CLINICAL REPORT

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Constitutional Trisomy 8 and Behçet Syndrome

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The characteristic clinical features of constitutional trisomy 8 include varying degrees of developmental delay, joint contractures and deep palmar and plantar creases. There is an established literature, which describes features of Behçet syndrome occurring in phenotypically normal individuals with myelodysplastic syndromes and trisomy 8 in their bone marrow. In this article, we describe four patients with constitutional trisomy 8, all with varying clinical phenotypes, who developed features of Behçet, in particular but not exclusively mucocutaneous ulceration. In addition, we examined gene copy numbers of the variable-number neutrophil defensin genes *DEFA1A3* in one of the cases (case 1) and her parents, together with 14 cases of Behçet syndrome in comparison with 121 normal controls. The gene copy number was highest in case 1 (copy number 14) and was also increased in her parents (both copy number 9). However the mean copy number for *DEFA1A3* among the 14 Behçet syndrome patients was actually lower (5.1) than among the controls (mean of 6.8 copies). Thus, we conclude that patients with constitutional trisomy 8 and those with trisomy 8 confined to the bone marrow are both at increased risk of developing features of Behçet syndrome. The mechanism may relate to increased chromosome 8 gene dosage with further analysis of candidate genes on chromosome 8 required.

Key words: trisomy 8; Behçet syndrome; defensin genes

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INTRODUCTION

The clinical phenotype associated with constitutional trisomy 8 is very variable. The main features are varying degrees of developmental delay, joint contractures and deep palmar and plantar creases. Agenesis of the corpus callosum, skeletal abnormalities and renal anomalies are also common. Chromosomal analysis usually shows trisomy 8/normal mosaicism. There is a well-recognized association between constitutional trisomy 8 and malignancies, in particular hematological myeloid malignancies and myelodysplastic syndromes [Brady et al., 2000]. Phenotypically normal individuals with a hematological malignancy and a leukemia related trisomy 8 cell line in the bone marrow are considered to have acquired rather than constitutional trisomy 8.

Behçet syndrome is a systemic inflammatory disease of unknown etiology characterized clinically by recurrent oral ulcers, genital ulcers, eye lesions and skin lesions including the "pathergy" phenomenon. One of the pathological hallmarks is that of

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neutrophil infiltration of involved tissue associated with neutrophil hyperfunction. Behçet syndrome has occurred in a number of patients with myelodysplastic syndromes who have trisomy 8 in their bone marrow [Yano et al., 1996; Ohno et al., 1997; Nawata et al., 1999; Oh et al., 1999; Kuttikat et al., 2005; Fine et al., 2007; Ahn et al., 2008; Lin et al., 2008]. One phenotypically normal patient with constitutional trisomy 8 mosaicism (CT8M) has been reported with recurrent mouth ulcers reminiscent of Behçet syndrome and macrocytosis, [Baidas et al., 2004], a second patient with CT8M and multiple congenital abnormalities had recurrent oral and genital ulcers as well as intestinal Behçet syndrome [Ando et al., 2005], and a third patient with CT8M and congenital malalignment of the halluces presented with recurrent aphthous stomatitis, episodes of genital ulceration, macrocytosis, Raynaud phenomenon, fibromyalgia, episodic knee pain, intermittent episodic abdominal pain and diarrhea and myelodysplastic syndrome [Fine et al., 2007]. The third patient did not fulfill the diagnostic criteria for Behçet syndrome, but she was found to be HLA-B51 positive, with a negative pathergy test.

In this article, we describe four additional patients with constitutional trisomy 8 who developed recurrent severe mouth ulcers with or without genital ulcers that could represent a *forme fruste* of Behçet syndrome. Furthermore, as defensin genes are possible candidates for a gene dosage effect of chromosome 8 contributing thus to the risk of Behçet's disease, we examined gene copy numbers of the variable-number neutrophil defensin genes *DEFA1A3* in one of the cases (case 1) and her parents, together with 14 cases of Behçet syndrome in comparison with 121 normal controls.

