Hypothyroidism and Levothyroxine-Responsive Liver Dysfunction in a Patient with Ring Chromosome 18 Syndrome

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Background: Ring chromosome 18 [r(18)] is a rare constitutional chromosomal aberration syndrome, characterized by dysmorphic face, hypoactivity, short stature, and delayed development. Autoimmune thyroiditis and immunoglobulin (Ig) A deficiency are occasionally associated with chromosome-18 deletion syndromes.

Summary: Here, we report a 2-year-old male child with r(18) syndrome and a selective IgA deficiency (<1.6 mg/dL, reference range [rr]: 20–149), who developed hypothyroidism and liver dysfunction. Thyroid function tests (thyroid-stimulating hormone [TSH]: 1031 μ IU/mL, rr 0.43–4.0; free triiodothyronine: 0.52 pg/mL, rr 2.37–4.65; free thyroxine: 0.11 ng/dL, rr 1.03–2.00) and positive thyroid antibodies (anti-TSH receptor 1.7 IU/L, cut-off index [coi]: <1.0, antithyroid peroxidase 171 IU/mL, coi <0.3, and antithyroglobulin 2.8 IU/mL, coi <0.3) indicated autoimmune hypothyroidism. Elevated levels of aspartate aminotransferase (AST, 240 IU/L, rr 17–39) and alanine aminotransferase (ALT, 315 IU/L, rr 4–23), but negative antibodies against LKM and mitochondrial M2, suggested no autoimmune hepatitis. Transaminase levels became normalized after he was given levothyroxine therapy to achieve the euthyroid state, but they repeatedly became elevated when levothyroxine was inadvertently discontinued (peak AST=409 IU/L; peak ALT=390 IU/L). A maintenance dose of levothyroxine has effectively maintained the euthyroid state and normalized liver function tests despite no immunosuppressive therapy.

Conclusions: The r(18) patient with autoimmune hypothyroidism and IgA deficiency suffered from idiopathic hepatitis. The liver dysfunction was associated with hypothyroidism that resolved with thyroid hormone treatment. While the former combination has been described, the latter has not. The reason for the development of hepatitis in association with hypothyroidism is unexplained. However, we postulate that it might be related, in ways that are not clear, to the deleted genes of r(18).

Introduction

RING CHROMOSOME 18 [r(18)] syndrome is a rare constitutional chromosomal aberration presenting with a dysmorphic face with blepharoptosis, hypotonia, short stature, and developmental delay (1). Clinical expressions of r(18) patients overlap appreciably with those of patients with deletion 18p [del(18p)] and/or 18q [del(18q)] syndrome (2,3), because the ring shape is formed by the loss and joining of both ends of chromosome. The individual phenotype of r(18) patients then depends on each size of the deleted regions of chromosome 18. Somatic mosaicism of the defective chromosome is another explanation for the phenotypical diversity in patients. Recently, specific features of del(18p) (4) or del(18q) (5) syndrome have been partly explained on the basis of each lost region in a series of patients assessed by a comparative genomic hybridization array. Autoimmune thy-

roiditis and immunoglobulin (Ig) A deficiency are reportedly associated with r(18), del(18p), and del(18q) syndrome, although the mechanism for the disease process and relevance of both remain unclear. However, no specific liver complications have been reported in patients harboring r(18).

We saw a 2-year-old male child with r(18) syndrome and a selective IgA deficiency, who developed autoimmune hypothyroidism with liver dysfunction of an unknown cause. Liver dysfunction was normalized with levothyroxine treatment. This is the first report of r(18) syndrome associated with relapsing liver dysfunction.

