

CASE REPORT**GRAVES' HYPERTHYROIDISM IN A PATIENT WITH PENDRED'S DYSHORMONOGENESIS**IM Ibrahim,¹ DO McDonald,² CJ Owen,^{1,2} P Kendall-Taylor,^{1,2} SHS Pearce^{1,2}¹Endocrine Unit, Royal Victoria Infirmary, Newcastle upon Tyne, UK and ²Institute of Human Genetics, Newcastle University, UK.

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Correspondence to:

Dr. Simon Pearce,
Institute of Human Genetics,
Newcastle University,
International Centre for Life, Central Parkway,
Newcastle upon Tyne, NE1 3BZ, UK.
Tel. 44-191-241-8674; Fax. 44-191-241-8666

ABSTRACT

The clinical details of a young woman with Pendred's syndrome who developed autoimmune hyperthyroidism are presented. Although the dysmorphonogenesis of Pendred's syndrome is associated with a defect in iodide organification, her hyperthyroidism was successfully treated with ¹³¹I radioiodine. The nature of the thyroid hormonogenic defect in Pendred's syndrome and the relative functional importance of the apical iodide transporting mechanisms are illustrated. In addition, the hyperthyroidism, and its subsequent treatment, clearly demonstrate that Pendred's syndrome results only from a partial block to thyroid hormone synthesis. Radioiodine, perhaps administered after recombinant TSH thyroid stimulation, may be an alternative treatment for goitre in Pendred's syndrome. (*Hot Thyroidol. 2009: e13*).

Key-words: dysmorphonogenesis; iodide transport; hyperthyroidism; Graves' disease; Pendred syndrome

Introduction

Pendred's syndrome (PDS) is an autosomal recessive disorder characterized by congenital sensorineural hearing loss and progressive goitre (1). Other features of PDS are enlargement of the vestibular aqueduct and "Mondini" malformation of the cochlea, which are typically present on imaging studies. In about 50% of patients, the circulating thyroid hormone levels are normal, while the remainder develop overt hypothyroidism due to defective iodide transport, which results in thyroid dysmorphogenesis (2). Typically, affected subjects demonstrate avid thyroidal iodide uptake but impaired iodide organification, as determined by an exaggerated release of uncoupled radioiodine tracer from the thyroid following perchlorate administration (a positive perchlorate discharge test) (3). PDS was assigned to chromosome 7q31 by linkage analysis (4,5), and mutations in the gene encoding an anion transporter, *SLC26A4*, also termed "Pendrin" were found in affected patients (6). There are now more than 50 such independent *SLC26A4* gene mutations that have been characterized as causing PDS (6-12). The mature *SLC26A4* transporter is located on the apical membrane of thyrocyte (13,14), where it is responsible for the transport of inorganic iodide into the colloid space. Iodide is then available for organification and subsequent incorporation into iodotyrosine compounds, the precursors of thyroid hormones. Pendrin acts as an anion exchanger, allowing iodide flux out of the thyrocyte with a reciprocal influx of chloride. In the presence of a loss of function in the *SLC26A4* transporter, apical iodide transport is defective, leading to impaired organification of iodide and the hypothyroidism of Pendred's syndrome. However, as many patients with PDS remain euthyroid, organification is only partially deficient, suggesting that there may be either functional heterogeneity in the activity of the abnormal transporters in PDS or that other mechanisms exist that can compensate for lack of the *SLC26A4* protein activity (15). In this paper we report a rare association of autoimmune hyperthyroidism in a patient with PDS, and its treatment.

Case report

The patient is the daughter of unrelated parents who were both known to have Pendred's syndrome (PDS). There was no family history of autoimmune disorders. At the age of 2 years, she was found to have sensorineural deafness and clinical examination showed her to have a large goitre. Because of her family background, she was thought likely to be an obligate carrier of two *SLC26A4* gene mutations, and compound heterozygosity for a 1101+1G>A and 2015G>A base changes within the *SLC26A4* gene were demonstrated (9). These DNA changes predict a donor splice-site mutation of exon 8 and a non-conservative G672E missense mutation in exon 17 of *SLC26A4*, respectively. Both mutations are likely to result in a non-functional protein, encoding a transporter either with a missing domain, or one that is unable to reach the cell surface due to misfolding, respectively (16).