Patient 1

Patient 1 was born after an uneventful pregnancy at term by normal delivery with a birth weight of 3.15 kg (25th centile). She is the second child of unrelated parents of European origin. A large dermoid cyst was surgically removed from her forehead at the age of 18 months. She has mild developmental delay and attends mainstream school with extra support. She has a prominent forehead, deep set eyes, mild hypertelorism with a broad nasal root, deep palmar and plantar creases, stiff PIP joints in both hands and the MTP joints are subluxated bilaterally. The wrists, elbows and subtalar joints are hypermobile, and she has mild thoracolumbar scoliosis. CT scans of the brain at the age of 4 years and 11 years showed agenesis of the corpus callosum. A renal ultrasound scan was normal, and full blood counts and immunoglobulins have been normal on several occasions.

Constitutional trisomy 8 was diagnosed at the age of 11 years. Blood chromosomes showed 47,XX,+8 in all 30 cells examined.

Mouth ulcers first appeared at the age of 5 years. When last reviewed in clinic at the age of 13 years, she had several mouth ulcers with some scarring over the mucosa of the lower lip. She has also had recurrent skin rashes in the last 2 years and on one occasion, erythema multiforme was diagnosed. To date she has not had any genital or eye symptoms nor has she demonstrated any pathergy with phlebotomy. The patient has been referred to a specialist Behçet clinic and is currently being monitored. Her mouth ulcers responded well to topical steroids in the past, but have recently become more difficult to control. At 13 years, her height was 160 cm (75th centile), her weight was 45.1 kg (50th centile) and her head circumference was 54.7 cm (75th–90th centile).

Patient 2

Patient 2, who is now 23 years old, was born following a normal pregnancy and delivery. His birth weight was 4.6 kg (98th centile). At birth, he was noted to have a cleft soft palate, an asymptomatic ventricular septal defect, large hands and feet, and a left hydronephrosis. Blood karyotype at birth showed, 47,XY+8[14]/46,XY-[4]. He has moderate developmental delay that required special education. At age 19, clinical examination showed abnormal dermatoglyphics, varus deformity of both wrists, facial asymmetry, dysplastic ears, scoliosis, leg asymmetry, and deep plantar creases bilaterally. A repeat blood karyotype at age 19 showed 47,XY+8[3]/46,XY[7].

He presented to the Rheumatology Clinic at 19 years with a 3-month history of painful ulcers on his scrotum, penis and peri-anal areas. He had a long history of recurrent crops of mouth ulcers and he also complained more recently of some headaches. He had no joint or other dermatological symptoms. On physical examination, no oral ulcers were apparent but well circumscribed punched out ulcers were present on his scrotum, penis and peri-anal areas. There was no evidence of pathergy following phlebotomy. His height was 188 cm (91st–98th centile), his weight was 88.9 kg (91st–98th centile) and his head circumference was 63 cm (>97th centile).

Investigations showed a normal full blood count. A blood film showed no features to suggest myelodysplasia and a bone marrow examination was therefore not performed. The erythrocyte sedimentation rate (ESR) was 34 mm/hr and C-reactive protein was 43 mg/L. Renal and hepatic function, serum calcium, rheumatoid factor and anti-nuclear factor were all normal or negative. A previous recent colonoscopy had given a normal result. Cultures for herpes simplex virus and hepatitis screen were both negative. MRI brain confirmed agenesis of the corpus callosum with no other abnormalities detected.

While there were insufficient criteria to make a definite diagnosis, a possible diagnosis of Behçet syndrome was made on the basis of recurrent oral and genital ulcers. For symptomatic relief, he was commenced on a trial of treatment with deltacortril 30 mg/day. Within 2 weeks, he was considerably improved and his deltacortril was gradually reduced to 10 mg/day. Ulcers recurred with steroid reduction below 10 mg and azathioprine 100 mg daily was added. At the time of last follow up, he was asymptomatic on azathioprine 75 mgs and deltacortril 5 mg daily.

