

Cutaneous and other lupus-like symptoms in carriers of X-linked chronic granulomatous disease: incidence and autoimmune serology

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Introduction

Chronic granulomatous disease (CGD) is a relatively rare immune deficiency, with an estimated incidence of 1 : 250 000 births [1]. It is characterized by severe bacterial and fungal infections, predominantly of the lymph nodes, subcutaneous tissues, lungs, liver and bones. Gastrointestinal manifestations include a colitis, which may be mistaken for Crohn's disease, perianal abscesses and obstruction (particularly gastric outlet and oesophageal) caused by non-infectious granuloma formation [1,2]. The disease is diagnosed normally in young children, but may manifest later [3].

The biochemical basis of the syndrome is a defect in one of the components of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, which is integral to the generation of the respiratory burst and the killing of catalase positive bacteria and fungi. A number of gene defects have been described, including X-linked chronic granulomatous disease (X-CGD) and autosomal recessive (AR) forms [4]. Seventy per cent of cases are X-linked [3]. The disease carries a significant morbidity and mortality

Summary

The objective of this study was to determine the utility of anti-nuclear antibody (ANA) testing in the investigation of cutaneous and other lupus symptoms in female carriers of X-linked chronic granulomatous disease (CGD). We undertook a prospective study of 19 carrier mothers attending our institution, with direct questioning of carriers concerning symptoms and testing for anti-nuclear and anti-phospholipid antibodies. A total of 58% reported significant photosensitive skin rashes, 42% reported mouth ulcers and 37% complained of joint pains that could not be attributed to other known causes. Anti-nuclear antibody (ANA) testing was negative in 73% of all carriers. The five positive ANAs were of low titre (maximum 1 : 320 on Hep 2 cells in two women) and only one weak positive double-stranded DNA antibody and no extractable nuclear antibodies were found. Several of the mothers, despite negative serology, benefited from referral to a specialist, and in some cases to specific treatment. A history of skin rashes, joint pain, fatigue and mouth ulcers should be sought actively in the female relatives of X-CGD patients but negative lupus serology should not preclude referral to appropriate dermatology or rheumatology services, as symptoms may respond well to appropriate treatment.

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despite the advent of modern anti-bacterial and anti-fungal agents [2,3].

As NADPH oxidase is not required for neutrophil development, carriers of X-CGD have two populations of neutrophils, depending on which of their X-chromosomes is inactivated during lyonization. Those neutrophils with inactivation of the X-chromosome carrying the defective gene will have a normal respiratory burst [as assayed by nitroblue tetrazolium (NBT) or dihydrorhodamine (DHR) reduction], while those with inactivation of the normal X will have an absent response in these assays [1]. It is recognized increasingly that carrier status may be associated with a variety of manifestations including infections and ocular lesions [3,5].

In 1957 Landing described lupus-like symptoms in the mother of a young patient with CGD [6]. US registry data suggest that 9% of kindreds with X-linked-CGD have at least one individual with discoid lupus erythematosus (DLE) [3]. Although lupus-like signs and symptoms, in particular DLE, are described in multiple anecdotal publications in carriers of X-linked CGD, serum autoantibodies are not always reported and it is not clear whether

autoimmune serology is consistent with classical discoid or other forms of lupus.

We noted that a number of our X-CGD patients' female relatives described symptoms compatible with lupus erythematosus (LE), but autoantibody testing did not reveal the typical patterns seen in lupus.

We therefore undertook a prospective study of carrier women attending our specialized CGD clinic to ascertain both the frequency of these symptoms and utility of autoantibody serology in assisting diagnosis.

Methods

Carrier mothers attending the clinic with their affected children were questioned systematically during a 18-month period between January 2004 and May 2006. Mothers were questioned about a number of symptoms that could be compatible with LE. They were also asked if they had ever seen a doctor [general practitioner (GP) or rheumatologist] concerning these symptoms. After informed consent, blood was either taken for autoimmune serology, or results requested from other centres if previously analysed there.

Precise methods for analysing autoantibodies varied between centres, and local reference ranges were used in interpretation. Because of evolving laboratory practice and differing practice between laboratories, not all patients had dsDNA antibodies or antibodies to extractable nuclear antigens (ENA) measured if anti-nuclear antibody (ANA) was negative.

Results

Clinical histories and autoantibody serology was obtained in 19 women (one grandmother, 18 mothers). Carriers had all been identified by intermediate reduction of NBT or DHR. The age of the carriers at the time of questioning ranged from 17 years to 59 years (mean 36 years). Results are summarized in Table 1.

Symptoms

Carriers were asked if they had recurrent mouth ulcers, photosensitive or other skin rashes, joint pain and fatigue. Any other symptoms volunteered were recorded.

Three carriers volunteered no symptoms. Two carriers suffered from acne and one had recurrent boils, on occasion requiring drainage.

Mouth ulcers were reported in eight carriers (42%), with significant photosensitive skin rashes in 11 (58%). Seven (37%) reported joint pains that could not be attributed to another cause (two carriers with history of trauma and osteoarthritis were excluded). Eight carriers (42%) reported fatigue that they felt was excessive to their lifestyle.