At the age of eleven years, she was first found to be biochemically hypothyroid with a serum TSH of 6.4mU/l; she was treated with thyroxine 150µg daily, with the aim to keep the serum TSH towards the lower limit of normal to suppress the growth of her goitre. She attended clinic sporadically, when her

mother and a sign-language interpreter were available to accompany her. However, at the age of 18 she lost 17 Kg in weight, associated with tremor, heat intolerance and palpitations. There were no eye signs or thyroid dermopathy. Her repeat thyroid function tests showed a raised free T4 of 64 pmol/l (normal range 11-23), free T3 of 13.7 pmol/l (3.5-6.5), and an undetectable TSH. Thyrotropin-binding inhibitory immunoglobulins (TBII) were raised at 36 U (normal <10) and thyroid peroxidase antibodies were positive at 89 kU/l (normal <60). Her serum thyroglobulin measured by RIA was 63.4 µg/l. Full details of the course of her thyroid function tests are shown in Table 1. A ^{99m}Tc thyroid uptake scan showed a patchy but widespread increase in uptake (Figure 1).

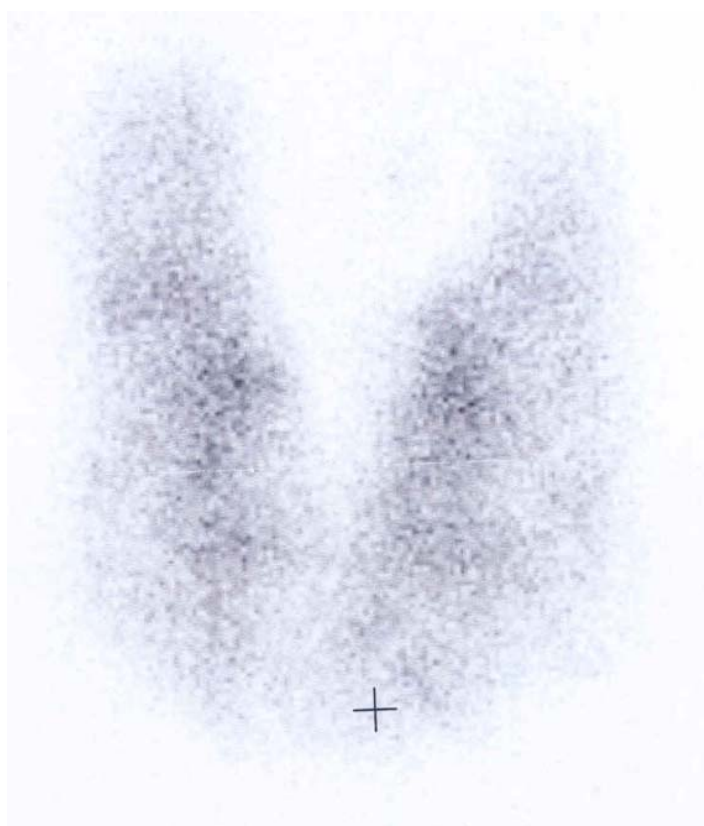


Figure 1. ^{99m}Tc (pertechnetate) thyroid uptake scan. The 20 minute thyroid uptake was 10% of tracer (normal <3.5%).

After repeat testing, her thyroxine medication was stopped, but she remained mildly hyperthyroid despite this. After some discussion about the uncertain outcome, she agreed to radioiodine as therapy for her hyperthyroidism and was treated with 400MBq (11mCi) ^{131}I . Her thyroid function tests became normal 7 weeks after the treatment and she was restarted on thyroxine and remains well at last follow up (Table 1). There was substantial reduction in her goitre noted over the 6 months following her radioiodine therapy.

