Hypothyroidism and Dyshormonogenesis Induced by D-Penicillamine in Children with Wilson's Disease and Healthy Infants Born to a Mother with Wilson's Disease

Aaron Hanukoglu, MD, Batya Curiel, MD, Drora Berkowitz, MD, Arieh Levine, MD, Joseph Sack, MD, and Mordehai Lorberboym, MD

Two siblings born to a mother with Wilson's disease, who was taking D-penicillamine, developed transient goitrous hypothyroidism. A prospective evaluation of 5 patients with Wilson's disease taking and not taking D-penicillamine for as long as 9.5 years showed subclinical hypothyroidism. D-penicillamine probably inhibited thyroperoxidase activity in utero in healthy infants and during childhood in patients with Wilson's disease. ***(J Pediatr 2008;153:864-6)***

Pregnant women with Wilson's disease should maintain therapy with chelating agents throughout pregnancy to prevent deterioration caused by copper toxicity and allow healthy pregnancy.[1,2] In untreated pregnant women, copper accumulation in the placenta and fetal liver may damage the fetus. D-penicillamine therapy prevents copper accumulation *in utero*[3] and has been considered beneficial for both the mother and the fetus.

Transient goitrous hypothyroidism was noted in an infant born to a mother with Wilson's disease who was treated with D-penicillamine during pregnancy. We prospectively evaluated another sibling born to this mother and 5 additional patients with Wilson's disease. All were documented to have hypothyroidism, which we suggest resulted from the inhibition of thyroperoxidase activity with D-penicillamine.

METHODS

Eight subjects from four families were evaluated. Family 1 included two siblings born to a mother with Wilson's disease and their mother. Families 2-4 included five patients with Wilson's disease (Table I). Four patients received D-penicillamine for 3.0 to 3.5 years. Subsequently, they received zinc therapy for as long as 6 years. In 1 patient, zinc was the sole therapy.

Free thyroxin (FT4), thyrotropin (TSH), and thyroid antibodies levels were determined with electrochemiluminescence immunoassays by using the Elecsys 2010 system in all patients (Roche Diagnostics, Indianapolis, Indiana). The measuring range of TSH is 0.005 to 100 μIU/L, and the reference range is 0.25 to 4.0 μIU/mL. Patients with a TSH level $\geq$4 μIU/mL were defined as having subclinical hypothyroidism. The reference range of FT4 is 12 to 22 pmol/L. Thyroglobulin, thyroid iodine uptake, and TSH receptor antibodies were measured only in subjects from Family 1. TSH receptor antibody activities were measured with cAMP functional bioassays by using cultured human thyrocytes only in infants from Family 1 and their mother.[4]

All subjects, except 1 sibling from Family 1 who had a palpable goiter at birth, underwent thyroid imaging studies with Technetium-99m.

The significance of the difference between mean TSH levels while taking and while not taking D-penicillamine was analyzed with a *t* test, and a *P* value $<$.05 was considered to be significant.

RESULTS

Family 1

Sibling 1 was born at 35 weeks of gestation after an uncomplicated delivery, weighing 2.4 kg. A goiter was palpable at birth. Neonatal screening results[5] and repeated thyroid function tests at the age of 18 days were compatible with severe goitrous hypothyroidism (Table II; available at www.jpeds.com). TSH receptor blocking antibod-

FT4	Free thyroxin	TSH	Thyrotropin

From the Divisions of Pediatric Endocrinology (A.H., B.C.), Pediatric Gastroenterology (A.L.), and Institute of Nuclear Medicine (M.L.), E. Wolfson Medical Center, Holon and Tel-Aviv University, Sackler School of Medicine (A.H., B.C., A.L., J.S., M.L.); Rambam Medical Center, Haifa (D.B.), National Screening for Congenital Hypothyroidism, Ministry of Health, Jerusalem (J.S.), Israel.

The authors declare no potential conflicts of interest.

Submitted for publication Dec 27, 2007; last revision received May 12, 2008; accepted Jun 17, 2008.

Reprint requests: Prof Aaron Hanukoglu, E. Wolfson Medical Center, Dept of Pediatrics, Halohamim St 62, 58100 Holon, Israel. E-mail: aaronh@science.co.il.

0022-3476/$ - see front matter

10.1016/j.jpeds.2008.06.015

Table I. Ethnic origin, D-penicillamine dose, and duration and thyrotropin levels of 5 patients with Wilson's disease from 4 families, taking and not taking D-penicillamine

Patient/ family (n)	Sex	Ethnic origin	Age at last examination (years)	Years taking penicillamine	Penicillamine dose mg (mg/kg)	TSH (mIU/L)	Years taking zinc	TSH (mIU/L)
1 (2)	F	Uzbek Jew	14 3/12	3	750 (31)	4.1	2	1.8
				3.5	750 (29)	4	4.1	3.8
							5	2.2
							6.2	1.0
2 (2)	F	Uzbek Jew	10	None		—	1	4.1
						—	3	2.5
						—	4.5	3.2
						—	6	2.8
3 (3)	M†	Morrocan Jew	13	3	625 (21)	4.2	4	1.2
4 (3)	M	Morrocan Jew	13	3	625 (21)	4.2	4	2.6
5 (4)	F‡	Druze	10.4	3	625 (22)	4.8	0.3	2.4
							0.4	2.2
Mean ± SD						4.28 ± 0.30		2.5 ± 0.9*

F, Female; *M*, male.
*$P < .001$.
†Patients 3 and 4, twin brothers.
‡FT4 = 10.68 pmol/L.

