



FIG. 1. Percentage of total patients in each category of test result, indicating proportions of patients with known prior BCG exposure.

of uninformative results was not seen in our cohort (9.9% indeterminate test results) and this was encouraging. BCG status did not significantly influence likelihood of an indeterminate test result ($P > 0.05$), and the relatively high proportion of negative QTG test results overall (83%), whilst not proof of a complete lack of BCG-associated false positives, is supportive of a specificity unconfounded by BCG status. Furthermore the absence of any cases of MTB, whether reactivation or *de novo*, over a relatively long period of follow-up, points to a favourable, albeit unquantifiable, test sensitivity.

We conclude that use of the QTG test as a screening tool amongst RA patients due to start anti-TNF- α treatment is feasible, that its informativeness appears unaffected by any impaired immunocompetence of our patient group, and that it is a useful and potentially cost-effective adjunct to existing protocols.

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Do Tc-99m-diphosphonate bone scans have any place in the investigation of polyarthralgia?

SIR, polyarthralgia with few clinical signs is a frequent complaint encountered by rheumatologists. In this situation Tc-99m-diphosphonate bone scans (BS) may be requested to rule out inflammatory arthritis. Whether the evidence justifies this approach is open to question. We conducted a retrospective audit to determine if BS influenced our practice. In the 6 months between April and September 2005, 44 BS were requested by our department. Of these, 25 were for investigation of polyarthralgia. Despite having equal numbers of lists, 20 of these were requested by specialist registrars and only 5 by consultants. Nuclear Medicine radiologists reported 3 as normal, 20 as having 'degenerative' or unspecified changes, and only 2 as having changes consistent with inflammatory disease. Changes reported as 'inflammatory' were deemed non-significant by the referring clinicians upon review of both patients. Of these 25 patients, 24 sets of notes were available for review. Only 4/24 had synovitis (mild or 'possible') prior to BS; none of whom had increased uptake in the affected joints. Where a pre-test diagnosis (inflammatory or non-inflammatory) was recorded in the notes (17 patients), this generally accorded with the BS report. In only three patients did it differ, one with palindromic symptoms, one who received i.m. steroid 10 days prior to BS, and one who had no recorded evidence to support a diagnosis of inflammatory arthritis. Only 4/24 scans highlighted joint regions not recorded in the notes as being affected; these comprised three shoulders, one acromioclavicular joint and two elbows. However, despite having BS thought to be negative for inflammatory disease, only 3/24 were discharged following this and further investigations (ultrasound or MRI) were requested in nine. Overall, we found little evidence that BS influenced diagnosis or management. We believe that the disproportionate number of requests from trainees reflects a misunderstanding of the sensitivity and specificity of BS for inflammatory arthritis. Non-specific uptake may lead to further investigation rather than patient reassurance.

Tc-99m-diphosphonates localize to bone and uptake is increased on blood pool and delayed images in both synovitis and sub-chondral bone damage (the hyperaemia of synovitis is shared by juxta-articular bone and vice versa, due to anastomotic vessels) [1]. Consequently, an increase in peri-articular uptake is not specific for synovitis and must be interpreted in the clinical context. Furthermore, Tc-99m-diphosphonates are taken up by all joints to a variable degree, making interpretation difficult [2]. The number of false positives is unknown but it is clear that BS are unable to reliably distinguish between 'active' and 'inactive' rheumatoid arthritis [2, 3]. This lack of specificity has been further highlighted by comparing different imaging modalities (ultrasound and MRI) [4]. Computerized image analysis yields only marginal improvement [5]. Despite these limitations, does a positive BS still have value in predicting joint damage in inflammatory arthritis? A careful study in early rheumatoid

arthritis found that erosions were predated by persistent scintigraphic activity in affected joints [5]. Of note, however, almost all finger joints that eroded were active on clinical examination. The sensitivity of clinical examination was inferior to scintigraphy in the foot joints, but as analysis was by joint rather than by patient and as the scintigraphic score was derived from multiple BS, the implications for routine clinical practice are not clear.

