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Cardiac Malformations in Congenital Hypothyroidism: A Case Report

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Abstract

Introduction: Congenital hypothyroidism is the most common causes of preventable mental retardation. It is associated with other births defects like cardiac malformations. Descriptions in Sub Saharan Africa are rare, justifying the present report. **Case Report:** We reported the cases of 3 female patients, diagnosed with hypothyroidism, presenting in addition pulmonary stenosis. The diagnosis was late in all the patients and we noticed clinical improvement under levothyroxine. **Conclusion:** Association congenital hypothyroidism and cardiac defect is not rare. Our patients are female with no history of consanguinity, presenting congenital hypothyroidism with a gland *in situ* associated with pulmonary stenosis. Systematic screening of other births defects is thus recommended in affected patients.

Keywords

Congenital Hypothyroidism, Cardiac Malformations, Children

1. Introduction

Congenital hypothyroidism is the most common causes of preventable mental retardation worldwide [1] [2]. Affecting around 1/4000 live births, it is mostly due to thyroid dysgenesis [3]. In absence of neonatal screening in Sub Saharan Africa, data on the disease are scarce. However, thyroid dyshormonogenesis seems to be the most frequent pattern found in some African countries [4]. The disease is associated with other malformations compared to general population through complex genetic pathway [5]. We report case of three patients presenting congenital hypothyroidism and congenital heart defect. Our aim is to draw

attention on systematic screening of other malformations in affected patients.

2. Case Report

2.1. Cases 1 and 2

These are two female siblings, from non-consanguineous family. The elder, an 19 months old infant, was brought for consultation for growth retardation and developmental delay. She was born post term with macrosomia (Birth weight 4000 gr). Emission of meconium occurred 72 hours after birth. No particular history was found in this family, and the pedigree tree had no specificity. She was somnolent. She presented psychomotor delay with a developmental DENVER score at 5 months, with axial hypotonia. We found both weight (7000 g, <−3 SDS) and height (64 cm, <−3 SDS) retardation. She had macroglossia and skin xerosis. Thyroid was palpable. We heard a mitral heart murmur, intensity 3/6. She presented distended abdomen with umbilical hernia. Serum TSH was 238.7 µUI/ml with undetectable T4. Thyroid gland was present, 14 mm right lobe and 11 mm left lobe. Heart ultrasound (Figure 1), revealed pulmonary stenosis (gradient 75 mmHg) with mitral regurgitation grade 1/4. She started treatment with L-thyroxine with improvement of growth parameters (Table 1, Table 3). She started walk at 24 months and entered school at 4 years.

Her junior sister was brought at 6 weeks of age for constipation. Delivered at term after C section with a birth weight of 3800 g, she was under exclusive breast milk. On physical examination, we found abundant hair, coarse cry and macroglossia. She also had a systolic mitral murmur, intensity 3/6. She had a distended

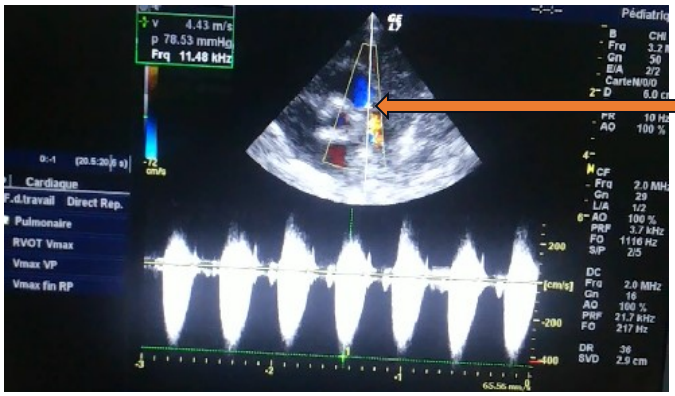

Figure 1. Image of heart ultrasound in patient 1.

Table 1. Evolution of patient 1.

Items					
Age in months	19	20	24	31	49
Weight (Kg)	7	7.5	9.8	12	15
Height (cm)	64	66	70	80	90
TSHus (µUI/ml)	238.7	63.9	13.9	6	0.88
LT4 µg/Kg	7	8.2	8.9	10	10

abdomen and umbilical hernia. Neurological exam was normal. TSH level was 199.87 µUI/ml with undetectable T4. Thyroid ultrasound showed a gland normally located. Heart ultrasound revealed mild pulmonary stenosis (gradient 45 mmHg) with mitral regurgitation grade 1/4 (Table 3). We started thyroxine at 15 µg/Kg/day with normalisation of TSH at 4 weeks.

2.2. Case 3

A female infant brought for consultation at 4 weeks for constipation. We noticed on past history a birth weight at 2600 g at term. She passed meconium 48 hours after birth. No consanguinity nor history of thyroid disease was found in the family. On physical exam, growth parameters were normal (0 SDS for both weight and height). She was presenting macroglossia. We found a sub clavicular heart murmur, intensity 3/6. Her neurological exam was normal. TSH level was >50 µUI/ml. She presented a hypoplastic thyroid gland (right lobe 7 × 4 mm, left lobe 9 × 6 mm) on ultrasound. She had patent ductus arteriosus and pulmonary stenosis on heart ultrasound. We started levothyroxine at 15 µg/Kg/day with normalisation of TSH at first control. Her psychomotor development remained normal under treatment, she started walking at 13 months (Table 2, Table 3 and Figure 2).

