A Japanese Patient of Congenital Hypothyroidism with Cerebellar Atrophy

TOSHIHIRO TAJIMA, FUMIE FUJIWARA, AKIRA SUDO, SHINJI SAITO AND KENJI FUJIEDA*

Department of Pediatrics, Hokkaido University School of Medicine, N15, W7, Sapporo 060-0835, Japan
*Department of Pediatrics, Asahikawa Medical College, 2-1-1-1 Midorigaoka Higashi, Asahikawa 078-8510, Japan

Abstract. We encountered a Japanese patient of congenital hypothyroidism with severe cerebellum atrophy. The boy was born after 40 weeks of gestation by normal vaginal delivery from nonconsanguineous parents. There were no abnormal physical findings; however neonatal mass screening for congenital hypothyroidism at 5 days of age demonstrated elevated thyrotropin (TSH) level (15.5 µU/ml, normal range 0.54–10.0 µU/ml). He was suspected to have subclinical or mild congenital hypothyroidism (CH). Thus he was treated with L-thyroxine using a regimen that rendered his serum TSH concentration within normal range from 27 days of age. Despite early and adequate treatment, he showed signs of global developmental delay and became gradually hypotonic and exhibited a staggering gait at 3 years of age. Brain magnetic resonance imaging (MRI) demonstrated marked cerebellar atrophy with an intact brainstem. Thyroidal uptake of radioiodide and thyroid gland size were normal, indicating a functional defect only. The relation between congenital hypothyroidism and severe cerebellar atrophy in our patient is not clear. As only a few cases of the combination of CH and cerebellar anomalies have been described previously, cerebellar symptoms in CH should be examined carefully.

Key words: Congenital hypothyroidism (CH), Cerebellar atrophy, Developmental delay

THE occurrence of neurological symptoms and developmental delay in patients with congenital hypothyroidism (CH) has been caused by the lack of thyroid hormone in the developing central nervous system [1]. Untreated CH results in neurological deficits, including mental retardation, disturbance of gait and coordination. As the introduction of neonatal screening for CH enables prompt diagnosis and early initiation of thyroid hormone replacement treatment, most CH patients develop normally [1].

Here, we describe a Japanese patient of CH, who showed developmental delay and ataxic gait, in whom severe cerebellar atrophy was observed by brain magnetic resonance imaging (MRI) despite early and adequate treatment.

A Report of Case

The patient was born after 40 weeks of gestation by normal vaginal delivery from nonconsanguineous parents. His birth weight was 2250 g (small for date) and length was 44.5 cm. There was no abnormal physical findings including goiter; however, neonatal mass screening using filter paper for CH at 5 days of age demonstrated mildly elevated thyrotropin (TSH) level (15.5 µU/ml, normal range 0.54–10.0 µU/ml). For further evaluation, he was referred to our hospital at 27 days of age. His body weight was 2945 g and no symptom of hypothyroidism was seen. At this time, his serum TSH was 12.07 µU/ml, free T4 1.16 ng/dl, free T3 3.75 pg/ml, and thyroid autoantibodies were negative. He was suspected to have subclinical or mild CH and thus L-thyroxine (L-T4, 20 µg/day) therapy was started. He was treated with L-thyroxine using a regime that rendered his serum TSH concentration within normal range. His dose was subsequently increased as he grew, and at 3 years of age, he was
receiving 75 µg/day. Despite early and adequate treatment, his physical growth did not catch up. His developmental milestones were gradually delayed; head control, 3 months, sitting 6 months, walk alone 1 year 7 months of age, first verbalized 2 years of age. In addition, he presented staggering gait at 3 years of age. Brain magnetic resonance image (MRI) showed marked cerebellar atrophy (Fig. 1). Thus, at 5 years of age he was admitted to our hospital for further evaluation. At this time, his height was 98.5 cm (–2.6 SD for normal Japanese boy), weight was 12.0 kg (Fig. 2), and head circumference 44.7 cm (–3.6SD for normal Japanese boy). His bone age was 4 year-old by Japanese TWII method. There were no biochemical results of his serum and urine for any metabolic diseases. Electrocardiogram and electroencephalogram were normal. Hearing test was also normal. $^{123}$I thyroid imaging was performed. The image of scintigraphy was normal and uptake was 24% at 24 hr. Serum TSH exhibited a high and delayed response to thyrotopin (TRH) simulation. TSH was 16.7 µU/ml before, 82.1 µU/ml at 30 min, 25.8 µU/ml at 120 min. These findings indicated a functional defect only. Reevaluation of brain MRI showed cerebellar atrophy and thin corpus callosum; however, the atrophy did not worsen.

