Neonatal hyperthyroidism with craniolacunia

Gunma Children's Medical Center
Division of Endocrinology and Metabolism Junko Igaki
Division of Neonatology Fumitaka Inoue Kenichi Maruyama
Division of Radiology Shinitsu Hatakeyama

≪disclosure≫
None of the authors declare a conflict of interest.

≪Summary≫
Case 1: He developed neonatal hyperthyroidism, however his mother had been treated with antithyroid drug from the second trimester. Some clinical findings were infrequent, and included liver dysfunction, hepatosplenomegaly, thymic enlargement, hyperviscosity, thrombocytopenia, hydrocephalus due to aqueductal stenosis, Arnold-Chiari malformation type I, and craniolacunia, but craniosynostosis.

Case 2: She had craniolacunia without craniosynostosis, however neeonatal hyperthyroidism ameliorated spontaneously.

≪Background≫
Overt neonatal hyperthyroidism is estimated to occur in 1-2% of offspring of pregnant women with Graves' disease.
Preterm delivery, enhancement of bone includigng advanced bone age, craniosynostosis and microcephaly may be present. Liver dysfunction, hepatosplenomegaly, thymic enlargement, hyperviscosity, and thrombocytopenia present rarely. Ventriculomegaly was reported in three cases previously. Hydrocephalus due to aqueductal stenosis and Arnold-Chiari malformation type I have not reported previously. Craniosynostosis is a risk factor for hydrocephalus.

Craniolacunia is an abnormality of the calvarial bones of the skull, and is characterized by cavitation in the cranial vault as honey comb pattern. It is caused by non-ossification of the membranous skull due to intracranial decompression. It develops prenatally and is present at birth, while digital markings are caused by increased intracranial pressure and only appear after the first year of life. It is almost always associated with meningocele, and rarely with craniosynostosis, Arnold-Chiari malformation type II, and Klippel-Feil syndrome. However craniolacunia with neonatal hyperthyroidism has not previously been reported.

≪Purpose≫
This is the first report of two cases with craniolacunia and one case with hydrocephalus and Arnold-Chiari malformation type I associated with neonatal hyperthyroidism due to maternal Graves' disease, although neither of them had craniosynostosis.

≪Conclusion≫
Neonatal hyperthyroidism may be included in a differential diagnosis for craniolacunia.

≪Case1≫ Male
【Mother】 27y/o: She developed Graves' disease at age 13 years and treated with ^{131}I at age 26 years because of persistent symptoms. She received l-thyroxine after ^{131}I . She was pregnant after last course of ^{131}I , and added Thiamazole (MMI) at 25th wk. of pregunacy because of TRAb>30 IU/L.

gestational age	normal value	6 wk.	10 wk.	15 wk.	21wk.
TSH (μIU/mL)	0.39-4.01	0.021	1.48	0.02	0.017
FT3 (pg/mL)	2.13-4.07	3.06	2.31	3.53	3.22
FT4 (ng/dL)	0.83-1.71	1.22	1.12	1.39	1.40
TRAb (IU/L)		< 2.0	> 30	> 30	> 30

【History】
He was delivered at 35w1d. BW 2342 g (0SD), Ht 45.0 cm (- 0.1 SD), HC 31.0 cm (- 0.3 SD).
He was referred to our hospital because of tachypnea (RR 70/min).
3 hours old: BT 37.2℃, HR 149/min, BP 55/24 mmHg, RR 41/min.
He had exophthalmos, goiter, thymic enlargement, hepatosplenomegaly (Fig1)
--- laboratory findings ----
TSH <0.005 μIU/mL FT3 11.45 pg/mL FT4 6.16 ng/dL TRAb 75.3 %
AST 44 IU/L ALT 12 IU/L LDH 1085 IU/L γ-GT 395 IU/L CK 116 IU/L
NH3 67 μg/dL WBC 19100 / μL Hb 19.3 g/dL PLT 7.3万/μL

