

## Familial thyroxin-binding globulin excess with ichthyosis: a case report

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**SUMMARY:** Önenli-Mungan N, Yüksel B, Özer G, Denli G, Topaloğlu AK, Teker Z. Familial thyroxin-binding globulin excess with ichthyosis: a case report. Turk J Pediatr 2004; 46: 174-176.

Thyroxin (T<sub>4</sub>) binding globulin (TBG) the major thyroid hormone transport protein in humans. Congenital or acquired problems lead to TBG excess. Inheritance of TBG excess follows an X-linked pattern. A 21-month-old boy with ichthyosis was referred to the Pediatric Endocrinology Clinic with high levels of thyroid hormones (TT<sub>3</sub>=325 ng/dl, TT<sub>4</sub> 23 µg/dl, FT<sub>3</sub>=3.49 pg/dl, FT<sub>4</sub>=1.44 ng/dl, TSH=2.48 µIU/ml). He was clinically euthyroidic. Thyroid gland was normal in size and homogeneous. Thyroid autoantibodies were negative. TSH responded normally to thyroid releasing hormone (TRH) stimulus. TBG was elevated (56 µg/ml). Family investigation revealed high levels of TBG in mother grandfather, and an uncle. To our knowledge, no other TBG excess with ichthyosis has been reported in the literature.

**Key words:** thyroxin-binding globulin (TBG) excess, ichthyosis.

Thyroid hormones are strongly bonded to the principal plasma thyroid hormone-binding proteins such as thyroxin-binding globulin (TBG), which is an acidic glycoprotein synthesized by the liver, prealbumin (transthyretin), and albumin and secreted into the blood stream. Major thyroid hormone transport protein TBG binds 70% of thyroxin (T<sub>4</sub>) and 50% of tri-iodothyronine (T<sub>3</sub>)<sup>1</sup>. Pregnancy, neonatal period, usage of oral contraceptives and estrogens, acute intermittent porphyria, acute infectious and chronic liver disease, hepatocellular carcinoma and human immunodeficiency virus infection are the acquired causes of increase in TBG levels. Inherited abnormalities in the level of serum TBG have been classified as partial deficiency, complete deficiency, and excess. TBG excess is transmitted in an X-linked fashion and encoded by a single gene copy located on Xq 21-22. Since TBG is not necessary for thyroid hormone action, affected subjects are generally healthy, clinically euthyroid, and do not have a goiter<sup>2,3</sup>. Lamellar ichthyosis is an autosomal recessive inherited disorder present at birth. It involves the entire cutaneous surface and is characterized by large grayish brown scales, which are strikingly quadrilateral, free at the edges, and adherent in the center.

Thyroxin-binding globulin excess is a rare disorder, and no association between TBG excess and lamellar ichthyosis has been reported in the literature. Here we present a case of TBG excess with lamellar ichthyosis.

### Case Report

A 21-month old boy was referred to the Pediatric Endocrinology Clinic because of high levels of thyroid hormones, which were detected during a routine laboratory examination done for the etiologic evaluation of ichthyosis and dry skin. He had been followed since birth in the Dermatology Clinic for his lamellar ichthyosis. He was born at term, after an uneventful pregnancy via normal spontaneous vaginal delivery. His developmental milestones were appropriate for his age. He had no past medical history of severe illness, hospitalization, or long-term use of any drugs except topical emollients. His family history revealed that he is the third living child of first-degree cousins. He had two healthy brothers, aged five and seven. His brothers and other members of the family had no similar dermatological problems or thyroid disease.