Patient 3

Patient 3 presented to the Genetics department at the age of 14 years. She was the youngest of five children born to unrelated parents at term by elective cesarean, weighing 2.92 kg (9th–25th centile). Anal atresia was noted after birth, which was subsequently corrected surgically. Ureteric stenosis was diagnosed at colostomy surgery. In addition, she was found to have triphalangeal thumbs bilaterally. She attended a special needs school because of learning difficulties. On examination, her height was 168.7 cm (91st centile), her weight was 53.6 kg (50th–75th centile), and her head circumference was

56 cm (97th centile). Hearing and vision were normal. Townes-Brocks syndrome was suspected clinically, and a nonsense mutation in the *SALL1* gene was identified. The patient had recently developed oral and genital/perianal ulceration. A biopsy taken from one of the oral ulcers showed stratified squamous non-keratinizing mucosa with an ulcer and a dense infiltrate of lymphocytes and neutrophils in subepithelial connective tissue. Small vessels showed swelling of their endothelium and were sometimes plugged with neutrophils and occasionally fibrin. A vulval introitus biopsy demonstrated intensely inflamed and ulcerated stratified squamous non-keratinizing mucosa, edematous epithelium containing intra-epithelial neutrophils and lymphocytes, and subepithelial tissue infiltrated by neutrophils and mononuclear cells. There was endothelial swelling of the small vessels with neutrophil extravasation and occasional fibrin plugs. The histological appearance was thought to be in keeping with Behçet syndrome. A full blood count, B12, ferritin and folate were normal, but the CRP was high at 115. The oral ulcers responded to benzydamine hydrochloride and chlorhexidine digluconate.

Blood chromosomes showed a mosaic 47,XX,+8/46,XX karyotype.

Patient 4

Patient 4 is a phenotypically normal 30-year-old woman who was karyotyped at the age of 28 years because of recurrent miscarriages, and was found to have constitutional trisomy 8 with a blood karyotype 47,XX,+8[2]/46,XX[8]. She was born at 42 weeks gestation weighing 4.64 kg (99.6th centile). She has suffered from severe recurrent mouth ulcers, up to a size of 2 cm, since the age of four years, which would take months to heal, and for which she found no effective treatment. She has recently been diagnosed with Graves disease. Her height is 1.64 m (50th centile), her weight 59 kg (50th–75th centile) and her head circumference is 56 cm (90th–97th centile).

Investigation of Defensin Copy Number

Defensin genes are possible candidates for a gene dosage effect of chromosome 8 contributing to the risk of Behçet syndrome. The defensins are microbicidal peptides with direct cytotoxic properties. Of the six known human alpha-defensins, *DEFA1* to *DEFA4* are expressed by granulocytes and certain lymphocytes, and *DEFA5* and *DEFA6* are located in the Paneth cells of the intestinal tract. The beta defensins are located on epithelial surfaces such as those of the respiratory tract, urinary tract and vagina. Defensins can also signal and activate other immune system components, including T-lymphocytes and NK-cells, making them respond as if they were confronting an infection. Human neutrophil defensins can induce TNF-α production by monocytes, and TNF-α can induce synthesis of several human beta defensins. Defensin genes form a cluster at 8p23 [Lehrer et al., 1991] and gene copy numbers of both alpha-defensin *DEFA1A* [Aldred et al., 2005] and seven beta-defensin genes, including *DEFB4* and *DEFB104*, on chromosome 8 [Hollox et al., 2003; Linzmeier and Ganz, 2005] are known to be (independently) variable in normal subjects. One of these genes, *DEFA1*, was shown to be up regulated in AML+8 patients [Virtaneva et al., 2001].

Neutrophil hyperfunction is well recognized in Behçet syndrome. We therefore investigated the copy numbers of the variable-number neutrophil defensin genes *DEFA1A3* in patients with Behçet syndrome. We analyzed *DEFA1A3* copy number in our patient 1 who has 100% trisomy 8 cells in peripheral blood using methods published elsewhere [Aldred et al., 2005]. Our patient 1 has a copy number of 14, the highest value recorded so far in studies of more than 100 unrelated individuals. Given that nearly all people have between four and ten copies of *DEFA1A3*, this value is at the extreme high end of the expected range even for trisomy 8. The parents of patient 1 both have measured copy number of 9 at *DEFA1A3*. We therefore investigated the hypothesis that high *DEFA1A3* copy number is a risk factor for Behçet syndrome by measuring the *DEFA1A3* copy number in a further 14 patients with classic Behçet syndrome and compared them to a set of 121 unselected controls whose phenotypic status with regard to ulceration is unknown; patient 1 and her parents are also included (arrowed) in Figure 1. Two of the 14 patients with classic Behçet syndrome had been karyotyped with a normal result. The mean copy number for *DEFA1A3* among these 14 Behçet syndrome

