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Age of onset in successive generations of patients with a spondyloarthropathy

Juvenile spondyloarthropathy (JSPA) is as yet not a fully defined disorder,¹ but can be considered as the juvenile form of the adult spondyloarthropathy (SPA). Preliminary criteria for the latter have been proposed,² the tip of the iceberg being ankylosing spondylitis. These criteria are also applicable for JSPA.³ The clinical presentation of JSPA may differ from adult onset SPA,⁴ but eventually a considerable percentage of patients with JSPA will develop a clinical picture indistinguishable from adult SPA.

Ankylosing spondylitis has a strong association with the presence of the HLA-B27 antigen.⁵ The risk for a first degree HLA-B27 positive relative of a patient with ankylosing spondylitis developing that disease is about 20%.⁶ The higher prevalence of SPA in parents of children with early onset pauci-articular juvenile chronic arthritis than in the general population was reported previously.⁷ Possibly, the prevalence of SPA among parents with a child with JSPA might also be higher than in the general population. We report that there is a tendency towards an earlier onset of SPA in the next generation.

Seven index patients were seen in the paediatric rheumatology clinic and presented with JSPA according to the European Spondyloarthropathy Study Group (ESSG) criteria,² around the age of 10 (table). The age of onset in the children varied from 5 to 10 years (mean 8.3) and in the parents from 21 to 42 years (mean 31.1). The year of onset is the year the first complaints relating to the SPA were noticed. The clinical picture of the

juvenile patients consisted of an asymmetric, IgM rheumatoid factor negative oligoarthritis with a predilection for joints in the lower extremities combined with features of enthesitis. Symptoms of inflammation of the lower lumbar spine were rare at presentation. All the children carried the HLA-B27 antigen. One of the parents of these seven index patients developed SPA (retrospectively diagnosed) according to the ESSG criteria² in their third or fourth decade.

There may be several explanations for our observation. It could be a coincidental finding or biased by our daily practice: a parent might pay more attention to joint or back complaints when his/her child is diagnosed as having JSPA. It might also be explained by a simultaneous infection in the presence of the HLA-B27 antigen in the family members of two generations. A marked discrepancy between the calendar years of onset for the children and parents pleads against temporal clustering. Another explanation might be genetic anticipation, which has been clearly delineated in some diseases, where there is a tendency for the disease to start with an earlier age of onset over subsequent generations. This phenomenon has been described in several monogenic neurodegenerative disorders and possibly exists in familial rheumatoid arthritis.⁸ Recent observations suggest that factors other than genetic factors may be associated with SPA.⁹ A variation in age of onset (8-51 years) was noted in one multicase family with a tendency towards an earlier age of onset in successive generations.¹⁰

Extended studies of HLA and non-HLA genes are required to answer the question whether the phenomenon of genetic anticipation occurs in SPA.

As unstable trinucleotide repeats have been described in neurodegenerative diseases correlating with the clinical phenomenon of genetic anticipation it may be worth looking for unstable genetic elements in familial SPA.

The authors are greatly indebted to Dr C M Deighton for his critical reading of the manuscript.

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Quinine induced lupus-like syndrome and cardiolipin antibodies

A large number of drugs are known to cause a clinical syndrome resembling systemic lupus erythematosus.¹ The antiarrhythmic agent quinidine has occasionally been reported to cause such a syndrome.²⁻⁴ Additionally, the presence of cardiolipin antibodies has been described in patients receiving phenothiazine,⁵ procainamide,⁶ and ethosuximide⁷ treatment.

Quinine is an antimalarial drug analogue to quinidine that can also produce several autoimmune abnormalities,^{8,9} but a lupus-like syndrome and production of cardiolipin antibodies induced by this drug have not been previously described. We report a case of well documented quinine induced lupus-like syndrome in which cardiolipin antibodies were also found.

A 30 year old white woman was admitted to our hospital in May 1994 because of fever, chills, and diaphoresis of three days' duration. Six weeks before admission the patient had been on vacation in Cameroon, but she did not take any prophylaxis for malaria. Physical examination was unremarkable at time of admission except for fever up to 40°C. Laboratory examinations disclosed a packed cell volume of 0.37, haemoglobin 117 g/l, white blood cell count $3.8 \times 10^9/l$ (76% neutrophils, 20% lymphocytes, 4% monocytes), and platelet count of $150 \times 10^9/l$. Thick smears showed *Plasmodium falciparum* parasitaemia of 1%. Direct examination of stool and stool cultures were negative for other parasites. Blood cultures were also negative. Antinuclear, antitissue, and phospholipid antibodies were not detected. The patient was diagnosed as having malaria and treated with quinine sulphate 600 mg three times daily.