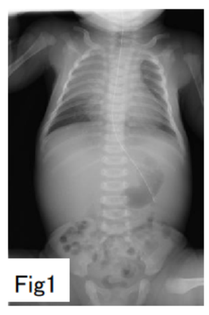
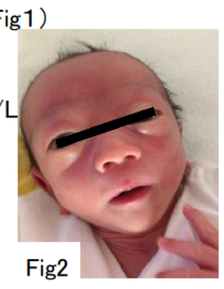


Fig1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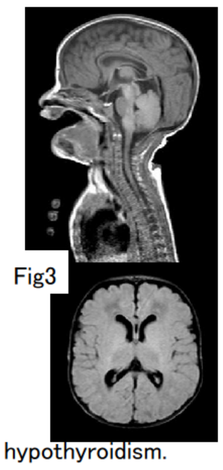


Fig3

3 days old BT 37℃, HR 120-150/min, BP 70/40 mmHg, RR40-60/min
irritability, jitteriness, restlessness, exophthalmos, periorbital edema (Fig2). Sunset phenomenon. Anterior fontanel 3cm.
TSH <0.005 μIU/mL, FT3 29.79 pg/mL, FT4 >7.77 ng/dL
KI 30mg/day (15mg/kg/day) and MMI 1 mg/day(0.5 mg/kg/day) were started

19 days old dilated lateral ventricles (Fig3 MRI)

KI, MMI were tapered from 11 days old and discontinued at 46 days old.
L-thyroxine (LT4) 10 μg/day (2.6 μg/kg/day) was started at 37 days old because of central hypothyroidism.
Liver dysfunction was ameliorated at 9 days. Hepatosplenomegaly was still detected at 46 days old.

4 months old Craniolacunia without craniosynostosis (Fig4).
Bone age (Roshe) 2 M/O

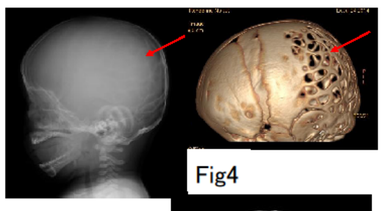


Fig4

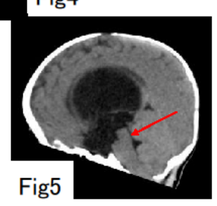
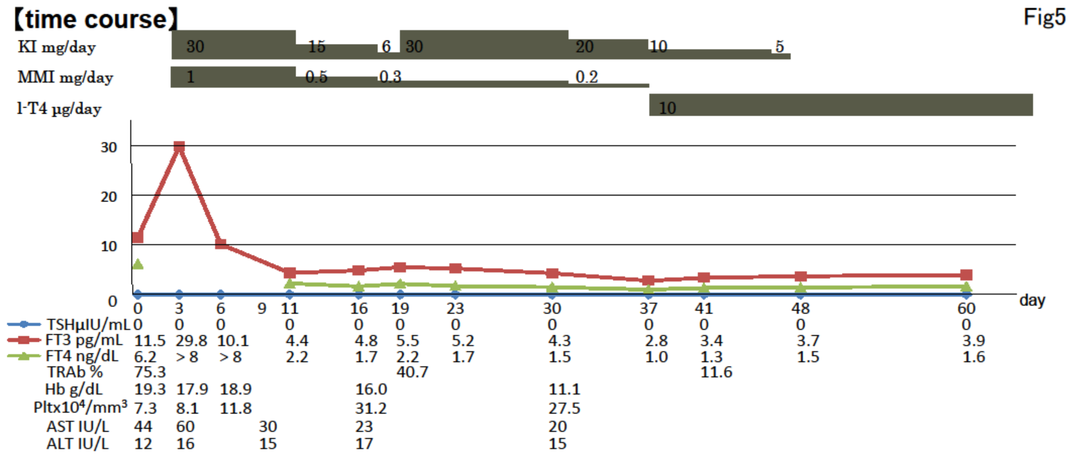


Fig5

5 months old sunset phenomenon, increased head circumstance (HC 45 cm(1.8 SD). Hydrocephalus (Fig5 CT) due to aqueductal stenosis.
Third ventriculostomy was done.
TSH 0.03 μIU/mL, FT3 3.36 pg/mL, FT4 1.34 ng/dL (with LT4 treatment)

16 months old no symptoms of hydrocephalus (HC 48.8 cm (1.1SD)).
Arnold-Chiari malformation type 1 (MRI)

【time course】



≪Discussion≫
1. Various rare clinical findings associated with Graves' disease were observed in case 1. Although pathogenesis of those features remains to be elucidated, all those abnormalities were ameliorated by age 17 months but Arnold-Chiari malformation type I.

