis | − | − | − | − | − | − | − | + | − | − |
| Uveitis | − | − | − | − | − | − | + | − | − | − |
| Papilloedema | − | − | − | − | − | − | − | + | + | − |
| Joints | | | | | | | | | | |
| Arthralgia | + | − | − | − | + | + | − | − | − | + |
| Arthritis | − | − | + | − | − | − | − | − | + | − |
| Skin | | | | | | | | | | |
| Maculopapular rash | + | − | − | + | − | − | + | − | − | − |
| Pustular rash | − | − | + | − | − | + | − | − | − | + |
| Acneiform rash | − | − | − | − | − | + | − | − | − | − |
| Bullous blisters | − | − | − | − | − | − | − | − | − | + |
| Multiform | − | − | − | − | + | − | − | − | + | − |
| Depigmentation | − | − | − | − | − | − | − | + | − | − |
| Central nervous system | | | | | | | | | | |
| Increased intracranial pressure | − | − | − | − | − | − | − | + | + | − |
| Headache | − | − | + | − | − | + | − | − | + | + |
| Other | | | | | | | | | | |
| Abdominal pain | − | − | + | + | + | + | − | − | − | + |
| Systemic presentation | − | − | − | − | − | − | − | + | + | − |
| Fe-deficiency anaemia | − | − | − | − | + | − | + | − | − | − |
| Lymphadenopathy | − | − | − | + | + | − | − | + | + | − |
| Cellulitis | − | − | − | − | + | + | − | − | − | − |

+, present; −, absent.

*Other manifestations.* Four children (40%) were noticed to have shotty generalized lymphadenopathy. Two developed iron-deficiency anaemia with a slow response to iron therapy. One child had a chest pain, which could not be explained by chest X-ray or echocardiogram. One patient had a basal cell carcinoma removed from his nose at the age of 17.5 yr, 5 yr after having been diagnosed as a case of BD. He did not receive immunosuppressive treatment to control his BD apart from colchicine and steroids before he developed the basal cell carcinoma. However he required azathioprine at a later date.

*Growth.* The mean height standard deviation score (HtSDS) ± standard deviation (S.D.) at the time of diagnosis was 0.38 ± 1.08; after 1 yr it was 0.31 ± 1.11 and after 2 yr it was 0.35 ± 1.29. The mean body mass index (BMI) at the time of diagnosis was 19.68 ± 4.37; after 1 yr it was 21.16 ± 5.14 and after 2 yr it was 23.55 ± 5.25. Therefore growth (HtSDS) was normal at the time of diagnosis and remained normal 2 yr from diagnosis. The BMI was within the normal range for all children except one, who had a BMI above 99.6% at diagnosis and continued to be obese after that.

## *Investigations*

Human leucocyte antigen (HLA) results were available in five children but none of them had HLA-B5, HLA-B52 or HLA-B51. Acute-phase reactants [erythrocyte sedimentation rate (ESR) and C-reactive protein] were high in some but not all patients during exacerbation. Antinuclear antibodies were negative except in two patients who had weak positive reactions. Antineutrophil cytoplasmic antibodies (ANCA), extracted nuclear antigens (ENA), and other autoantibody screening was negative in all patients. Two children had a trace of protein in their urine but their kidney function was normal.

## *Treatment*

*Non-steroidal anti-inflammatory drugs (NSAID).* Five children received NSAID (naproxen, ibuprofen and diclofenac sodium) before the diagnosis of BD was made with some improvement in their joint symptoms but no significant improvement in their other symptoms.

*Steroids and immunosuppressants.* Nine children received systemic steroids during exacerbation of the disease with a remarkable improvement in their symptoms initially. Three children received azathioprine, one child received cyclosporin and another child received mycophenolate mofetil as maintenance therapy to control their symptoms before they required colchicine or thalidomide as additional treatment or as replacement therapy for the immunosuppressants.

*Colchicine.* Colchicine was used in five children with a mean ± S.D. starting dose of 13.5 ± 8.1 μg/kg/day increasing to a total of 26 ± 9.2 μg/kg/day. There was either a good response with no requirement for additional therapeutic agents in two patients, or a partial

response in three others. Side-effects reported included an itchy rash (one patient), itchy skin (one patient), hair loss (one patient), diarrhoea and abdominal pain (one patient).

