CASE REPORT

Prolonged Neonatal Jaundice with Deranged Thyroid Function Test

Jin Earn Choo, Subashini C. Thambiah, Intan Nureslyna Samsudin

Department of Pathology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia

ABSTRACT

Congenital central hypothyroidism (CCH) is a rare disorder that results from deficient biosynthesis of thyroid hormone due to defective thyroid gland stimulation by thyroid stimulating hormone (TSH). Diagnosis is typically established biochemically by low free thyroxine (fT4) and inappropriately low or normal TSH levels after excluding all other causes of discordant thyroid function test (TFT). Here, we report a case of a baby girl who presented with prolonged jaundice at day 15 of life with normal cord blood TSH performed as routine screening for congenital hypothyroidism. Serial TFT revealed declining serum fT4 with normal TSH consistent with CCH. Her jaundice resolved prior to levothyroxine replacement. CCH is commonly missed on cord blood TSH-based newborn screening leading to a delay in diagnosis, potentially resulting in neurodevelopmental delay. Hence, although CCH has a lower incidence than congenital primary hypothyroidism, a high index of suspicion is essential for timely diagnosis.

Keywords: Prolonged neonatal jaundice, Congenital central hypothyroidism, Thyroid function test, Newborn screening

Corresponding Author:
Subashini C. Thambiah, MPath
Email: subashini@upm.edu.my
Tel: +603-9769 2779

INTRODUCTION

Congenital hypothyroidism (CH) is a preventable cause of neurodevelopmental delay (1). Although congenital primary hypothyroidism (CPH) is more common, there is another form of CH known as congenital central hypothyroidism (CCH). The incidence of CCH was reported as being 1:16000-1:100000, which is much lower than CPH (2). CCH is a rare disorder that results from deficient biosynthesis of thyroid hormone due to defective thyroid gland stimulation by thyroid stimulating hormone (TSH) (2).

In CCH, the functional or anatomic pathology of the hypothalamus and/or pituitary results in a qualitative or quantitative defect in TSH synthesis and secretion (2,3). The underlying molecular basis is often undefined (3). TSH deficiency is isolated in a minority of cases, occurring from mutations in regulatory genes of the TSH biosynthetic pathway (TRHR, IGSF1, TSHB). Instead, mutations in early (LHX3, HESX1, LHX4, OTX2, SOX3) or late (POU1F1, PROP1) pituitary transcription factors may cause CCH presenting with multiple pituitary hormone deficiencies (3). Here we report a rare case of CCH in a 15-day old female neonate who presented with prolonged neonatal jaundice (NNJ).

CASE REPORT

The baby was born at 38 weeks and 1 day weighing 2615g via elective lower segment caesarean section with no complications. The mother's antenatal history was unremarkable and she was not on any medication. Her cord blood TSH was 5mIU/L (cut off<21mIU/L). She was well until day 3 of life when mild jaundice was noted. She was then admitted for phototherapy on day 6 and discharged well on day 8 of life. On follow up, persistent jaundice over her lower limbs up to the chest was noted on day 15 of life. Otherwise she was active as usual, no fever, passing normal coloured urine and stool with unremarkable physical examination. She was adequately fed, tolerated on demand 2-hourly breastfeeding of 30 minutes duration with good suckling effort. She was not on any medications or supplements. The neonate was the third in the family. Other siblings had a history of non-prolonged NNJ. On demand breastfeeding was encouraged. All initial laboratory investigations were unremarkable except for an unconjugated hyperbilirubinaemia (Table I). Both TSH and free thyroxine (fT4) were within the reference interval (Table II).

Subsequently, at 1 month and 26 days old, no growth delay was noted and her body weight was 4.55kg. Total serum bilirubin was not done as the jaundice had resolved. Her TSH level was within normal range. However, fT4 showed a declining trend with values at the lower limit of normal (Table II). No treatment was commenced at this point.

On follow up at 2 months and 9 days old, the fT4 level had fallen below the reference interval although her TSH level remained normal. The baby was diagnosed with CCH and started on levothyroxine 25mg daily. The resolved NNJ was attributed to breast milk jaundice. She was scheduled for a repeat TFT and serum cortisol.