Table 2. Evolution of patient 3.

Items				
Age in months	1	14	20	24
Weight (Kg)	3.9	9.7	10	11
Height (cm)	54	77	80	82
TSHus µUI/ml	>50	2.9	34	6
LT4 µg/Kg	15	5	7.5	7.9

Table 3. Summary of clinical, morphological and hormonology findings of patients at diagnosis.

Items	Case 1	Case 2	Case 3
Sex	F	F	F
Age at diagnosis	19 months	6 Weeks	4 weeks
Height (SDS)	<−3	−1	0
Heat murmur	Mitral	Mitral	Sub clavicular
Intensity	3/6	3/6	3/6
Neurological findings	Severe psychomotor delay	Axial hypotonia	Normal
Other abnormalities	Macroglossia Umbilic hernia Myxoedema	Macroglossia Umbilic hernia	Macroglossia
TSHus (µUI/ml)	238.7	199.87	>50
Gland *in situ*	RL* 14 mm LL** 11 mm	Yes	RL 7 mm LL 9 mm
Heart ultrasound	Pulmonary stenosis RV/PA*** gradient 75 mmHg	Pulmonary stenosis RV/PA gradient 45 mmHg	Patent ductus arteriosus Pulmonary stenosis

*RL: right lobe, **LL: left lobe, ***RV/PA gradient: right ventricle/pulmonary artery gradient.

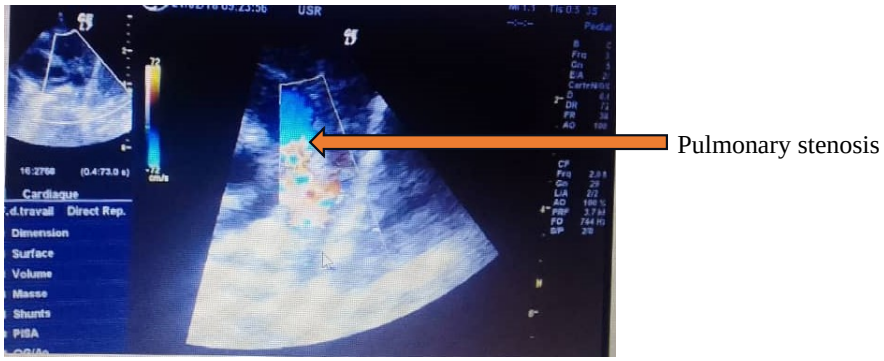

Figure 2. Image of heart ultrasound of patient 2.

3. Discussion

Congenital hypothyroidism with a prevalence of 1/4000 new born is the leading cause of preventable mental retardation worldwide [2] [3]. Birth defects are more frequent in patients with hypothyroidism compare to general populations, found in about 37.5% of cases [4]-[9]. Cardiac malformations are found in approximately 10% to 18.5% of patients depending of authors [8] [9]. Yan Lee *et al.* found 11.7% of congenital heart defect in patient with congenital hypothyroidism in Japan [10]. Incidence of extrathyroidal congenital abnormalities seems to vary according to genetics, ethnicity [11]. There are no data on prevalence of heart defect in congenital hypothyroidism in African setting. This is the first description of this association in Sub Saharan populations. As previously described, all patients had dsyhormonogenesis and the diagnosis was late, in absence of neonatal screening [4].

Interestingly, these patients are distinct of those with the association Down syndrome and hypothyroidism which is more common. In fact, Down syndrome itself is a common provider of hypothyroidism and heart defect [10] [11]. None of our patients had the clinical profile of this condition. Hence, this association emphasises a genetic link between heart and thyroid development. There are some evidences that, there are common nuclear transcription factors involved in heart and great vessels organogenesis and embryonic development of thyroid gland [10] [11].

Thus mutation or modification of genes coding for these factors might lead to both congenital hypothyroidism and cardiac defect. One of the recent incriminated gene in this association is mutation of NKX2-5. The later is a transcription factor in the development of cardiac and thyroid tissue. This mutation is mostly found in consanguineous populations. This is not the case of our patients. Unfortunately, biomolecular analysis was not performed in our patients. However many other genes might possibly been involved in this situation and further studies are needed. Specific description in African descendent populations could help better understanding the link between development of congenital hypothyroidism and heart defect.

Patent ductus arteriosus, auricular septal default and Fallot are the most de-

scribed heart defect found in NKX2-5 mutations [9] [10] [11]. Surprisingly, our three patients had pulmonary stenosis which is not common. The three patients had their gland *in situ* which is also unusual. This raises the question on possible abnormal development of thyroid or structural anomaly, even when in normal place in cases of hypothyroidism.

Systematic screening of other birth defects should be performed in all patients with congenital hypothyroidism.

4. Conclusion

Association congenital hypothyroidism and heart defect is not rare. The patient profile seems to be in our setting: female patients with no history of consanguinity, presenting dyshomonogenesis and pulmonary stenosis. This profile seems to be unusual and raise the question of genetic eatiology of dyshormogenesis in our context. Neonatal screening is urgent as the diagnosis is late, in addition to systematic screening of other birth defects in diagnosed patients.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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