One mother reported intermittent diarrhoea, and another had had a transient ischaemic attack aged 37 years and a cerebrovascular accident aged 39 years.

Table 1. Summary of symptoms and results.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	
Symptoms																				
Photosensitive rash	+	+	+	+	+	+	+	+	+	+					+		+			+
Joint pain	+		+	x	+											x	+			
Mouth ulcers		+	+					+		+				+	+					
Fatigue	+		+	+								+		+	+					
Acne		+										+		+						
Skin infection											+									
TIA/CVA												+								
ANA (on Hep2 cells)	1 : 160	N	1 : 320	N	1 : 160	1 : 320	N	N	N	N	N	N	N	1 : 160	N	N	N	N	N	N
dsDNA antibodies	N	N	N		N	N			N		N			WP	N	N	N	N	N	N
ENA antibodies	N	N	N		N	N			N		N			N	N	N	N	N	N	N
Antiphospholipid antibodies (anticardiolipin and lupus anticoagulant)	N	N	N		N	N			N		N	WP		N	N	N	N	N	N	N
% Reduction NBT	42	56	39	25	38	35	78	30	90	33	50	24	70	50	50	61				10

+Symptom present; x: osteoarthritis/previous trauma; N: negative; WP: weak positive; TIA: transient ischaemic attack; CVA: cardiovascular accident; ENA: antibodies to extractable nuclear antigens; NBT: nitroblue tetrazolium; ANA: anti-nuclear antibody.

Symptoms in nine carriers were of sufficient severity that they had been referred to a rheumatologist. In five of these a diagnosis of attenuated lupus or cutaneous discoid lupus was made after skin biopsy. This represents 26% of the cohort of mothers tested, or 12% of all our total X-linked kindreds ($n = 32$). There was significant improvement or resolution of skin problems on appropriate treatment (hydroxychloroquine or related drugs). Other symptoms (joint pains, mouth ulcers) also improved on these treatments.

Autoimmune serology

All 19 carriers had had an ANA undertaken; this was negative in 14 (73%) and positive in five women. However, three of these had only weak positive results (1 : 160 on Hep2 cells) and the maximum titre in the other two was only 1 : 320 (on Hep 2 cells). These positive results occurred in four women reporting a photosensitive rash, and one woman who reported only joint pains and mouth ulcers. She also had a weak positive dsDNA antibody (15.5, normal < 10). All other dsDNA antibody tests (14 performed in total) were negative.

Fourteen carriers (including all five with positive ANAs) had antibodies to extractable nuclear antigens (SS-A, SS-B, Sm, RNP, SCL-70, Jo-1) measured; these tests were all negative.

Anti-cardiolipin antibodies were negative in all 16 carriers where they were measured. A lupus anti-coagulant test was performed in 17 cases; this was negative in 16 patients and weak positive in one mother.

Carrier status by NBT

Results were available for percentage reduction of NBT by neutrophils after phorbol myristate acetate (PMA) stimulation in 17 carriers. The range was 10–90 (mean 46%, median 42%). Both the 10% and 90% carriers had photosensitive skin rashes, and there was no correlation between the degree of lyonization and symptoms.

Discussion

Lupus-like symptoms have been reported anecdotally in carriers of X-CGD, but only a few small case-series are available (summarized in Table 2). Most studies report DLE-like cutaneous manifestations, frequently with photosensitivity [7–14], and aphthous ulceration [7–9,11,15]. Raynaud's phenomenon is also well described [7,11,16]. We were aware of a fatal outcome in one carrier mother with CGD and lupus symptoms (not included in the present series), and had become increasingly aware in our clinical practice of carrier mothers reporting a variety of joint, skin and other symptoms. We therefore set out to look more systematically at this group, with particular reference to serological findings as it was our impression that symptoms may be ignored by medical professionals if lupus-serology is negative.

We found cutaneous symptoms (skin rashes, photosensitivity) in 58% of our carrier cohort, with a similar incidence of mouth ulcers (42%). These figures are comparable to a Dutch 1990 questionnaire study of X-CGD carriers: 63% reported skin eruptions and 77% recurrent aphthous ulcers [11]. The incidence of definite cutaneous LE we noted (12%) is similar to the incidence described in larger registry studies [3]. Both the published literature and our series suggest that DLE-like lesions and mouth ulcers in X-CGD carriers respond favourably to standard treatment regimens (hydroxychloroquine, mepacrine) [7–10,17].