After commencing levothyroxine replacement therapy, the serum fT4 increased to a level between mid to upper limit of normal, indicating adequate levothyroxine replacement (3). The reduced TSH level further supported the diagnosis of CCH. The early morning serum cortisol concentration was 88nmol/L (reference range 119-618nmol/L). Hypocortisolism was suspected in view of morning cortisol less than 100nmol/L. Hence short synacthen test (SST) was done (Table II). Baseline serum cortisol level within normal range with post SST level showing a peak of more than 500nmol/L ruled out hypocortisolism. The baby was continued on levothyroxine 25mg daily with follow up appointments to monitor growth, neurodevelopmental progress as well as serum fT4 concentration. She was not planned for genetic analysis.

Table I : Laboratory Results of Prolonged Jaundice at Day 15 of Life

Test and Parameters	Result	Unit	Reference Interval
FBC			
White cell count	10.7	X 10^9/L	10.0 - 18.0
Red blood cells	4.4	X 10^{12}/L	4.0 - 6.0
Haemoglobin	15.1	g/dL	14 - 21
Haematocrit	44.3	%	42.0 - 63.0
Platelet	448	X 10^9/L	150 - 500
LFT			
Total protein	59	g/L	41 – 63
Albumin	36	g/L	35 – 52
Globulin	23	g/L	22 – 34
Total bilirubin	180.8	µmol/L	5.0 – 21.0
Direct bilirubin	15.7	µmol/L	< 3.4
Indirect bilirubin	165.1	µmol/L	< 21.0
Alkaline phosphatase (ALP)	288	U/L	48 – 406
Alanine aminotransferase (ALT)	14	U/L	13 – 45
Aspartate aminotransferase (AST)	34	U/L	25 – 75
Urinalysis			
Parameters	**Result**		**Reference Interval**
Colour	Pale Yellow		
Blood/RBC	Negative		
Urobilinogen	Normal		
Bilirubin	Negative		
Ketone	Negative		
Protein	Negative		
Nitrite	Negative		
Glucose	Normal		
Leucocytes	Negative		
pH	7.0		5.0 - 8.0
Specific gravity	1.005		1.000 - 1.030

Table II : Serial Thyroid Function Test (TFT) and Short Synacthen Test (SST)

Serial TFT

Patient's age	D15 of life	1M 19D	2M 2D	3M 16D	Unit	Reference Interval
TSH	5.107	3.599	3.045	0.200	mIU/L	0.770 - 5.640
fT4	13.7	9.9	8.4	15.8	pmol/L	9.7 - 19.2

SST (Patient's age: 3M 26D)

Time	Serum cortisol (nmol/L)
0 minute	248
30 minutes	694
60 minutes	735

D: days; M: months

DISCUSSION

A diagnosis of CH in a neonate is difficult, as most do not have apparent clinical features of hypothyroidism at birth (1), as in this patient. Prolonged NNJ in this baby can be attributed to reduced conjugation of bilirubin due to thyroid hormone deficiency resulting in unconjugated hyperbilirubinaemia. Hence, due to the high index of suspicion of CH, the paediatrician continued to monitor the patient's TFT although the initial results were normal. This is because changes in TFT usually evolve with time and as the disease progresses (3), as evident in this case. However, the prolonged jaundice resolved prior to levothyroxine replacement treatment, attributing its cause to breast milk.

Most neonatal CH screening programmes with the TSH-based criteria will unfortunately only identify CPH because TSH is typically low or inappropriately normal in CCH (1). The biochemical picture of overt CCH is unequivocal with low TSH and low fT4. However, diagnosis becomes a challenge when fT4 is subnormal in mild CCH or when there is increased immunoreactive TSH with subnormal bioactivity due to hypothalamic disorder (3). This phenomenon is attributed to the presence of mutated, heterodimeric TSH with epitopes recognised by the anti-TSH monoclonal antibody in immunoassays. This leads to measurable immunoreactive TSH that lack normal bioactivity (3), giving a biochemical misdiagnosis of subclinical or mild primary hypothyroidism (4). Impaired TSH bioactivity, if suspected, can be supported by reduced increment of fT4 following TSH response upon thyrotropin releasing hormone (TRH) stimulation (2).

The 2018 European Thyroid Association Guidelines states that in a subject with low serum fT4 and low normal TSH, confirmed by two independent analyses, a diagnosis of CCH should be considered after excluding other conditions with similar TFT results such as non-thyroidal illness, drugs inhibiting TSH secretion or analytical interference in TSH or fT4 measurements (4). Declining fT4 levels may also be an early sign of CCH, (3) with progressive decrease in fT4>20% of the initial value supporting the diagnosis of mild or 'hidden' CH, provided it is measured repeatedly in the same laboratory with the same assay (2, 5). This time-related decrease in fT4 was evident in this patient (Table II). Children with POU1F1 mutations show this fT4 decline and are also associated with impaired growth hormone (GH) and prolactin secretion (2). They may have dysmorphic features (2), which fortunately was absent in this case, making it an unlikely diagnosis.