Because of growth failure, we reevaluated his pituitary function at 5.6 years of age. Arginine and insulin tolerance tests showed partial deficiency of GH (Table 1). At this time, thyroid function was normal by L-thyroxine replacement. There was a normal response of LH and FSH levels after GnRH stimulation (Table 1). Plasma ACTH and serum cortisol responses after insulin tolerance test were within normal range (Table 1).

We have been following the patient up to the current age of 9 years. His thyroid status is within normal range by L-thyroxine treatment, but his neurological symptoms have not progressed. Neurological exami-
nation showed mental retardation with IQ 68 by WISC III at 6 years of age. GH therapy was initiated at 6 years of age and his growth has moderately improved by treatment (Fig. 2).

Discussion

We reported a patient of CH with cerebellar atrophy. As serum levels of free T4 and T3 were adequately maintained since early period, the unfavorable neurological outcome and cerebellar atrophy appear to be caused by other etiologies in the brain and cerebellum than thyroid status.

To our knowledge, there are only three reports of cases with congenital hypothyroidism and cerebellar anomalies. Jung et al. [2] reported two patients who had facial anomalies, anterior chamber-cleavage disorder in addition to CH and cerebellar hypoplasia. The patient of Hallermann-Streiff syndrome reported by Hou [3] had multiple anomalies other than congenital hypothyroidism and small cerebellum. Mauceri et al. [4] described a patient with CH, craniofacial anomalies, bachycephay, large ears, pectus carinatum and severe hypoplasia of the right cerebellar hemisphere and vermis. Our patient did not have any anomalies and thus the disease of our patient appears to be different from previous cases.

Recently, it has been reported that mutations of the NKX2-1 gene cause CH and neurodevelopment deficits [5–7]. Neurological findings caused by the NKX2-1 defects include global developmental delay, ataxia and choreoathetosis, but not cerebellar atrophy. Krude et al. [6] have reported brain MRI in CH patients caused the NKX2-1 gene defects showed changes of basal ganglia and cystic mass in the pituitary. In addition, NKX2-1 plays a critical role in lung morphogenesis and respiratory epithelial cell gene regulation especially of surfactant protein genes, so that patients caused by this gene defect have been reported to present symptoms like neonatal respiratory distress syndrome [5]. These findings of the NKX2-1 gene abnormality are not consistent with our patient. The analysis of the NKX2-1 gene did not show any mutation in our patient (data not shown).

In the rodent model, it is well established that maternal hypothyroidism in late gestational period or early postnatal hypothyroidism leads to the alteration of morphology and functional anatomy of the cerebellum [8–10]. These abnormalities involve delayed proliferation and migration of granule cells, stunting of the dendritic arborization of Purkinje cells, diminished axonal myelination and cell loss [10]. In our patient, the thyroid function of his mother was not tested, and thus it is unclear whether maternal hypothyroidism in late gestation would affect cerebellar development, or not. Generally, children born from maternal hypothyroidism do not present any cerebellum abnormality. This fact suggests that the cerebellar atrophy of our patient is likely to be caused by unknown defects involving in thyroid function and cerebellum development, rather than a deficit of thyroid hormone in late gestation. However, we cannot completely exclude any environmental insults in utero during late gestation [10].

We reported a patient with CH and severe cerebellar atrophy. During follow-up of CH, we should pay careful attention to cerebellar symptoms.

References