Patient

The patient was born to nonconsanguineous Japanese parents at 38 weeks of gestational age. His family history was unremarkable for inherited diseases. At birth, he was a

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symmetrical small-for-gestational age infant (birth weight 1962 g, length 45 cm) with hypertelorism and a cleft palate. Neonatal screening tests for inborn errors of metabolism, including for congenital hypothyroidism, were negative. He had feeding disabilities and a poor weight gain during the infancy. At 4 months of age, he was found to have r(18) syndrome based on G-band chromosome staining of peripheral blood lymphocytes; 46, XY, r(18)(p11.2q23) (Fig. 1a). The developmental milestones were delayed (head control at 4 months, unsupported sitting at 8 months, and walking alone at 18 months of age). He suffered from bronchitis and otitis media frequently, but had no serious infections. Selective IgA deficiency (serum IgA: <1.6 mg/dL, reference range [rr]: 20–149) and aortic stenosis were diagnosed at 18 months of age. At 2 years of age, he had surgical treatment for cleft palate. At this time, liver and thyroid function tests were unremarkable (thyroid-stimulating hormone [TSH]: 3.47 μ IU/mL, rr 0.43–4.0; free triiodothyronine [T3]: 5.06 pg/mL, rr 2.37–4.65; and free thyroxine [T4]: 1.03 ng/dL, rr 1.03–2.00).

At 6 years of age, asymptomatic liver dysfunction was found by chance (aspartate aminotransferase [AST] 62 IU/L, rr 17–39, and alanine aminotransferase [ALT] 63 IU/L, rr 4–23). AST and ALT levels increased to 200–300 IU/L within a few months. He was then referred to our hospital for further evaluation.

On admission, he was a small boy (height: 93 cm [–5.3SD], weight: 13.3 kg [3 percentile], and head circumference: 47 cm [–3.3SD]) with puffy eyelids, but no pretibial edema. He had hypertelorism, epicanthic fold, flat nasal bridge, micrognathia, and postpalatoplasty. He had a short webbed neck, short fifth fingers, right inguinal hernia, and vitiligo vulgaris. He was a listless boy with a developmental delay and hypotonia, but no paresis. Auscultation revealed a systolic ejection heart murmur and normal respiratory sounds. There was no goiter, lymphadenopathy, or hepatosplenomegaly.

Serum chemistry data were as follows: total protein: 8.0 g/dL (rr 6.2–7.8), albumin: 4.4 g/dL (rr 3.8–4.7), total bilirubin: 0.5 mg/dL (rr 0.3–1.2), AST: 240 IU/L, ALT: 315 IU/L, alkaline phosphatase: 476 IU/L (rr 291–891), lactate dehydrogenase: 432 IU/L (rr 281–586), γ -glutamyl transpeptidase:

48 IU/L (rr 6–18), cholinesterase: 466 IU/L (rr 252–488), total cholesterol: 275 mg/dL (rr 113–217), creatine kinase: 592 IU/L (rr 53–277), and ammonia: 61 μ g/dL (rr 12–66). Prothrombin time (PT, 63% of normal) and activated partial thromboplastin time (aPTT, 45.1 s [cont. 33.2 s]) were marginally prolonged. Serum Ig concentrations showed high IgG (2101 mg/dL, rr 630–1490), borderline IgM (71 mg/dL, rr 72–305), and undetectable IgA levels (<5 mg/dL, rr 45–258). Serum autoantibody tests were positive for antinuclear antibody: 160 titer (cut-off index [coi]: <10), anti-SS-A antibody: 34 (coi <10), anti-SS-B antibody: 25 (coi <15), anti-Scl-70 antibody: 23 (coi <16), anti-Jo-1 antibody: 25 (coi <9), anti-RNP antibody: 21 (coi <15), and anti-Sm antibody: 28 (coi <7). No anti-LKM antibody or antimitochondrial M2 antibody was detected. There was no evidence of Wilson's disease, drug intoxication, or infections with hepatitis A, B and C viruses, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, human herpes virus 6 and 7, parvovirus B19, and mycoplasma. Normal levels of serum hyaluronic acid and type IV collagen 7S indicated no hepatic fibrosis. Thyroid function tests were consistent with hypothyroidism (TSH: 1031 μ IU/mL, free T3: 0.52 pg/mL, and free T4: 0.11 ng/dL), and thyroid autoantibodies were positive for anti-TSH receptor antibody (1.7 IU/L, coi <1.0), antithyroid peroxidase antibody (171 IU/mL, coi <0.3), and antithyroglobulin antibody (2.8 IU/mL, coi <0.3). Flow cytometric analysis of peripheral blood mononuclear cells showed no increase of activated T cells (CD3⁺ HLA-DR⁺ cells 9.6%). Echocardiogram disclosed mild stenosis of bicuspid aortic valves. Abdominal ultrasonography and computed tomography revealed normal size and brightness/density of the liver having no space-occupying lesions. The anterior pituitary was slightly enlarged as assessed by magnetic resonance imaging brain scan.