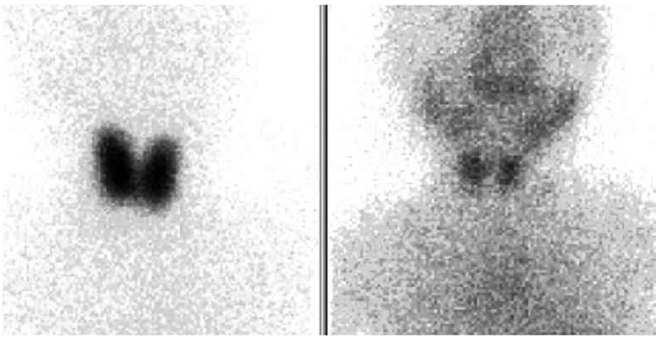

Figure. Thyroid scan showing a diffusely enlarged thyroid gland on diagnosis (*left panel*) and a month after stopping thyroxin (*right panel*).

ies were negative. He remained well balanced with a small dose of Eltroxin (25 μg/day) throughout follow-up. The goiter disappeared within 5 months. The therapy was stopped at 4 years of age without any adverse effects.

Sibling 2 was born as a full term infant, weighing 3.1 kg. His perinatal course was uneventful. Neonatal screening revealed severe hypothyroidism and was confirmed with a venous blood sample. Thyroglobulin levels were extremely elevated (Table III; available at www.jpeds.com). With a thyroid scan, a diffusely enlarged gland with increased uptake was revealed (Figure). With Eltroxin therapy, the thyroid functions normalized within 2 months. Because of the transient nature of hypothyroidism in his brother, the therapy was stopped at 7 months of age without adverse effects (Table III). The results of a thyroid scan a month after stopping therapy were normal (Figure).

The mother was diagnosed with Wilson's disease at the age of 8 years. D-penicillamine was her sole therapy (for the last 15 years, 1.5 g/day). During pregnancies she required an increased dose (2 g/day). Her thyroid function tests were evaluated at 31 years of age, after the birth of sibling 2. FT4 and TSH levels were normal (FT4, 19.5 pmol/L; TSH, 0.87 mIU/L). On physical examination, the thyroid gland was not palpable. A thyroid scan revealed diffuse enlargement of the thyroid gland, and thyroid uptake study with I-131 revealed an increased uptake (32% after 24 hours, normal as high as 30 %). Serum levels of thyroglobulin and thyroperoxidase were normal; TSH receptor antibodies were undetectable. There was no history of thyroid disease in the family. When the patient was 35 years old, a multinodular goiter developed. FT4 and TSH concentrations remained normal.

Families 2 to 4

At the start of D-penicillamine therapy, the patients were 4 to 7 years old (mean ± SD, 5.5 ± 1.2 years). On D-penicillamine, TSH concentrations were significantly higher than those during zinc therapy (Table I). FT4 concentrations were normal (data not shown), except for in 1 patient who had low FT4 levels on D-penicillamine (Table I). These data were suggestive of subclinical hypothyroidism. With zinc, TSH concentrations normalized in all patients (Table I).

DISCUSSION

Our cases displayed a hitherto unknown cause of congenital goitrous hypothyroidism in newborn infants. Two siblings born to a mother with Wilson's disease had goitrous hypothyroidism. Extremely elevated thyroglobulin level in sibling 2 was consistent with dyshormonogenesis caused by iodination and organification defects.[6] In both siblings, hypothyroidism was transient, suggesting a non-genetic etiology. Undetectable TSH receptor blocking antibody levels in the mother ruled out hypothyroidism caused by in utero passage of antibodies from the mother to the fetus. The most likely candidate for hypothyroidism in these infants was D-penicillamine. In in vitro studies, D-penicillamine has been reported to inhibit iodination reaction[7,8] and human myeloperoxidase activity.[8] Myeloperoxidase that catalyses iodination and coupling reactions shares homology with thyroid peroxidase.[9] Thus D-penicillamine most likely inhibits the iodination and coupling reactions catalyzed by thyroid peroxidase as well.

We propose that in utero exposure to D-penicillamine results in congenital goitrous hypothyroidism in infants and in subclinical hypothyroidism in older children. Different presentations in age groups may be a consequence of the timing of the insult. Usually, the D-penicillamine dose in adults is 1.0 to 1.5 g/day. The high dosage in the mother (2 g/day) during pregnancy probably also contributed to severe hypothyroidism in both siblings.