His length (86.5 cm, 50-75%), weight (12.21 kg, 50%), and head circumference (75%), were within normal standards. Pulse was 86 beats/min and

blood pressure was 90/60 mmHg. He looked well except for moderate ichthyosis. The thyroid gland was nonpalpable. The rest of the physical examination was unremarkable. Mental-motor development was appropriate for his age. Laboratory investigations revealed high levels of total T<sub>3</sub> (TT<sub>3</sub>) and total T<sub>4</sub> (TT<sub>4</sub>), despite normal levels of free T<sub>3</sub> (FT<sub>3</sub>), free T<sub>4</sub> (FT<sub>4</sub>), and thyroid stimulating hormone (TSH) levels measured by chemiluminescence. Thyroid gland was normal in size and homogeneous in the ultrasonography and normoactive in the Tc 99 scan. TSH responded normally to thyroid releasing hormone (TRH) stimulus. Antithyroglobulin antibodies were negative. Thyroxin-binding globulin measured by radioimmunoassay was elevated (56 µg/ml) (Dia Sarin kit [RIA] was used in the measurement of TBG interassay variations were mean: 13.12 µg/ml, SD: 0.47 µg/ml, W: 3.58%, and intraassay variations were: mean: 13.14 µg/ml, SD: 0.62 µml W: 4.72%).

His mother, maternal grandfather, and an uncle had high levels of TT<sub>4</sub>, TT<sub>3</sub>, and TBG (Table I). His brothers had normal levels of TBG (25 µg/ml, 23 µg/ml).

As the patient was clinically euthyroid, he has been followed without any medication.

**Discussion**

T<sub>4</sub>-binding globulin is a major liver glycoprotein that transports iodothyronines in serum. TBG probably facilitates the transport of maternal T<sub>4</sub> and iodide to the fetus so the newborn has high levels of TBG. The disorders related with TBG excess are inherited or acquired. The mechanisms of inherited TBG excess remains unproven. Gene amplification of TGB may be a common cause<sup>1,2</sup>.

Our patient's TBG level was 56 µg/ml TBG levels increased up to 4.5 times normal in affected individuals, and carrier females have serum concentrations intermediate between normal values and the high levels in affected males. In one study, two Japanese families with inherited TBG excess were analyzed and it was found that serum TBG levels in hemizygous males were 44 and 58 µg/ml, two and three-fold above the normal value, respectively<sup>4</sup>. In another study, in an additional three Japanese families, one familial and two sporadic, TBG excess with the levels of 73, 42 and 42 µg/ml TBG were reported. As in our patient, all the members of these families and the other reported sporadic cases were

**Table I.** Laboratory Results of the Family

	TT3 * (100-260 ng/dl) ** (115-190 ng/dl)	TT4 * (6.8-13.5 µg/dl) ** (4.2-13 µg/dl)	FT3 * (2.3-4.2 pg/dl) ** (2.3-4.2 pg/dl)	FT4 * (0.8-2.2 ng/dl) ** (0.8-2.3 ng/dl)	TSH * (0.5-5 µIU/ml) ** (0.5-5 µIU/ml)	Thyroglobulin * (0-46 ng/ml) ** (0-46 ng/ml)	TBG * (15-34 µg/ml) ** (15-34 µg/ml)	Antithyroid antibody
Patient	325	23	3.49	1.44	2.48	41	56	(-)
Mother	277	15.7	2.71	1.06	2.4	34	70	(-)
Uncle	312	18.3	3.1	1.2	1.4	23	64	(-)
Grandfather	265	16.2	2.6	1.9	1.6	29	62	(-)

\* Normal values for children.

\*\* Normal values for adults.

TBG: thyroxin-binding globulin.

TSH: thyroid stimulating hormone.

clinically euthyroid<sup>5,6</sup>. Nakai<sup>6</sup> reports a patient with X-linked co-dominant inheritance of TBG excess. We also suspected X-linked co-dominant inheritance of TBG excess at first, but the high levels of TBG detected in the patient's grandfather excluded this means of inheritance. Inherited TBG excess is reported as an isolated disorder. Only Nakai<sup>6</sup> published a case associated with growth hormone deficiency. Our patient had lamellar ichthyosis in addition to TBG excess. As far as we know this is the first case of inherited TBG excess coexisting with lamellar ichthyosis.

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