A number of serological markers are included in the case definition for lupus, including positive anti-nuclear antibodies (ANA) and Smith antibodies. More than 95% of patients who fulfil American College of Rheumatology criteria for SLE have a positive ANA. Patients with cutaneous forms of lupus are less likely to have positive serology, although anti-Ro/Sjögren's syndrome A (SS-A) antibodies are noted in up to 70% of cases of subacute cutaneous LE [18] and about 50% of cases of discoid LE have a positive ANA [19]. Anticardiolipin antibodies are also described in discoid lupus, with a frequency of 68% [20]. In our cohort the ANA was negative in most carriers (73%) and of low titre in the others. Only two of the five carriers with definite discoid LE had a weak positive ANA, none had Ro/SSA antibodies and none of these five had anti-phospholipid antibodies. Thirty-seven cases of cutaneous lupus-like problems in carriers of X-CGD have been reported in the literature. Autoantibodies were measured and reported in only 25 patients and the majority ($n = 20$, 80%) of these were negative (see Table 2) [8,10,17,21]. Thus, definitive LE serology is not found in X-CGD carriers with discoid lupus or other lupus-like symptoms.

Patients with SLE with C2 deficiency have marked skin manifestations and autoantibody profiles that differ from classical SLE [22]. Reduced clearance of apoptotic cells, which express lupus autoantigens as cryptic epitopes, is a recognized feature of systemic lupus erythematosus, especially when associated with deficiency of an early complement component [23]. Data on protein levels or activity of the classical complement pathway are not available in our group of carrier mothers. However, both the process of apoptosis and clearance of apoptotic cells are impaired in patients with X-CGD with impaired expression of phosphatidyl serine, which is crucial for apoptotic cell clearance, and impaired production of prostaglandin D₂ and transforming growth factor β , both potent anti-inflammatory agents, during the phagocytosis of opsonized and non-opsonized apoptotic targets [24,25]. Together this suggests that in X-CGD damaged cells undergo abnormal apoptosis, are poorly cleared by the reticuloendothelial system and the normal anti-inflammatory response is impaired. This could result in chronic inflammation at sites of increased apoptosis (e.g. light-exposed skin) and generation of autoimmune responses. Manifestations of CGD have been linked to a

Table 2. Summary of literature review of cutaneous manifestations of X-linked chronic granulomatous disease (X-CGD) carriers.

Ref.	Author	Year	No. carriers in series	No. carriers affected	Skin manifestation	ANA	Other autoantibodies	Comments
[6]	Landing & Shirley	1957	1	1	'Lupus'	?		
[27]	McFarlane <i>et al.</i>	1967	1	1	Chronic DLE	?		Jessners-like histology
[16]	Thompson & Soothill	1970	8	2	LE-like	?		
[7]	Schaller	1972	2	2	DLE	Neg.		Photosensitive, treated chloroquine, Reynaud's, stomatitis, arthritis
[28]	Humbert <i>et al.</i>	1976	2	2	LE-like	Neg.		
[29]	Nelson <i>et al.</i>	1977	1	1	Arcuate rash	Neg.		Jessners-like histology
[8,9]	Kragballe <i>et al.</i> , Brandrup <i>et al.</i>	1981	15	5	DLE-like	Neg.		10 cases: aphthous ulcers. All DLE photosensitive. Treated hydroxychloroquine
[30,31]	Finlay <i>et al.</i> , Chowdhury <i>et al.</i>	1983	2	2	LE-like	Neg.		Also aphthous ulcers
[17]	Levinsky <i>et al.</i>	1981	1	1	LE-like	Pos 1 : 60	dsDNA weak pos.	Mouth ulcers. Treated chloroquine
[10]	Barton & Johnson	1986	2	2	DLE-like	Low titre pos	dsDNA neg one RNP pos.	Photosensitive, treated mepacrine
[32]	Garioch <i>et al.</i>	1989	5	5	2 DLE-like 3 photosens rash	Neg.		
[11]	Sillevis <i>et al.</i>	1990	16	5	DLE-like	?		11/16 aphthous ulcers, 10/16 skin rash, 7/16 photosensitive
[12]	Yeaman <i>et al.</i>	1992	1	1	LE-like	Neg.	ENA neg.	Oral ulcers/photosensitive
[13]	Hafner <i>et al.</i>	1992	1	1	LE-like	Neg.	dsDNA neg, Sm neg.	Photosensitive
[33]	Bernhard	1987	1	1	LE-like	?		Stomatitis
[34]	Lovas <i>et al.</i>	1995	1	1	DLE-like	?	Oral ulcers	Oral ulcers,
[14]	Cuny <i>et al.</i>	1990	1	1	LE-like	Neg.	ENA neg.	photosensitive
[35]	Cordoba-Guijarro <i>et al.</i>	2000	1	1	LE-like	Neg.	dsDNA neg, ENA neg.	
[21]	Rupec <i>et al.</i>	2000	2	2	DLE	Pos 1 : 320	dsDNA neg, ENA neg.	

?Not available.

variety of polymorphisms, including variant alleles of Fcγ receptor IIa genes [26]. Further investigation of this in carrier females may help to predict the occurrence or severity of the symptoms we report here.

Conclusion

Symptoms of photosensitive and other skin rashes, joint pains, fatigue and aphthous ulceration are common in carriers of X-CGD. If significant, consideration should be given to referral to a rheumatologist or dermatologist and appropriate treatment initiated. Negative autoimmune serology is probable, and should not influence diagnosis and treatment.

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