Case Report

Kocher-Debre-Semelaigne syndrome with arrhythmogenic right ventricular cardiomyopathy: A hitherto unrecognized association

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ABSTRACT

Kocher-Debre-Semelaigne (KDS) syndrome is a rare form of hypothyroid myopathy, with associated hypertrophy of muscles. Although cardiac manifestations of hypothyroidism are well known, reports of cardiac involvement in KDS have only described the occurrence of pericardial effusion as an association. This report describes an adolescent male presenting with typical features of this rare syndrome along with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), an association not yet described in the literature.

Key words: Arrhythmogenic right ventricular cardiomyopathy, congenital hypothyroidism, echocardiography, Kocher-Debre-Semelaigne syndrome

Introduction

The Kocher-Debre-Semelaigne (KDS) syndrome consists of congenital hypothyroidism with generalized muscular hypertrophy, particularly involving the muscles of the extremities, giving the child a "herculean" or athletic appearance. The cardiovascular manifestations are usually secondary to the long standing hypothyroidism and have been limited to reports describing only pericardial effusion. Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a potentially lethal genetically determined myocardial disorder primarily involving the right ventricle, and manifesting with recurrent ventricular tachyarrhythmias or even sudden cardiac death. The association of KDS and ARVC/D has not yet been reported in the literature.

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Case Report

A 14-year-old male child was referred to our cardiology outpatient department with history of easy fatiguability, generalized edema, proximal muscle weakness, and occasional paroxysmal palpitations for 2 years. He denied any history of presyncope or syncope. The parents informed that his milestones had been delayed and he had subnormal intelligence and poor school performance. His three siblings were normal; there was no family history of sudden cardiac death or syncope.

On examination he had coarse facies, large protruding tongue, athletic build, short stature, mental retardation, and generalized non-pitting edema with protuberant abdomen. His calf muscles were hypertrophied [Figure 1] with a firm feel; the muscle power was slightly depressed (4/5). Cardiovascular system examination revealed mildly elevated jugular venous pulse, muffled heart sounds, and a grade III/VI pansystolic tricuspid regurgitation murmur. A 12 lead ECG revealed low-voltage complexes with prominent epsilon waves in the right-sided chest leads [Figure 2a]. Chest radiograph showed cardiomegaly with a cardiothoracic ratio of 0.65 [Figure 2b]. Hemogram showed normocytic normochromic anemia. Laboratory

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data revealed total T3 <25 ng/dl, range 70–200 ng/dl, total T4 <1 μg/dl, range 5.5–13.5 μg /dl, TSH : 125 μIU/ml, range 0.2-5.0 μIU/ml), serum CPK 2972 U/L, confirming severe hypothyroidism and myopathic involvement. Transthoracic 2D-echocardiography revealed dilated right atrium and right ventricle [Figure 3a], a hyper-refractile moderator band, moderate right ventricular systolic dysfunction, with localized areas of akinesia and dyskinesia with multiple RV apical aneurysms [Figure 3b] and mild pericardial effusion. These echocardiographic features as well as the findings on the 12-lead ECG suggested an associated diagnosis of ARVC/D. Although a 24-h Holter monitoring revealed frequent ventricular premature beats, no episodes of VT or VF were documented.

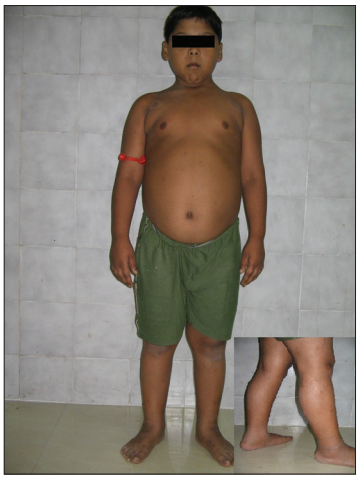

Figure 1: Image of child having coarse facies, athletic built, short stature, generalized non pitting edema with protuberant abdomen and prominent hypertrophied calf muscles.

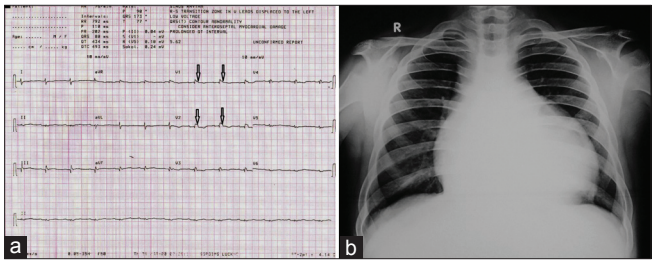

Figure 2: (a) Electrocardiogram showing low voltage complexes with epsilon wave (arrow) characteristically seen in right sided chest leads. (b) Chest radiograph showing cardiomegaly secondary to moderate pericardial effusion.