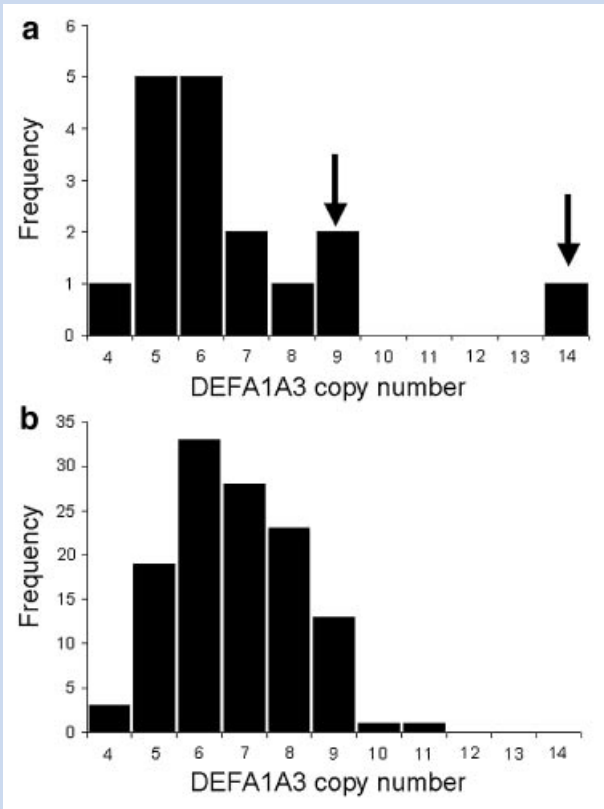

FIG. 1. a: Copy numbers of the variable-number neutrophil defensin genes *DEFA1A3* in case 1 (arrowed, 14 copies), her parents (arrowed, both nine copies) and in 14 unrelated patients with Behçet syndrome. b: Corresponding distribution of copy numbers in 121 unaffected controls.

patients was actually lower (5.1) than among the controls (mean of 6.8 copies). Similarly, measurement of copy number for the variable beta-defensin genes, including *DEFB4* and *DEFB104*, did not show an unusually high copy number in patient 1, nor was copy number markedly elevated in the 14 unrelated patients (data not shown).

DISCUSSION

In this study, we report four patients with constitutional trisomy 8 who have variable clinical phenotypes but who all have features of Behçet syndrome, chiefly mucocutaneous involvement. Behçet syndrome has been suspected in constitutional trisomy 8 three times previously in single case reports [Baidas et al., 2004; Ando et al., 2005; Fine et al., 2007]. The first patient, a phenotypically normal 32-year-old female with constitutional trisomy 8, was found to have macrocytosis and recurrent severe oral ulcers unresponsive to steroids, but responsive to thalidomide [Baidas et al., 2004]. The second patient, a 49-year-old male with multiple congenital abnormalities, suffered from recurrent oral and genital ulcers since the age of 20 years, and subsequently developed intestinal Behçet syndrome [Ando et al., 2005]. The third patient, a female 28-year-old patient with congenital malalignment of her halluces and retention of deciduous teeth as possible physical manifestations of mosaic trisomy 8, had experienced recurrent aphthous stomatitis since the age of 10 years, and she also had several episodes of genital ulceration. She subsequently developed myelodysplastic syndrome, fibromyalgia, intermittent abdominal pain and diarrhea, episodic knee pain, Raynaud phenomenon and possible early scleroderma with positive ANA. She was shown to be HLA B51 positive, but the pathergy test was negative. A diagnosis of Behçet syndrome was strongly suspected, but there was insufficient evidence for a confident diagnosis.