Replacement of thyroid hormone (levothyroxine) was started for the treatment of autoimmune hypothyroidism. Transaminase levels, PT, and aPTT returned to normal paralleled with the development of the euthyroid state during the first 3 months of levothyroxine therapy. Six months later, the levothyroxine replacement was accidentally stopped by his mother for 3 months. AST and ALT levels increased to 409 and

FIG. 1. (a) G-banding karyotype and high-resolution analysis of peripheral blood lymphocytes obtained from the patient showed 46, XY, r(18)(p11.2q23). r corresponds to the ring formation of chromosome 18. (b) Clinical course of the present patient. The relationship between transaminase levels and thyroid functions was observed after starting and stopping thyroid hormone replacement therapy. ♦, alanine aminotransferase (ALT); △, aspartate aminotransferase (AST); □, thyroid-stimulating hormone (TSH); ●, free thyroxine (T4).

390 IU/L, respectively, in concert with the elevated TSH (888.1 μ IU/mL) and declined free T4 (0.10 ng/dL) levels. Transaminase levels were normalized again 3 weeks after the resumption of levothyroxine therapy. Accidental cessations of levothyroxine repeatedly led to the dysfunction of both the liver (AST: 116 IU/L, ALT: 120 IU/L) and the thyroid (TSH: 426.9 μ IU/mL, free T4: 0.16 ng/dL). Restarting levothyroxine therapy immediately improved the conditions (Fig. 1b).

Discussion

Autoimmune thyroiditis has been reported in patients with chromosome-18 deletion syndromes, including r(18) (6). Winter *et al.* (7) first reported a 10-year-old female child with r(18) and hypothyroidism, whose hypothyroid symptoms, including constipation, started from birth. Apparent thyroid tissues, but no thyroid antibodies, favored the diagnosis of congenital hypothyroidism, arising from a potential defect in T4 synthesis associated with hemizygous lost ends of chromosome 18. Table 1 summarizes 10 reported cases of hypothyroidism in association with r(18) syndrome, including the present one (7–11). Because of the mimicking features of hypothyroidism, ptosis, short stature, and delayed development between r(18) syndrome and congenital hypothyroidism, it may be hard to determine when hypothyroidism occurred. In the literature review, most patients (80%) were positive for antithyroglobulin or antithyroid microsome tests. The treatment response to T4 therapy unraveled the individual phenotype of r(18) syndrome. Dysgammaglobulinemia represented by IgA deficiency is another manifestation of r(18) syndrome. Previous studies reported that 39% of r(18) patients had IgA deficiency (12) and suggested a candidate gene responsible for IgA production on distal end of 18q21.32 (5). Not all, but some subjects having selective IgA deficiency are at risk of autoimmune diseases such as thyroiditis (13). Lomenick *et al.* (14) have recently reported that severe autoimmune thyroiditis occurred in two patients having del(18q), but no IgA deficiency at age 4 and 15 years, respectively. They suggested no causative link of IgA deficiency with autoimmune thyroiditis, but noted other autoimmune diseases in patients with del(18q). As shown in the low frequency of IgA deficiency (20%) (Table 1), hypothyroidism is a common and indiscernible feature of r(18) patients irrespective of the presence of selective IgA deficiency. Jain *et al.* (6) reported that a female, who harbored r(18), developed autoimmune polyglandular endocrinopathy and had hyperthyroidism, type 1 diabetes mellitus, vitiligo, and IgA deficiency. This could either have been a coincidental occurrence, but more likely was related to the same predisposing factors. In this regard, there may be certain genes on chromosome 18 that could have an immune regulatory role.