Forty eight hours into treatment the patient was afebrile and a thick smear became negative for malaria. After six days of treatment the patient complained of dyspnoea and constant retrosternal chest

Age of onset and year of onset of index patient and parent with a spondyloarthropathy

Child	Age of onset (years)	Year of onset	Parent	Age of onset (years)	Year of onset
M*	9	1988	M	21	1967
			F	35	1985
F*	5	1981	M	30	1980
M	9	1988	F	40	1993
M	8	1983	F	25	1977
M	9	1990	F	31	1979
M	10	1990	M	25	1983
M	8	1989	M	42	1990

*M = male; F = female.

tightness aggravated by deep respiration as well as pain in ankles and knees. Physical examination showed a pericardial friction rub and polyarthritis affecting ankles and knees. The electrocardiogram showed widespread elevation of ST segments and chest x ray examination an increase in heart size compatible with pericardial effusion. Laboratory tests showed haemoglobin 73 g/l, packed cell volume 0.22, reticulocytes 3%, platelets $119 \times 10^9/l$, and white blood cell count $3.78 \times 10^9/l$ (56% neutrophils, 1% eosinophils, 2% basophils, 34% lymphocytes, 6% monocytes, 1% myelocytes). Erythrocyte sedimentation rate was 118 mm/h. Blood and urine chemistries were within normal limits. A thick smear for malaria was negative. The Coombs direct test (polyspecific anti-globulin, anti-IgG, anti-C3b/C3d) was negative and Coombs indirect test was also negative. Antinuclear antibody test was positive at a titre of 1/800 (speckled pattern), dsDNA antibodies (Farr's technique) were not detected, and complement levels were normal. Cardiolipin antibodies (enzyme linked immunosorbent assay (ELISA)) were detected (IgG isotype at high level and IgM at moderate level) and lupus anticoagulant was negative. Tissue antibodies were present (antiparietal cells 1/100, antismooth muscle 1/200). Antinuclear cytoplasmic and histone antibodies were negative. Circulating immune complexes were 76 $\mu g/ml$. The same day, treatment with quinine was withdrawn with a prompt relief of symptoms within 24–48 hours and laboratory tests returned to normal within two weeks. After a one year follow up the patient remains asymptomatic and no autoantibodies are detected in her serum.

Multiple quinine dependent antibodies have been reported as being responsible for a variety of clinical syndromes associated with anaemia, leucopenia, thrombocytopenia, coagulopathies, renal failure, and disseminated intravascular coagulation.^{8,9} However, a lupus-like syndrome and production of cardiolipin antibodies induced by this drug have not been previously described. Interestingly, histone antibodies, which are often found in other drug induced lupus-like syndromes, were not detected in our patient. On the other hand, although malaria itself may produce a number of immunological abnormalities—including the production of cardiolipin antibodies,¹⁰ it is unlikely that this infection was the cause of the lupus-like syndrome and the cardiolipin antibodies because these appeared when the patient was afebrile and with a thick smear negative for *Plasmodium falciparum*, and disappeared after withdrawal of quinine.

Quinine should be considered as the potential cause when patients receiving this drug present with either a lupus-like syndrome or with signs of a coagulation disorder. Failure to consider quinine as a possible cause for the symptoms will lead to delay in diagnosis and prolonged morbidity, whereas both syndromes will disappear quickly when quinine treatment is stopped.

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Scleroderma and the watermelon stomach

The watermelon stomach is an unusual cause of gastrointestinal blood loss and iron deficiency anaemia. We report on two patients who presented with the watermelon stomach and subsequently developed typical features of scleroderma.

A previously healthy 72 year old white woman was found to have a haemoglobin of

62 g/l. Colonoscopic evaluation disclosed non-bleeding rectal arteriovenous malformations. A small bowel series was unremarkable. Oesophagogastroduodenoscopy showed parallel hyperaemic longitudinal rugal folds (stripes) across the gastric antrum with intervening normal appearing mucosa consistent with the watermelon stomach. Nd:YAG laser coagulation treatment was given, with resolution of blood loss. Over the next six months she developed Raynaud's phenomenon, arthritis, and sclerodactyly.

A diagnosis of limited scleroderma was made and over the next several months her arthritis and Raynaud's phenomenon improved and she had no progression in skin thickening. Five months after the diagnosis of limited scleroderma she developed melena and her haemoglobin dropped to 70 g/l. At that time the scleroderma was otherwise quiescent. Oesophagogastroduodenoscopy again showed vascular lesions consistent with watermelon stomach and she was treated with Nd:YAG laser coagulation, with resolution of the bleeding.

A 40 year old African American man with a history of hypertension and hypothyroidism presented with fatigue and swelling of his hands. Laboratory evaluation showed a haemoglobin of 116 g/l (previous haemoglobin 159 g/l). Colonoscopy showed small haemorrhoids. Oesophagogastroduodenoscopy showed linear erythematous streaking of the antrum consistent with a watermelon stomach (figure).

Eight months after the onset of his illness, physical examination showed tendon friction rubs and diffuse skin thickening, and he was diagnosed with diffuse scleroderma. Gastric antral vascular ectasia, or the watermelon stomach, so called because of its distinctive endoscopic appearance which resembles the stripes of a watermelon, is a rare cause of chronic gastrointestinal bleeding. Endoscopically, longitudinal rugal folds are seen traversing the antrum and converging on the pylorus.¹ Histopathologically, ectatic mucosal blood vessels with capillary thrombi characterise watermelon stomach.²

The watermelon stomach has been reported to occur in association with autoimmune diseases.¹ Patients with gastric antral vascular ectasia and scleroderma have been

Watermelon antrum with erythema (patient No 2).