

## PIBI(D)S: clinical and molecular characterization of a new case

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### ABSTRACT

The term PIBI(D)S has been used to indicate a rare recessively inherited genetic disorder characterized by photosensitivity, mild non-congenital ichthyosis, brittle sulphur-deficient hair with trichoschisis (trichothiodystrophy), impaired intelligence, occasionally decreased fertility and short stature. To the best of our knowledge, about 20 cases have been reported in the literature. Here we report the characterization of the hair, brain, ultraviolet sensitivity and DNA excision repair defects of a new patient affected by PIBI(D)S. The diagnosis of PIBI(D)S syndrome was made in our patient on the basis of the clinical features and then confirmed by hair microscopy and biochemical analysis. Our patient has increased muscular tone, alteration of the deep tendon reflexes and psychomotor retardation, all consistent with hypomyelination of the brain showed by magnetic resonance imaging and computed tomography. A deficiency of DNA repair capacity was demonstrated in our patient. Furthermore, complementation analysis by cell fusion assigned our patient to xeroderma pigmentosum group D. The nucleotide excision repair defect of the other reported patients with PIBI(D)S falls generally into the same group as xeroderma pigmentosum group D and carry a mutation on the same repair gene (XPD). The relationship between these molecular characteristics and the clinical spectrum of PIBI(D)S is discussed.

**Key words:** DNA repair, PIBI(D)S syndrome, trichothiodystrophy, xeroderma pigmentosum group D

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### Introduction

The term PIBI(D)S has been used to indicate a rare recessively inherited genetic disorder characterized by photosensitivity, mild non-congenital ichthyosis, brittle sulphur-deficient hair with trichoschisis, impaired intelligence, and occasionally decreased fertility and short stature.<sup>1,2</sup> PIBI(D)S differs from other syndromes with brittle cystine-deficient hair (trichothiodystrophy) because of the association of severe photosensitivity with the defective repair of ultraviolet (UV)-induced DNA lesions as seen in xeroderma pigmentosum (XP). In most cases, the repair defect is in the same gene as in the xeroderma pigmentosum group D (XPD).<sup>3,4</sup> However, despite the defect in excision repair, PIBI(D)S patients do not develop skin neoplasms.<sup>5,6</sup> Furthermore, the main features of the disorder, namely sulphur-deficient brittle hair, physical and mental retardation, ichthyosis, and abnormal facies are not found in XP. To the best of our knowledge, about 20 cases have been reported in the literature.

Here we report the characterization of the hair, brain, UV sensitivity and DNA excision repair defects of a new patient affected by PIBI(D)S and discuss the genotype–phenotype relationship in this disorder.

### Case report

#### Clinical features

A 10-year-old boy had first presented at the age of 5 years. He showed short stature (108 cm, 25–50th percentile) and low weight (16 kg, 10th percentile) for his age. His facies (fig. 1) was bird-like, with narrow, beaked nose and protuberant ears. He had short, sparse and brittle hair, dystrophic nails, ichthyosis on the skin of the abdomen not present at birth. A skin biopsy to confirm the diagnosis of ichthyosis was not performed as the clinical features of the lesions were consistent with the diagnosis. Atopic dermatitis developed at the age of 3. He showed developmental delay and mild psychomotor



**fig. 1** The child at 5 years. Note the characteristic PIBI(D)S face.



**fig. 2** Osteo sclerosis of the vertebral column.

retardation, but remarkably sociable behaviour. The neurological examination showed a slight reduction of the deep tendon reflexes and an increased muscular tone. His hearing was normal. Bilateral cataracts and bilateral cryptorchidism



**fig. 3** Light microscopy reveals clean transverse fractures through the hair shaft (trichoschisis).

were present. Dental caries were noted. The boy also showed extreme photosensitivity, suffering severe sunburns after a few minutes of sun exposure. Routine blood chemistry and urinalysis were negative. A slight increase of IgE (239 kU/L) was found, with a rise in specific IgE against several allergens. Radiographs revealed marked osteosclerosis of the vertebral column and cranium; his skeletal age was 5 years (fig. 2). Electroencephalogram, visual and auditory evoked potentials, electromyography, motor and sensory nerve conduction velocities were normal. Phototesting showed extreme UVB and UVA photosensitivity: the minimal dose (UVB-MED < 0103 J/cm<sup>2</sup>, UVA-MED < 0.34 J/cm<sup>2</sup>) provoked blisters.