Such difficulties led to the suggestion that a negative joint scan is of greater importance in the investigation of polyarthralgia [1]. This appears to be supported by one retrospective study; after 3.6 yrs mean follow-up, none of 22 patients with a negative BS had evidence of inflammatory joint disease [6]. Of interest, however, is that 19 of these patients had a pre-scan diagnosis of non-inflammatory joint disease. The remaining three had joint tenderness or pain on passive motion, but no synovial thickening or effusion. The eventual diagnosis in these patients was SLE, polymyalgia rheumatica and undifferentiated connective tissue disease. It is known that SLE patients with synovitis or arthralgia may have normal BS [7]. The excellent correlation between pre-study diagnosis and negative BS is supported by our study.

In conclusion, Tc-99m-diphosphonate BS suffer from lack of specificity and add little to clinical evaluation. Furthermore, they lack the detailed anatomical information provided by MRI and ultrasound. Musculoskeletal ultrasound in particular, has the advantage of being cheap and safe and is now becoming more widely available. In addition, there is no ionizing radiation with either MRI or ultrasound. In comparison, the typical radiation dose of a BS is 3.6 mSv (equivalent to 90 chest X-rays) and the typical cost has been set at around £148. We argue that their role in the evaluation of polyarthralgia has been largely superseded.

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Mutations of the tissue non-specific alkaline phosphatase gene (*TNAP*) causing a non-lethal case of perinatal hypophosphatasia

Introduction

Hypophosphatasia is a heritable metabolic bone disease first described in 1948 by Rathbun [1]. It is characterized by defective bone mineralization and deficiency of the tissue non-specific isoform of the enzyme alkaline phosphatase (encoded by the *TNAP* gene). There are four isoforms of alkaline phosphatase in humans, each encoded by separate genes (tissue non-specific, intestinal, placental and placental-like). *TNAP* maps to chromosome 1p36.1-34 and consists of 12 exons and 11 introns over 50 kb, although the coding sequence starts at the second exon [2]. In hypophosphatasia, numerous *TNAP* mutations have been reported, the different consequences of which on biological activity of the enzyme account for the clinical heterogeneity of the condition [3].

There are five clinical subtypes, four of which depend on the age of onset (perinatal, infantile, childhood and adult onset types). The fifth, odontohypophosphatasia, is characterized by premature loss of primary teeth with no associated skeletal abnormalities [4]. Clinical expression of the disease is highly variable ranging from still-birth without evidence of bone mineralization to pathological fractures only detected in adulthood. The severe perinatal and infantile forms of the disease are transmitted as autosomal recessive traits, whereas the clinically milder forms, including childhood onset, adult onset and odontohypophosphatasia may apparently exhibit both autosomal dominant and recessive transmission [5, 6].

Recent studies have suggested the existence of a sixth clinical form, termed 'benign prenatal' type [7, 8]. These reports have described several cases with severe bowing of the long bones *in utero* in whom there was subsequently a more benign clinical course. This contrasts dramatically with the lethal course often seen with perinatal onset disease. In contrast to the normal autosomal recessive pattern of inheritance associated with early onset disease, there may be autosomal dominant inheritance [7].

In this report we document the case history and *TNAP* sequence analysis of a proband and her family with 'benign prenatal type' disease.

Case history

The proband is a 16-year-old Caucasian girl who is the younger of two children born to non-consanguineous parents (Fig. 1). Both parents are asymptomatic but whilst her mother has a normal serum alkaline phosphatase level, her father has a reduced level of 74iu (Table 1). Bone mineral density scanning of the parents report a normal Z score of +1.19 for the father and a low score of -1.78 for the mother indicating osteopenia. They have no known family history of hypophosphatasia.

The proband was born by emergency caesarean section 12 weeks prematurely. She weighed less than 2lbs and required ventilation for 44 weeks followed by a prolonged period of oxygen dependency due to the pulmonary sequelae of prematurity.

At birth she had severe femora and tibia vara bilaterally which had been detected during the pregnancy on ultrasound scanning at 24 weeks. She also had metaphyseal dysplasia and premature closure of the cranial sutures. She is now of small stature and, at 13 yrs, remains below the third centile for height (93 cm). She has