In mild or equivocal cases, investigations supportive of CCH include TRH stimulation test (2, 3) and lack of nocturnal TSH rise (5). However, the role of TRH testing in children is controversial in differentiating between hypothalamic and pituitary pathology (3). Nevertheless, measurement of other hormones during TRH stimulation test may distinguish between a TSHβ and TRHR mutation where in the former, prolactin and α-subunit responses are preserved and blunted responses are recorded in the latter (3). In our case, TSHβ mutation was unlikely due to absence of its typical severe hypothyroidism presentation at birth (3,5). TRHR mutation has been described in a female with prolonged NNJ (4) and even complete TRHR does not cause severe neonatal hypothyroidism (4), making it a likely cause in our case. Neither test was done in this baby who was followed-up as an outpatient as the TFT improvement following levothyroxine replacement supported the diagnosis of a mild CCH (4).

Thorough investigations of the hypothalamic-pituitary axis may be required in CH as other pituitary hormone deficits are common with GH, adrenocorticotropic hormone (ACTH) and gonadotropin deficiencies at 89%, 78% and 46%, respectively whilst posterior pituitary hormone deficiencies are reported at 13% (3). Insulin hypoglycaemic test was not done in this patient as it is relatively contraindicated in the paediatric age group due to the risk of hypoglycaemia. However, regular growth monitoring is a good indicator for GH deficiency as disproportionate growth can be detected during routine follow up. Magnetic resonance imaging (MRI) may identify structural pituitary anomalies or any other defects, which may direct genetic testing (3).

Regardless of the findings from radiological or genetic testing, the ultimate therapy for CCH is still levothyroxine replacement. Although, she was clinically and biochemically euthyroid following levothyroxine treatment, ideally, genetic testing should be performed as it not only predicts evolution of other pituitary hormone deficiencies but will also expose potential carriers and enable timely diagnosis in affected families (4).

Coexistent adrenal insufficiency should be ruled out before commencing thyroxine replacement therapy to avoid precipitation of adrenal crisis (4). In this patient, morning cortisol and SST were done after levothyroxine was commenced as to not delay treatment of CCH.

Further monitoring of treatment response in this baby with CCH can be done with fT4 alone (4) because TSH secretion is suppressed even by low doses of levothyroxine (2). This is in contrast to the monitoring of treatment of CPH where TSH effectively reflects adequate replacement therapy (2). TSH and fT3 concentrations may be beneficial in CH to rule out under- and over-treatment, respectively (2).

CONCLUSION

CCH is commonly missed on cord blood TSH-based newborn screening leading to delayed diagnosis with resulting neurodevelopmental delay. Biochemical diagnosis of CCH of subnormal fT4 with low or inappropriately normal TSH, after excluding other conditions with similar discordant TFT becomes more challenging in mild cases. Furthermore, unlike CPH, TSH-based treatment monitoring is unreliable in most CCH cases. Ideally, genetic testing would allow prediction of concomitant pituitary hormone deficiencies and cascade family screening.

ACKNOWLEDGEMENT

The authors would like to thank the Director General of Health Malaysia for his permission to publish this article.

REFERENCES

1. LaFranchi SH. Newborn screening strategies for congenital hypothyroidism: an update. J Inherit Metab Dis. 2010; 33: 225-33.
2. Persani L, Cangiano B, Bonomi M. The Diagnosis and Management of Central Hypothyroidism in 2018. Endocrine Connections. 2019; 8: R44-R54.
3. Schoenmakers N, Alatzoglou KS, Chatterjee VK, Dattani MT. Recent Advances in Central Congenital Hypothyroidism. Journal of Endocrinology. 2015; 227: R51-R71.
4. Persani L, European Thyroid Association Guidelines on the Diagnosis and Management of Central Hypothyroidism. European Thyroid Journal. 2018; 7: 225-237.
5. Persani L. Central Hypothyroidism: Pathogenic, Diagnostic and Therapeutic Challenges. J Clin Endocrinol Metab, 2012; 97 (9): 3068 – 3078.