An almost complete loss of scalp hair was observed soon after a surgical operation for dental caries and during periods of infection.

At present the boy is 10 years old and the clinical features are substantially unchanged, with the exception of a slight improvement in his ichthyosis and motor co-ordination and some freckles and telangiectasias on his face and neck as a result of sun damage.

#### Characterization of hair

Light microscopy of scalp hair revealed numerous clean-cut transverse fractures (trichoschisis) and alterations of the cuticle (fig. 3). Polarizing microscopy showed a typical abnormal appearance of alternating light and dark bands probably due to the varying sulphur content along the hair axis that gives the



**fig. 4** Polarizing microscopy of hair shows alternating bright and dark bands ('tiger tail' hair).

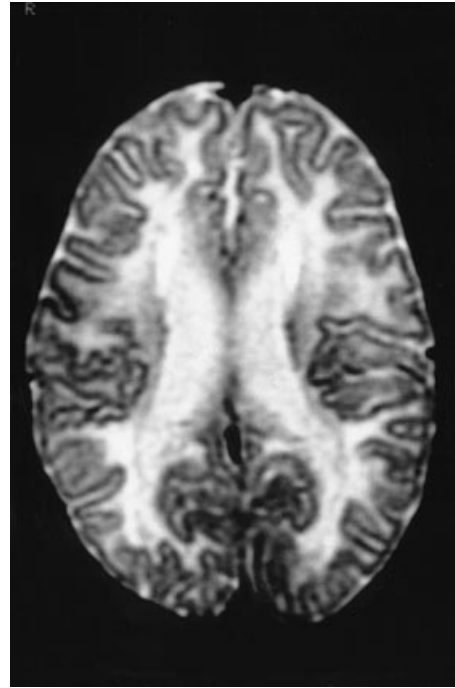
shafts a tiger-tail pattern (fig. 4). Amino acid analysis of scalp hair revealed a very low level of cystine (9.12%; normal value 16.3%).

### Brain imaging

Cerebral computed tomography (CT) showed absence of calcification and high signal from white matter. Magnetic resonance imaging (MRI) disclosed diffuse signal hyperintensity throughout the cerebral white matter on T2-weighted images (fig. 5). In normal brain, the signal intensity of white matter on T2-weighted images is dark compared with the cerebral cortex due to myelin sheaths. This finding is compatible with a diffuse hypomyelination of cerebral white matter. The lateral ventricles were moderately dilated, indicating a loss of periventricular tissue, probably as a consequence of hypomyelination.

### DNA repair studies

DNA repair studies were carried out as previously reported by Stefanini *et al.*<sup>3,7</sup> Unscheduled DNA synthesis (UDS) was analysed in the skin fibroblasts of the patient and three healthy individuals after exposure to UVC (254 nm) doses of 5, 10 and 20 J/m<sup>2</sup> per s by measuring the incorporation of tritiated thymidine into DNA for 2 h after UV irradiation using the autoradiographic method. Moreover, survival of stationary phase fibroblast after UV irradiation was investigated. In



**fig. 5** T2-weighted axial magnetic resonance imaging of brain shows diffuse signal hyperintensity throughout the white matter.

both experiments we observed a drastic reduction in UDS and UV survival levels when compared with those of normal controls.

Genetic analysis of the DNA repair defect was performed by complementation studies. The patient's cells were fused with different XP strains and UDS was measured in the heterodikaryons. Fusion with xeroderma pigmentosum group D fibroblast failed to restore UDS levels to normal. This indicates that in our patient the repair alteration is due to a mutation in the XPD gene.

### Discussion

The diagnosis of PIBI(D)S syndrome was made in our patient on the basis of the clinical features (extreme photosensitivity, non-congenital ichthyosis, brittle hair, impaired intelligence, short stature). Decreased fertility (D) is indicated in parentheses because of his age. The diagnosis of PIBI(D)S was then confirmed by hair microscopy and biochemical analysis. In fact, light microscopy of scalp hair showed trichoschisis and polarizing microscopy showed the typical tiger-tail pattern. Amino acid analysis of scalp hair revealed a very low level of cystine; previous studies by X-ray microanalysis showed that the sulphur content varies along the length axis of the trichothiodystrophic hair.<sup>8,9</sup> Our patient has increased muscular tone, alteration of the deep tendon reflexes and psychomotor retardation, all consistent with the alterations

shown by MRI and CT of the brain. These findings have been documented in other patients with PIBI(D)S.<sup>10,11</sup> Our patient also presented dental caries that are sometimes reported in PIBI(D)S patients.<sup>12</sup> This alteration may be the consequence of an impaired dentinogenesis probably related to the sulphur-deficient metabolism.

