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LETTER

Analysis of whole blood protoporphyrin and plasma porphyrin in patients on dapsone

Dear Editor,

Dapsone is a sulphonamide antibiotic that also has anti-inflammatory effects and is commonly used to treat of a range of dermatological conditions with different causes including dermatitis herpetiformis, pyoderma gangrenosum, Sweet's syndrome, urticarial vasculitis and leprosy.[1] Dapsone is known to cause haemolytic anaemia especially in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency[2] and always causes some degree of haemolysis. It has also been reported to precipitate episodes of acute intermittent porphyria and variegate porphyria.[3,4] For more than 35 years, photosensitivity has been reported as an infrequent side-effect of dapsone treatment for leprosy and more recently for linear IgA bullous dermatosis.[5]

We aimed to find out whether or not dapsone is associated with elevated protoporphyrin in the blood. The prompt for this was an observation in one of our patients on dapsone. This patient was fifty-one when he was referred to the Scottish Photobiology Service for phototesting with suspected chronic actinic dermatitis (CAD). Monochromator phototesting did not show features of a cutaneous porphyria: abnormalities were to ultraviolet B and ultraviolet A2 (long wavelength ultraviolet A) rather than visible light and was most marked at 24 h (not at 7 h as seen in photosensitive porphyrias)—which confirmed the diagnosis of CAD.

Porphyrin biochemistry was requested alongside phototesting to determine whether Porphyria Cutanea Tarda was underlying the CAD. Initial blood porphyrin biochemistry showed raised total erythrocyte porphyrin which was predominantly metal-free protoporphyrin in the absence of a plasma porphyrin peak. Two further blood samples were analysed whilst the patient continued on dapsone that gave abnormal results, but these returned to normal when retested after dapsone was stopped for more than a year (Figure 1A,B).

We considered that dapsone might be the explanation for raised erythrocyte porphyrin, possibly related to increased turnover in his bone marrow to compensate for dapsone haemolysis—his reticulocyte count was approximately 4%–5% whilst on dapsone. We found only one reported study, investigating porphyrin levels in people with leprosy on dapsone treatment and untreated.[6] This study found leprosy to be associated with increased blood protoporphyrin but did not find an increase attributable to dapsone.

This was a retrospective study measuring blood protoporphyrin and plasma porphyrin levels in consenting patients on dapsone in samples stored by Scottish Health Research Register and Biobank (SHARE), a research initiative by NHS research Scotland.[7] SHARE is a database of volunteers (aged 11+) who consent to the access and use of their health records to identify them as potentially eligible for research projects. Participants gave permission for any spare blood remaining after routine clinic tests, to be retained for anonymised research. The inclusion criteria for this study were male or female on dapsone treatment with a sample of ≥5 mL stored.

Plasma, blood protoporphyrin (zinc/metal-free) and total erythrocyte protoporphyrin levels were analysed in 10 anonymised blood samples by fluorescence spectroscopy using standard, published methods[8–10] by the Scottish Cutaneous Porphyria Service. Internal quality control samples were included with each assay to demonstrate acceptable performance. Biobank samples had not been light protected prior to storage, but were wrapped in foil upon retrieval from storage and protected from light throughout analysis.

50% of samples from patients on dapsone showed increased metal-free protoporphyrin with metal-free protoporphyrin levels ranging from 35% to 46% (normal <30%). All samples had normal total erythrocyte porphyrin concentrations ranging from 0.3 to 0.7 μmol/L rbc (Figure 1C,D). No plasma porphyrin peak was detectable in any of the biobank samples. All samples were noted to be haemolysed—it is unclear whether this is related to dapsone treatment and/or storage of the samples.

Interestingly, we found that increased metal-free protoporphyrin was not isolated to the original patient and was increased in half of the 10 patients on dapsone whose blood samples were obtained from the SHARE biobank and may help to explain the photosensitivity observed in some patients on dapsone.[5] The increase seen in biobank samples was not as dramatic as that seen in the initial patient and the total erythrocyte porphyrin levels were normal in all 10 samples. This could be because none of the biobank samples had been light protected prior to storage and as protoporphyrin is light labile it is possible that this had degraded prior to analysis. Prospective studies on light protected samples may give a better understanding of these findings.