2. Hydrocephalus due to aqueductal stenosis and Arnold-Chiari malformation type I was found in case 1. Hydrocephalus due to aqueductal stenosis has not previously been reported in neonatal hyperthyroidism. Arnold-Chiari malformation type I with mild ventriculomegaly was reported in only one patient with mutation in thyrotropin receptor gene. It is not know whether the presence of the both disorders was consequence of fetal and neonatal hyperthyroidism or they are just coincidental representations.

3. Craniolacunia was presented in both of our two cases. Craniolacunia has never been reported in neonatal hyperthyroidism. Neither encephalocele nor craniosynostosis was observed in our cases. The cause of craniolacunia in our cases is not clear. Craniolacunia might be a consequence of fetal hyperthyroidism, considering the following. 1) Intracranial decompression during the fetal life is assumed to be the etiologic factor in the development of craniolacunia. 2) Hyperthyroid state during fetal life is suggested to have adverse effects on brain growth. 3) Head circumstances of our cases at birth were slightly small for the gestational age.
Further study including more patients with neonatal hyperthyroidism is needed to elucidate whether craniolacunia is associated with neonatal hyperthyroidism or not.

≪Case 2≫ Female
【Mother】 36 y/o: Leg edema and hypertension were recognized at 24th wk. of pregnancy. She was recognized as having exophthalmos and goiter, and diagnosed as having Graves' disease at 1 day post partum (TSH <0.005 μIU/mL, FT3 13.71 pg/mL, FT4 5.42 ng/dL, TRAb 23.5 %).

【History】 Ventricular septal defect (VSD) was revealed at 27th wk. of gestation.
She was delivered at 33w5d. BW 1640 g (-1.1 SD), Ht 38.0 cm (- 2.3 SD), HC27.8 cm (- 1.6 SD). (Apgar score 5-8). BT 37.5℃, HR 120 /min, BP 69/40 mmHg, RR 40/min. Anterior fontanel 1.5 cm. No signs of hyperthyroidism. Hb 18.8 g/dL, Plt 5.8万/mm3, AST 46 IU/L, ALT 9 IU/L

3 days old HR 180 /min.
5 days old poor weight gain, irritability, jitteriness, restlessness.
Diuretics were started for heart failure (cardiomegaly, increased pulmonary blood flow).
6 days old Propranolol was started for tachycardia (HR 180-200/min) and discontinued at 40 days old.

Hyperthyroidism was ameliorated until 1month old. L-T4 15 μg/day (5 μg/kg/day) was started for central hypothyroidism at 62 days old.

6 months old Craniolacunia without craniosynostosis (Fig6)
Bone age (Roshe) 12months HC 37.5 cm (-2.8 SD)
Radical operation for VSD was done.

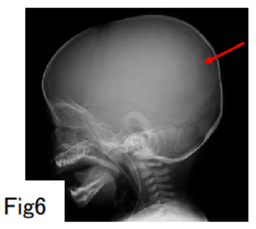


Fig6

8 months old normal development. Euthyroid with L-T4 treatment.

【time course】

age in days	cord blood	5	12	19	27	40	48	54	61	68
TSH (μIU/mL)		0.007	0.01	0.01	0.01	0.015	0.077	0.127	0.413	0.067
NR 0.39-4.01										
FT3 (pg/mL)		3.98	4.05	4.22	3.43	2.81	2.61	2.6	2.75	3.95
NR 2.13-4.07										
FT4 (ng/dL)		3.52	2.57	2.16	1.56	0.97	0.86	0.71	0.7	1.7
NR 0.83-1.71										
TRAb (%)	33.8									6.7
NR <15										
AST (IU/L)		62	22							
ALT (IU/L)		17	13							
Hb (g/dL)		20.3	18.3	17.1	15.2					
PLT (x10⁴/mm³)		15.0	38.8	45.0	44.3					

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