*Thalidomide.* Thalidomide was used as a last option in five patients (three females). The median (range) age at the start of thalidomide treatment was 11.4 (7–16) yrs and the duration of therapy was 2.2 (1.3–4.3) yr. British guidelines for its clinical use were followed as far as possible [20]. Patients and parents were counselled about its side-effects including teratogenicity and peripheral neuropathy and consent to utilize the drug was obtained. Nerve conduction studies (NCS) were undertaken before starting the thalidomide and every 2–6 months thereafter. There was a good clinical response in all patients with rapid disappearance of pain and healing of the aphthae. In one child there was no recurrence but in others the frequency of occurrence and the severity of mouth ulcers were reduced. Likewise genital ulceration was markedly improved both in frequency and severity. Uveitis healed with improvement in vision in one patient. Two patients were commenced initially on a once weekly dose of thalidomide (1–1.6 mg/kg/week). One achieved control of his symptoms on two doses weekly (3.7 mg/kg/week) and the other achieved control on three doses weekly (2.4 mg/kg/week). The other three children initially had a daily dose (0.6–1.1 mg/kg/day). Two of the five children treated with thalidomide (one on 1 mg/kg/day and the other on 1.6 mg/kg/week) experienced pins and needles of their hands and in one the feet as well, but NCS were normal and hence thalidomide treatment was continued. This differs from the guidelines which recommend stopping thalidomide in symptomatic patients regardless of the result of NCS. However, in these two cases because of the severity of their BD symptoms and the lack of alternative agents to bring the disease under control, the thalidomide was continued. One child had a drop in the sural nerve potential 6 months after starting treatment (dose 0.6 mg/kg/day) and thalidomide was stopped but his symptoms flared up severely. He was re-started 4 months later, after his NCS returned to normal, on a smaller dose of 0.5 mg/kg/week increasing slowly to 2 mg/kg/week. His symptoms continued to be under control on this dose and remained so when the dose was reduced to 1.8 mg/kg administered at 10-day intervals. Thalidomide had to be stopped permanently in another patient as she developed pronounced sensory axonal polyneuropathy and impaired motor conduction after 1.3 yr of treatment at a dose of 1 mg/kg/day. The third child who had a dose of 1.1 mg/kg/day did not have complications and his symptoms continued to be under control as he grew, with the dose proportionately reducing to 0.8 mg/kg/day. Table 3 summarizes the thalidomide doses and complications in different children. Control of the symptoms was achieved with thalidomide alone as a maintenance therapy in one child. Two children needed low-dose prednisolone on alternate days in addition to thalidomide and the fourth patient had colchicine in addition to thalidomide to achieve control (Table 1). Birth control therapy was not prescribed as none of these patients was sexually active, but the risks were especially discussed with the parents and their families, with the need to consider such steps should the situation change.

## Discussion

We found, like others [11], that although most cases of BD were diagnosed in late childhood (median 11 yr, mean 10.1 yr), the first presentation was as early as 1.2 yr (median 4 yr). We found that more females were affected, with a ratio of 1.5 : 1, as has been reported by others [3]. This is in contrast to some reports of a male predominance [10, 21] or no sex difference [11, 22]. There was no positive family history in any of our patients to support the hypothesis of a genetic component in the pathogenesis of BD. This finding differs from that of Kone-Paut *et al.* [23] who reported a high frequency of disease in siblings and parents of paediatric BD probands (12.3%). Fresko *et al.* [24] demonstrated that genetic anticipation was present in 15 of 18 (84%) of the families with BD in the form of earlier disease onset in children compared with their parents.

The clinical picture of BD in our patients was similar to that in adults and to previous paediatric reports [8, 11]. Mucosal lesions and cutaneous symptoms were the most commonly reported features with genital aphthosis in 60%, which is similar to the finding in a recent large international study [11]. However, Krause *et al.* [22] reported lower incidences of genital ulcers in Israeli children with BD. We observed peri-anal ulcers in 30% of our patients and these are considered to be more common in childhood than in adults with BD [11]. Only one child (10%) had uveitis, which is similar to the low frequency reported in a Japanese study [3]

Table 3. Thalidomide doses and complications

| Patients | Starting dose | Maximum dose | Final dose | Complications |
|---|---|---|---|---|
| 1 | 1 mg/kg/week | 2.4 mg/kg/week (3 doses) | 2.4 mg/kg/week (3 doses) | None |
| 2 | 1.6 mg/kg/week | 3.7 mg/kg/week (2 doses) | 3.7 mg/kg/week (2 doses) | Pins and needles (normal NCS) |
| 3 | 0.6 mg/kg/day | 0.6 mg/kg/day | 1.8 mg/kg/every 10 days | Reversible neuropathy |
| 4 | 1.1 mg/kg/day | 1.1 mg/kg/day | 0.8 mg/kg/day | Pins and needles (normal NCS) |
| 5 | 1 mg/kg/day | 1 mg/kg/day | 1 mg/kg/day | Permanent neuropathy |

compared with the high frequency reported in an international collaborative study of 45% [11] and the 42% in Israeli children [22]. Neurological features including headache and intracranial hypertension were similar to those reported previously [10, 22].