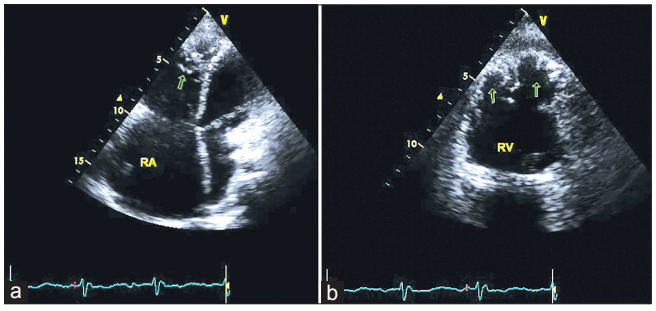

Figure 3: (a) Transthoracic echocardiogram showing hugely dilated RA and RV. (b) Transthoracic echocardiography showing multiple aneurysms (arrows) in the RV apex.

The patient was started on oral L-thyroxine 50 μG/day and had immediate dramatic symptomatic improvement. At 6-month follow up, he had significant improvement in the myopathy and some regression of the calf muscle hypertrophy. Although the pericardial effusion disappeared, the other features of ARVC remained unchanged.

Discussion

KDS syndrome (also labeled as Cretinism-muscular hypertrophy, hypothyroid myopathy, hypothyroidism-large muscle syndrome, hypothyreotic muscular hypertrophy in children, myopathy–myxedema syndrome, myxedema–muscular hypertrophy syndrome, etc.) is a rare disorder causing pseudohypertrophy of muscles due to longstanding hypothyroidism.[1] Although the usual age of presentation is between 18 months and 10 years, neonatal presentation has also been reported. Our patient was diagnosed at a relatively late age of 14 years, which is not uncommon in developing countries, where patients often seek medical attention late in course of the disease.[1-3] Patients generally present with features of hypothyroidism along with muscle pseudohypertrophy, involving the muscles of extremities, limb girdle, trunk, hands, and feet. Since the hypertrophy is more prominent in muscles of the limbs, it is common for the patients to have an athletic or herculean look, an appearance also noted in our patient. Even though generalized muscle involvement is characteristic of KDS, myocardial involvement (apart from pericardial effusion) (10) has not been described in the literature.

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a genetically heterogeneous disorder, linked to several chromosomal loci and characterized pathologically by progressive fibrofatty replacement of the RV myocardium.[4] In the early stage of the disease, structural changes may be absent or subtle and confined to a localized region of the RV, typically the inflow tract, outflow tract, or apex of the RV, which is called the "triangle of dysplasia."[5] Although a definite diagnosis of ARVC requires histologic confirmation of transmural fibrofatty replacement of the RV myocardium, echocardiographic features are quite characteristic. Our case had all the typical echocardiographic features, namely localized RV aneurysms with regional akinesia and dyskinesia, multiple RV apical aneurysms and RV

systolic dysfunction, along with epsilon waves in the 12-lead ECG. The predominant presenting symptoms are due to ventricular arrhythmias, including palpitations, sustained ventricular tachycardia, or uncommonly, sudden cardiac death. Although our patients did give history of paroxysmal palpitations, there was no history of syncope or a documented tachyarrhythmia.

Among the molecular mechanisms by which thyroid hormones regulate expression of nuclear genes encoding for regulatory proteins of mitochondrial respiratory function, the mitochondrial transcription factor A (h-mt TFA) has been proposed to be a target of thyroid hormone action. Thyroid hormone is also necessary for the expression of fast myofibrillar proteins in muscles and in hypothyroidism; there is an increased accumulation of slow myofibrillar proteins. The muscle hypertrophy results from increased connective tissue and mucopolysaccharide deposits.[6-8]

Whether any of these mechanisms could lead to ARVC/D in genetically susceptible individuals remains conjectural in our case; it is well possible that the ARVC/D detected in our patient may have been be an incidental detection unrelated to KDS. Whatever be the underlying operative mechanism, the case highlights the fact that cases of KDS should be evaluated by detailed 2D echocardiography to rule out potentially lethal cardiac association, as occurred in our case.

As has been documented in the literature, our case also had a good response to thyroxin supplementation, with improvement of the symptoms of myopathy, some regression of the calf muscle hypertrophy,[1-3] and disappearance of the pericardial effusion;[9] expectedly the features of ARVC/D remained as before.

Conclusion

Kocher-Debre-Semelaigne (KDS) syndrome and arrhythmogenic right ventricular cardiomyopathy (ARVC) are separate entities but rarely they can occur together in the same patient. However, detailed genetic studies are required before this fact is accepted because it may add a different pathogenic mechanism to the existing knowledge in both KDS and ARVC.

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