Table 1. Thyroid function testing and weight

| Date | TSH | Free T4 | Free T3 | Thyroxine dose | Weight |
|----------------------|------------------------------------------|---------------------|-----------------------|-------------------|-----------|
| <i>Normal ranges</i> | <i>0.3-4.7 mU/l</i> | <i>11-23 pmol/l</i> | <i>3.5-6.5 pmol/l</i> | <i>µg per day</i> | <i>Kg</i> |
| 09/04/98 | 2.82 | 15 | - | 150 | 82 |
| 06/07/00 | 3.54 | 14 | - | 175 | 104 |
| 09/12/02 | 0.55 | 17 | - | 200 | 115 |
| 03/02/03 | 0.15 | 31 | 6.0 | 200 | 118 |
| 28/02/05 | <0.05 | 64 | 13.7 | 200 | 100 |
| 16/05/05 | <0.05 | 67 | 13.4 | Discontinued | 100 |
| 13/06/05 | <0.05 | 26 | 7.6 | - | 101 |
| 14/07/05 | Radioiodine 400 MBq (11mCi) administered | | | | |
| 22/08/05 | 1.13 | 12 | - | 150 Re-started | 104 |
| 20/03/06 | 0.06 | 21 | - | 150 | 105 |
| 12/06/06 | 0.28 | 20 | 4.8 | 150 | 104 |

Methods

Mutational analysis.

The genetic analysis of this patient (III-1) and her family have been previously reported, with her paternal and maternal relatives being designated as families 14 and 13, respectively (9).

Biochemical assays.

Serum thyrotropin (TSH) was analyzed using the Bayer ADVIA Centaur analyzer (Bayer Diagnostics Division, Newbury Berkshire, UK) by 2 site sandwich immunoassay using direct chemiluminescence. Serum free T4, free T3 and anti-thyroid peroxidase antibodies were measured by competitive immunoassay using direct chemiluminescent technology (Bayer centaur). Thyrotropin-binding inhibitory immunoglobulins (TBII) assay (RSR Ltd, Pentwyn, Cardiff, UK), measure the ability of TBII in the patient sample to inhibit the binding of ¹²⁵I-Labelled TSH to recombinant thyroid receptors on coated polystyrene tubes. The % inhibition is calculated as an index.

Thyroglobulin (Tg) was measured using coated tube 2 site immunoradiometric sandwich assay, using 4 monoclonal anti (Tg) antibodies to specific sites on (Tg) molecule on coated tubes (CIS Bio international). The intra-assay coefficients of variation for each measurement (at the given concentration) were: TSH 3.8% (5.3mU/l), FT4 7.9% (13.5pmol/l), FT3 6.3% (4.5pmol/l), thyroid peroxidase antibodies 3.7% (522kU/l), TBII 8% (37U), Tg 8.4% (17µg/l).

Discussion

Our investigations show that this young woman who had Pendred's syndrome, a state of thyroid dyshormonogenesis, developed hyperthyroidism owing to Graves' disease. Although at first, the diagnosis of thyrotoxicosis 'factitia' due to excessive thyroxine ingestion was suspected, several factors suggested true autoimmune hyperthyroidism as the cause of the thyrotoxicosis. These include a progressive rise in circulating thyroid hormone levels during treatment with a stable dose of L-thyroxine, detectable serum thyroglobulin at the time of thyrotoxicosis, positive thyroid peroxidase and thyrotropin-binding inhibitory autoantibodies, and a low serum thyroxine to triiodothyronine ratio once thyroxine was discontinued. Her thyroid uptake scan is particularly difficult to interpret, since a rapid uptake of pertechnetate tracer has been reported in untreated Pendred's syndrome, probably driven by a high-normal or high TSH. However, in the context of an undetectable TSH, the high pertechnetate uptake (10% at 20 mins; normal <3.5%) is caused, at least in part, by her endogenous hyperthyroidism due to thyroid stimulation with TSH-receptor antibodies (Figure 1). In a person with no underlying thyroid disease, low isotope uptake would be expected in the presence of an undetectable TSH during exogenous thyroxine administration. The improvement in thyrotoxicosis following the radioiodine and the subsequent reduction in goitre size are also in keeping with the diagnosis of Graves' disease.