A deficiency of DNA repair capacity was demonstrated in our patient. Furthermore, complementation analysis by cell fusion assigned our patient to XPD. The nucleotide excision repair defect of the other reported patients with PIBI(D)S falls generally into the same group as XPD and carry a mutation on the same repair gene.<sup>3,4</sup> However, the exact relationship between these molecular characteristics and the clinical spectrum of PIBI(D)S remain to be fully elucidated. The clinical heterogeneity and the genetic overlap found between XPD and PIBI(D)S raise the question as to how mutations in the same genetic locus can be associated with disorders characterized by distinct phenotypes. It has been suggested that the distinct clinical phenotypes of XPD patients and PIBI(D)S patients may be associated with different mutations in the XPD gene.<sup>13</sup> In support of this hypothesis, there is an investigation by Taylor *et al.*<sup>14</sup> showing that PIBI(D)S and XPD are characterized by distinct mutations of the XPD gene. The product of the XPD gene has a dual function, both in nucleotide excision repair of DNA damage and in basal transcription.<sup>15</sup> The findings of Taylor *et al.* are consistent with the idea that XP results from mutations that affect only DNA repair, whereas the features of PIBI(D)S result from mutations that affect both the repair and transcriptional activities.

The product of the XPD gene was found to be a subunit of the RNA polymerase II basal transcription factor BTF2, also designated TFIIH.<sup>16,17</sup> It is conceivable that the XPD protein regulates the expression of genes specifically implicated in development during embryogenesis or in specific events involved in hair growth, neurological development, etc. For example, the brittle hair characterized by a low sulphur content is thought to be the result of a defective transcription of a cysteine-rich matrix protein caused by a defect in the XPD gene product.<sup>18</sup>

Despite the same genetic mutations affecting the excision repair mechanism, XPD patients develop skin neoplasms, whereas PIBI(D)S is not a cancer-prone disease. Therefore, a deficiency in UV-induced DNA repair ability is not sufficient to give rise to tumours. It has been suggested that differences in cellular catalase activity may partly explain the different tumoral phenotypes observed in the two disorders.<sup>19</sup> UV produces intracellular H<sub>2</sub>O<sub>2</sub> that has been indicated to play a part in the promotion phase of carcinogenesis after DNA damage. Catalase is the enzyme that catalyses H<sub>2</sub>O<sub>2</sub> dismutation into water and molecular oxygen. There is evidence that cell lines obtained from XP patients are markedly deficient in catalase activity, whereas cells from PIBI(D)S patients exhibit normal catalase activity. However, the cause of catalase deficiency is still unknown and analysis of the catalase gene at a molecular level

did not reveal specific differences in catalase-deficient cells compared with cells with normal catalase activity.<sup>19</sup> It has also been suggested that the variable incidence of cancer among patients with mutations of the XPD gene that affect DNA repair activity may be the result of differences in immunosurveillance ability.<sup>6,20</sup> In particular, there are studies demonstrating that different from XP patients, PIBI(D)S patients show normal immune response.<sup>6</sup> However, the relationship between the putative immunodeficiency in XP patients and the genetics of the two diseases is not clear. A defective nucleotide excision repair process without evidence of an elevated risk of cancer is also present in Cockayne's syndrome, which presents some clinical aspects similar to those observed in PIBI(D)S, notably skin sensitivity to UV light, peculiarly sociable behaviour, and central nervous system MRI alterations.<sup>10,21</sup> Specific gene-targeted mouse models may help to determine the molecular basis of the different risks of cancer observed in XP, PIBI(D)S and Cockayne's syndrome.

In conclusion, we have presented a case of PIBI(D)S characterized by typical clinical features and both UV sensitivity and DNA excision repair defects similar to those found in XPD individuals. Further investigations of both the XPD gene and the genes whose expression is regulated by the XPD protein may help to elucidate the complex genotype–phenotype relationship associated with this disorder.

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