The mother of the 2 siblings initially had diffuse enlargement of the thyroid gland with an increased uptake. Later, a multinodular goiter developed. D-penicillamine therapy for years probably inhibited thyroid peroxidase activity in the mother as well.

D-penicillamine-induced anti-myeloperoxidase antibody was implicated in a patient with Wilson's disease with severe renal vasculitis.[10] None of our patients had evidence of vasculitis.

Zinc therapy has been shown to be an effective chelating agent in patients with Wilson's disease during pregnancy[11] and D-penicillamine during pregnancy may result in severe embryopathy.[12] In women with Wilson's disease who are pregnant, replacing D-penicillamine therapy with zinc acetate may prevent congenital hypothyroidism in their offspring. In children taking long-term D-penicillamine, thyroid function should be periodically examined.

REFERENCES

1. Sternlieb I. Wilson's disease and pregnancy. Hepatology 2000;31:531-2.

2. Furman B, Bashiri A, Wiznitzer A, Erez O, Holcberg G, Mazor M. Wilson's disease in pregnancy: five successful consecutive pregnancies of the same woman. Eur J Obstet Gynecol Reprod Biol 2001;96:232-4.

3. Oga M, Matsui N, Anai T, Yoshimatsu J, Inoue I, Miyakawa I. Copper disposition of the fetus and placenta in a patient with untreated Wilson's disease. Am J Obstet Gynecol 1993;169:196-8.

4. Kraiem Z, Baron E, Kahana L, Sadeh O, Sheinfeld M. Changes in stimulating and blocking TSH receptor antibodies in a patient undergoing three cycles of transition from hypo- to hyper-thyroidism and back to hypothyroidism. Clin Endocrinol (Oxf) 1992;36:211-4.

5. Sack J, Amado O, Frucht H, Ekstein A. Screening for neonatal hypothyroidism in Israel. Isr J Med Sci 1981;17:294-5.

6. Vulsma T, Rammeloo JA, Gons MH, de Vijlder JJ. The role of serum thyroglobulin concentration and thyroid ultrasound imaging in the detection of iodide transport defects in infants. Acta Endocrinol (Copenh) 1991;124:405-10.

7. Degroot LJ. Stimulation and inhibition of thyroid iodinating enzyme systems Biochim Biophys Acta 1967;136:364-74.

8. Mahlis E, Christophidis N. Modulation of the iodination reaction in normal human neutrophils and in whole blood by D-penicillamine, congeners and intracellular enzyme catalase and superoxide dismutase. Clin Exp Rheumatol 1989;7:365-71.

9. Taurog A, Dorris ML. Myeloperoxidase-catalyzed iodination and coupling. 1: Arch Biochem Biophys 1992;296:239-46.

10. Bienaimé F, Clerbaux G, Plaisier E, Mougenot B, Ronco P, Rougier JP. D-penicillamine-induced ANCA-associated crescentic glomerulonephritis in Wilson's disease. Am J Kidney Dis 2007;50:821-5.

11. Brewer GJ, Johnson VD, Dick RD, Hedera P, Fink JK, Kluin KJ. Treatment of Wilson's disease with zinc. XVII: treatment during pregnancy. Hepatology 2000;31:364-70.

12. Pinter R, Hogge WA, McPherson E. Infant with severe penicillamine embryopathy born to a woman with Wilson's disease. Am J Med Genet 2004;128A:294-8.

Table II. Clinical and laboratory data in sibling 1 with goitrous hypothyroidism at diagnosis and follow-up

Age*	18 days	1.5 months	5 months	1.7 years	4 years	9 years	Normal
FT4 (pmol/L)	<3.8	20.6	18	21.9	28.3	20.6	12-22
TSH (mIU/L)	>100	0.6	1.2	0.9	1.5	2.1	0.25-4
TG (ng/mL)		33	16	15			<85
Eltroxin (μg/d)	50	25	25	25	Stopped		
Goiter	+	+	no				

*On neonatal thyroid screening, total T4 = 0.2 μg/dL (reference range, 8.5-18 μg/dL), TSH >200 mIU/L.

Table III. Laboratory data in sibling 2 at diagnosis and follow-up

Age*	1 month	1.5 months	2.5 months	7 months	2 years
FT4 (pmol/L)	<3.8	12.9	21.9	15.4	15.4
TSH (mIU/L)	>100	16.3	0.7	1.7	1.2
TG (ng/mL)	8156	3937	34	41	32
Eltroxin (μg/d)	50	50	50	Stopped	
Thyroid scan	Diffuse goiter			Normal†	

*On neonatal thyroid screening T4 = 1.3 ug/dL (reference range, 8.5-18), TSH = 126 mIU/L.

†99m Tc-pertechnetate thyroid scan, performed a month after stopping eltroxin.