Mild gastrointestinal symptoms occurred in 50% of children, which is higher than in adults and other reports in children. Five children were investigated for inflammatory bowel disease as this could cause indistinguishable oral aphthae. However, it is interesting to observe that HtSDS was normal in our patients while it is known that over 50% of Crohn's patients have a subnormal height velocity, and approximately 25% short stature [25]. The BMI was also normal in our patients, while low BMI is an indicator of disease activity in Crohn's disease [26]. Two children had pseudo-tumour cerebri, which is in accordance with previous reports [8, 11]. Neuro-Behçet's is potentially the most serious manifestation of BD and can cause meningo-encephalitis, neuropsychiatric symptoms, brain stem involvement, cranial nerve palsy, focal defects such as paralysis or ataxia, in addition to intracranial hypertension.

The frequency of headaches, arthritis and arthralgia was similar to findings in other series [10, 11]. We had two patients with iron-deficiency anaemia which was difficult to treat, which is in accordance with previous studies which showed low ferritin levels in 15% of BD patients [27].

Among BD patients, a higher than baseline prevalence of histocompatibility class HLA-B5 has been found in Middle Eastern [28] and Far Eastern countries [29], and HLA-B51 and HLA-B52 have been found in Israel [30], Iraq [31] and eastern Asia [1]. We did not find HLA-B5, HLA-B51 or HLA-B52 in any of the patients tested. As the pathergy test is known to be unhelpful in British patients [32], it was only performed in three children and was negative on each occasion.

The treatment of BD is difficult and this is reflected in the many therapeutic agents that have been utilized in attempting to control it. Amongst these agents is colchicine, which is a relatively safe and in some cases effective medication [33]. It suppresses inflammatory neutrophil function by inhibiting neutrophil endothelial cell interaction through down-modulation of adhesion molecules, which are up-regulated by inflammatory cytokines [34]. Colchicine also inhibits neutrophil migration and phagocytosis through the stabilization of microtubules [35]. It was used with some benefit and minor side-effects in five children. However, three children required thalidomide to be added to achieve complete control of their symptoms.

Thalidomide was developed in the 1950s as a sedative but was withdrawn in 1961 after its teratogenic effect was recognized. It has been used in a variety of dermatological conditions during the past few decades. The list of disorders thought to have an autoimmune or inflammatory basis for which there has been a more recent selective reintroduction of thalidomide includes BD. Diseases for which thalidomide has been found to be effective include erythema nodosum leprosum, prurigo nodularis, actinic prurigo, discoid lupus erythematosus, aphthous stomatitis, graft-versus-host disease as well as BD [36]. Thalidomide acts as an immunomodulating agent on T-cell subsets [37]. It has been used successfully in adult BD, particularly for mucocutaneous lesions [17, 18, 37]. Recently Shek *et al.* [19] reported its use in a young child with BD when multiple treatment regimens had failed. Hamuryudan *et al.* [17] found that in adults thalidomide in a dose of 100 mg/day was as effective as 300 mg/day but was associated with neuropathy in four of 63 patients. In our patients we observed neuropathy in two patients, which was irreversible in one of them. This number is too small to draw any conclusion about the appropriate dose, but in our experience small doses like 1–2 mg/kg/week appear safe to start with and may be as effective as higher doses. What is more, they can be increased to twice or thrice weekly, titrated against the benefit, and may eliminate the risk of unnecessarily high doses causing neurological sequelae that may result in discontinuation of the drug as a therapeutic agent. Regular NCS are crucial to detect neuropathy as early as possible before it becomes irreversible. What is clear is that the benefit of the drug is so striking that patients and their families are prepared to run the risks of adverse sequelae because of the symptomatic relief the drug offers. We have attempted to adhere to the British guidelines for thalidomide use but found it difficult to discontinue the drug in some patients who experienced paraesthesia but had normal NCS. These particular patients and their parents were reluctant to stop thalidomide in view of the severity of their symptoms. In one of our patients we observed a mixed sensory and motor neuropathy, which was unusual as thalidomide usually causes sensory paraesthesiae. However, proximal weakness has been reported as a side-effect of thalidomide [12] and recently it has been demonstrated to affect smaller diameter motor nerve fibres even before changes in sural sensory nerve action potentials occur [38]. By titrating the dose to the minimal amount that is effective, the risks of neuropathy are lowered but clearly teratogenic complications will still be present for girls of reproductive age. In the future, thalidomide analogues could provide a safer and more effective option for treatment. Recently developed thalidomide analogues are currently being assessed in laboratory studies and clinical trials [39–41].

## Conclusion

BD in children is similar to that in adults. Thalidomide provides a useful therapeutic option in cases with severe oral and genital ulceration which had not responded to other therapies. The paediatricians must remain vigilant to the continuing danger of axonal neuropathy and teratogenesis at all times during thalidomide therapy.

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