The unique aspect of our patient's medical condition is the development of his liver dysfunction. No specific hepatitis has ever been reported in association with r(18), del(18p), and/or del(18q) (Table 1). Moreover, he had no known causes of hepatitis, including autoimmunity, exposure to infectious agents, or toxins. Hepatitis is not usually a feature of hypothyroidism, but thyroid dysfunction may perturb liver function. Liver dysfunction might be associated with poor hepatic perfusion caused by hypothyroidism. However, the patient had no suggestive data for the defective perfusion in the liver and the kidney such as hepatorenal syndrome. Cholestatic

TABLE 1. REPORTS OF HYPOTHYROIDISM IN PATIENTS WITH A RING CHROMOSOME-18 SYNDROME

Pt	Sex	Age (years) at diagnosis of hypothyroidism	Antithyroid antibodies against thyrogl./mic.	Delivery, birth size	Manifestations at the diagnosis					Karyotype	Reference
					Short stature	Hypotonia/low active	Ptosis	PMR	IgA deficiency	Liver dysfunction	
1	Female	1	Neg./pos.	Term, SGA	Yes	No	ND	Yes	No	No	Fukushima <i>et al.</i> (8)
2	Female	1	Neg./pos.	Term, AGA	Yes	Yes	ND	Yes	No	No	Fukushima <i>et al.</i> (8)
3	Male	2	Pos./pos.	Term, SGA	Yes	Yes	Yes	Yes	Yes	Yes	This study
4	Male	4	Pos./pos.	Term, AGA	Yes	Yes	No	Yes	ND	No	Dacou-Voutetakis <i>et al.</i> (10)
5	Female	10	Neg./ND	Term, AGA	Yes	Yes	Yes	Yes	No	No	Winter <i>et al.</i> (7)
6	Male	16	Neg./pos.	Term, AGA	Yes	Yes	ND	Yes	Yes	No	Fukushima <i>et al.</i> (8)
7	Female	17	Hashimoto	Term, AGA	Yes	Yes	No	Yes	ND	No	Gereltul <i>et al.</i> (9)
8	Male	6	Neg./neg.	Preterm, SGA	Yes	No	ND	Yes	No	No	Fukushima <i>et al.</i> (8)
9	Female	9	Pos./ND	Term, AGA	No	No	No	Yes	No	No	Lo-Castro <i>et al.</i> (11)
10	Male	12	Pos./pos.	Term, AGA	Yes	No	ND	Yes	No	No	Fukushima <i>et al.</i> (8)

Pt 7 had hypogonadism and ectodermal dysplasia. Pt 9 presented insulin-dependent diabetes mellitus. Pts 8–10 had mosaic r(18) syndrome.

Pt, patient; thyrogl., thyroglobulin; mic., microsome; PMR, psychomotor retardation; neg., negative; pos., positive; SGA, small for gestational age; ND, not described; r(18), ring chromosome 18; AGA, appropriate for gestational age; mos., somatic mosaicism with normal karyotype.

hepatitis can occur in patients with hypothyroidism (15). Columbano *et al.* (16) reported that T3 stimulated the proliferation of hepatocytes in rat models of liver regeneration. T3 could reduce cellular oxidative stress, which may help attenuate reactive oxygen species (ROS)-mediated damage, along with improving mitochondrial function and energy status in cells with mitochondrial DNA defects (17). The *NADH* dehydrogenase flavoprotein 2 gene located on 18p11.22 encodes a component of mitochondrial complex 1. Hemizygous loss of function of this gene may lead to the vulnerable hepatocytes, because an excess production of ROS by mitochondrial dysfunction impairs the homeostatic balance between ROS and antioxidants. In this setting, the hepatitis in our r(18) patient might in some way be related to cellular oxidative stress mediated by hypothyroidism. Further studies of the nature of the deleted genes in our patient may provide hypotheses to explain the apparent relationship between hypothyroidism and hepatitis in this setting, and these could be tested further in experimental models.

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Disclosure Statement

The authors declare that no competing financial interests exist.

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