Radioiodine was selected as treatment for this patient because she was keen to avoid thyroid surgery, which both her mother and her maternal uncle (who was also affected with PDS) had undergone, and there was the additional possibility of shrinkage of her goitre with the treatment. We were unsure whether radioiodine would be efficacious in this circumstance: there are no previous reports of radioiodine use in PDS. Nevertheless, as we were confident she had endogenous hyperthyroidism, it was clear she could trap and organify enough iodide to become thyrotoxic. Therefore, it seemed reasonable to assume there would be a therapeutic effect from radioiodine. Since she had a reduction in goitre size with the radioiodine, it is possible that this may be a useful therapeutic option for goitre reduction in other patients with PDS, perhaps administered following recombinant TSH stimulation, rather than with the endogenous TSH-receptor stimulation from autoantibodies as in this case. This is an area of practice where there is little published experience.

Thyroid autoantibodies, including TSH receptor stimulating antibodies, have been previously reported in Pendred's syndrome (17), which suggests that there may be a predisposition to thyroid autoimmunity in PDS patients. The large size of the thyroid gland in PDS, together with increased expression or turnover of the proteins involved in thyroid hormone biosynthesis, which are also the targets of the autoimmune attack, could explain an association of thyroid autoimmunity and this form of dyshormonogenesis. In particular, there is evidence of upregulation of thyroid peroxidase activity in PDS thyroid tissue (18, 19). Although, one study has shown genetic linkage of a large family with autoimmune thyroid disease to the chromosomal interval containing the PDS locus (20), there is currently no formal evidence to support the idea that genomic variation in the *SLC26A4* gene itself is

responsible for autoimmunity. Interestingly, autoantibodies recognizing Pendrin protein have recently been described in Hashimoto's thyroiditis and, to a lesser extent in Graves' disease, using immunoblotting with patient sera (21).

During thyroid hormone synthesis, the initial transport of iodide from the circulation (extracellular fluid) occurs at the basolateral surface of the thyrocyte through the sodium-iodide symporter (NIS). This has the ability to transport iodide up a 20-fold concentration gradient to allow its accumulation in the thyrocyte. Inorganic iodide is then transported across the apical membrane of the thyrocyte, to bring it into close proximity to thyroid peroxidase, which is anchored to the apical membrane but with its catalytic "head" in the colloid space. Iodide crossing the apical membrane via SLC26A4 is available to TPO to organify, whence it is rapidly incorporated into the tyrosyl residues of thyroglobulin to form the iodotyrosine thyroid hormone precursor molecules. Thus, one might predict that it would be difficult or impossible for an individual with the defective apical iodide transport found in PDS to become hyperthyroid. However, it is clear from our clinical findings in this case, that under certain conditions SLC26A4-mediated iodide transport is not a significantly rate-limiting step in thyroid-hormone synthesis. Since many patients with PDS remain euthyroid for many years, iodide organification is only partially deficient in many individuals with this condition, suggesting that other mechanisms of iodine transport exist that can compensate for lack of the SLC26A4 protein (15). Some studies (22, 23) have suggested that iodide efflux can also be mediated through a TSH-induced iodide porter via either a cAMP or a Ca^{2+} PIP₂ pathway. Golstein *et al.*, (24) used a membrane vesicle preparation of bovine thyroid to characterize two iodide channels with distinct biophysical properties. A second iodide transport mechanism has recently been proposed, termed the human apical iodide transporter (hAIT or SLC5A8), with substantial structural homology to the basolateral NIS co-transporter, but with an apical distribution in thyrocytes (25). This report goes some way to confirming the physiological relevance of an additional apical iodide channel(s) in man, that can compensate for defective transport mediated by SLC26A4.

To summarize, we report the probably unique case of a young woman with PDS who developed hyperthyroidism owing to Graves' disease. The clinical findings are used to illustrate the normal physiology of thyroid hormone synthesis, the mechanisms of apical iodide transport in the thyrocyte and the pathophysiology of dyhormonogenesis. The patient was successfully treated with a conventional dose of radioiodine, and this treatment may be worthy of further investigation in this condition.

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