Endocrine Journal 2008, **55** (1), 231

Letter to the Editor

Congenital Hypothyroidism, Cerebellar Atrophy, and the Incomplete Phenotypic Expression of PHACES Syndrome

Dear Sir;

We read the recent interesting report by Tajima T *et al.* [1] describing a patient suffering from congenital hypothyroidism and cerebellar atrophy. The patient was reported to have a normal *in situ* thyroid gland with a functional defect only. The Authors commented on the extremely rare association between congenital hypothyroidism and cerebellar anomalies, described currently only in 3 subjects (but always associated to other malformations). NKX2-1 defect and hypothyroidism-induced cerebellar developmental failure have been discussed and excluded.

We would like to add a remark based on our own experience with a girl (which case report is currently in press) affected by a neurocutaneous condition known as PHACES syndrome, which acronym refers to the association of facial haemangiomas, the hallmark of the syndrome, and a spectrum of malformative anomalies including posterior *fossa* malformations of the brain, arterial anomalies, cardiac defects, eye abnormalities, and sternal clefting [2].

Several reports and review commented on the broad constellation of anomalies and wide variable phenotype of this syndrome, in which partial forms seem to exist too as in resembling disorders as Sturge-Weber syndrome. Owing to the variable expression, PHACES syndrome is thought to be an underrecognized condition. Several cases of cerebellar atrophy, large posterior fossa cyst, or Dandy-Walker anomaly variants have been described in patients suffering from PHACES syndrome. A developmental field defect occurring between 6 and 8^weeks of gestational age has been hypothesized as causative of the disease. Neural crest anomalies have been invoked, but the involvement of the cerebellum, a structure not derived from neural crest, has not been explained as yet.

Hypothyroidism is an extremely rare manifestation in this condition (9 cases described currently to the best of our knowledge) and was previously reported as the result of thyroid disgenesis or TSH deficiency related to major central nervous system anomalies [3, 4]. Four out of 5 cases of primary congenital hypothyroidism studied by brain MRI in PHACES syndrome presented cerebellar anomalies. Unfortunately, the aetiology of the congenital hypothyroidism was available only in two patients, consistent both with thyroid disgenesis. We recently observed a girl presenting with congenital hypothyroidism with an *in situ* thyroid gland, ventricular septal defect, optic atrophy and no brain anomalies; the clue to the diagnosis was the presence of small and sparse facial haemangiomas. Even if in PHACES syndrome facial haemangiomas are usually large congenital lesion with aggressive growth and invasion of tissues, small facial haemangiomas with no tendency to grow were reported too, as well as cases in which they appear later in infancy [3, 5]. One of the cases of late-onset haemangiomas occurred actually in one of the infants suffering also from congenital hypothyroidism [3].We hypothesize, hence, that partial forms without haemangiomas may exist too at the extremity of the malformative spectrum.

For the reasons abovementioned, we believe the case reported by Tajima T *et al.* could represent a disorder somehow related to PHACES syndrome. Unfortunately, the aetiology of this disorder is still unknown and no genetic test is currently available to assess this interesting hypothesis.

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