The association between constitutional trisomy 8 and an increased risk of myelodysplasia is well recognized, as is the association between genotypically normal individuals who have myelodysplastic syndromes and the finding of trisomy 8 in their bone marrow. Some of these patients have been reported to have developed Behçet syndrome [Yano et al., 1996; Ohno et al., 1997; Nawata et al., 1999; Oh et al., 1999; Kuttikat et al., 2005; Fine et al., 2007; Ahn et al., 2008; Lin et al., 2008]. Most of these reported myelodysplasia cases had complete trisomy 8, one patient had trisomy 8p23-pter [Oh et al., 1999]. Our additional four cases with CT8M confirm that not only patients with trisomy 8 in their bone marrow, but also patients with constitutional trisomy 8 may be at increased risk of developing symptoms suggestive of Behçet syndrome, in the absence of a demonstrated bone marrow disorder.

Recurrent mucocutaneous ulceration is the main clinical manifestation of Behçet's disease in our patients with only some demonstrating additional features. The mouth ulcers seen in our patients were more severe and deeper than those seen in common aphthous-type ulcers, and they also occurred in non-traumatic sites. It certainly could be argued that some of these patients do not in fact have Behçet syndrome as they do not meet criteria for diagnosis [Disease ISGfBs, 1990]. While they demonstrate a paucity of other Behçet features such as ophthalmologic or neurologic involvement, it is clear that they have severe mucocutaneous disease and that this is immune-mediated as demonstrated both by the findings on biopsy and by their therapeutic response to immunemodulators.

AML trisomy 8 blast cells have been shown to over express genes on chromosome 8 by microarray studies on the bone marrow of 10 AML+8 patients and 7 normal controls, suggesting gene dosage effects underlying AML+8 [Virtaneva et al., 2001]. Of 29 genes most significantly up regulated in AML+8, for which a chromosomal assignment could be made, seven map to chromosome 8. To date, the association between constitutional trisomy 8 and features of Behçet syndrome, in particular orogenital ulceration, is poorly understood. It is conceivable that genes on chromosome 8, possibly 8p23-pter, could be over-expressed in these individuals and account for these clinical features. Further analysis of these patients' chromosome 8-related genetic profile may provide clues to our understanding of Behçet syndrome in the wider community.

One such candidate gene grouping contains the alpha- and beta-defensins, important in immune activation at epithelial surfaces. This study therefore also examined the question of defensin gene copy number in one of our cases (patient 1), her parents and also in classic Behçet syndrome in comparison with a matched set of normal controls. While results indicate a high copy number of the alpha-defensin gene *DEFA1A3* both in our patient 1 and to a lesser extent in her parents, there was no such elevation observed in our classic Behçet cohort. While we have taken great care over copy number measurement at *DEFA1A3*, these measurements remain technically extremely challenging, and although the mean *DEFA1A3*copy number in the classic Behçet syndrome samples is lower than in the unselected population, taking our *DEFA1A3*typing alongside further analysis of the same samples (data not shown) we have no convincing evidence that *DEFA1A3* copy number is *significantly* lower. The very high *DEFA1A3* copy number in trisomy 8 patient 1 is therefore an interesting but isolated observation. Over expression of *DEFA1A3* may therefore possibly contribute to disease expression in our constitutional trisomy 8 patients but dosage of other chromosome 8 genes may be more important, and our results make it very unlikely that *DEFA1A3* copy number contributes to the expression of disease in classic Behçet syndrome.

TNF-α, with its gene located on chromosome 6p21.3, is implicated in the pathogenesis of Behçet syndrome. Peripheral blood CD45 gamma-delta T cells in Behçet's disease produce >50-fold more TNF-α than controls when stimulated with phorbol myristate acetate and anti-CD3 [Travis et al., 2001]. Treatment with a chimeric IgG1 monoclonal antibody directed against TNF-α (infliximab) has been shown to induce remission of gastrointestinal ulceration, ocular inflammation and other manifestations of Behçet syndrome [Goossens et al., 2001; Sfikakis et al., 2001; Travis et al., 2001]. The improvement and remission of long-lasting symptoms of Behçet syndrome directly after an infusion of infliximab indicates a central role of TNF-α in the pathogenesis of Behçet syndrome. It remains to be seen whether TNF-α can up-regulate genes expressed on chromosome 8 such as the defensins.

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