The underlying cause or clinical implications of increased metal-free protoporphyrin levels in dapsone-treated patients is not

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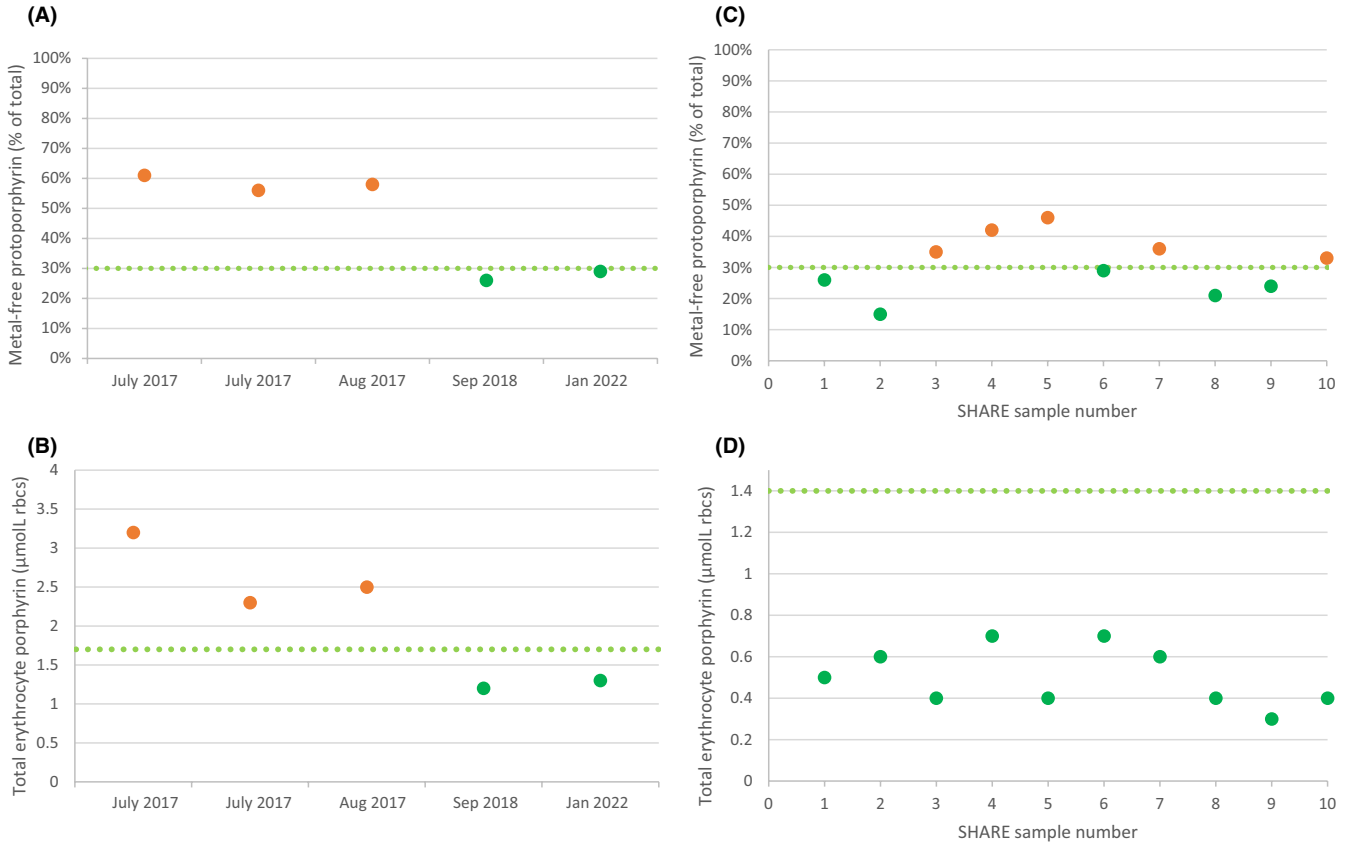

FIGURE 1 Porphyrin biochemistry results. (A, B) Initial testing in 2017 showing elevated metal-free protoporphyrin and total erythrocyte porphyrin on dapsone and returning to normal after stopping in September 2017. Total erythrocyte porphyrin was measured on whole blood and the blood haematocrit value used to enable results to be expressed in relation to the volume of packed erythrocytes. Dotted lines indicate blood metal-free protoporphyrin normal range <30% (A) and whole blood TEP normal range <1.7 µmol/L rbcs (B). (C, D) SHARE samples. 50% of samples show elevated metal-free protoporphyrin but all have normal TEP. Dotted lines indicate blood metal-free protoporphyrin normal range <30% (C) and packed red blood cell TEP normal range <1.4 µmol/L rbcs (D). Orange indicates outwith the normal range, green indicates within normal limits.

understood, but analysis of blood porphyrins in patients experiencing photosensitivity would help to inform on this. We hypothesise that dapsone could affect the enzymatic activity of ferrochelatase (which catalyses metal atom insertion into protoporphyrin) and/or perhaps the increased bone marrow activity to compensate for dapsone haemolysis is relevant. Further studies would be needed to understand the effects of dapsone on porphyrin levels and metabolism considering its widespread usage for different conditions.

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CONFLICT OF INTEREST STATEMENT

None to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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