RESEARCH LETTER

Prenatal bilateral adrenal calcifications, hypogonadism, and nephrotic syndrome: beyond Wolman disease

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Funding sources: None
Conflicts of interest: None declared

When a rare finding, such as prenatal bilateral adrenal calcifications, is identified, the search for the genetic diagnosis is more targeted. Bilateral adrenal calcifications have been thought to be highly suggestive of Wolman disease,[1] a progressive condition characterized by hepatosplenomegaly, abdominal distention, and failure to thrive during the first months of life. Here we report on prenatal and postnatal findings of two fetuses with bilateral adrenal calcifications, increased nuchal translucency\increased nuchal fold, micropenis, hypogonadism, and congenital nephrotic syndrome. We propose that this constellation of findings represents a new clinical entity, likely of autosomal recessive inheritance, which should be considered in the differential diagnosis of bilateral adrenal calcifications.

CASE REPORTS

Patient 1

A 35 year old woman presented to the genetics clinic during her fourth pregnancy due to prenatal screening tests indicating an increased risk for Down syndrome.

Patient 1's parents were healthy double first cousins of Muslim Arab origin who had three healthy children (Figure 1). There was no history of genetic disease or early death in the family. At 15 weeks of pregnancy, an increased nuchal fold (5.8 mm) was detected. The results of the second trimester maternal serum biochemical screening test showed an elevated risk for trisomy 21 of 1:126 (AFP 0.89 MoM; HCG:2.28 MoM; uE3:0.32 MoM), while the age-related risk was 1:1240. Fetal karyotype performed following genetic counseling was of a normal male (46,XY). At 22 weeks of pregnancy, during a routine ultrasound examination, a diagnosis of micropenis was made. The child was born at 38 weeks of gestation and weighed 3270 grams (50th percentile). The placenta was not examined. At the age of 6 weeks, the patient was hospitalized with generalized edema and massive proteinuria in the nephrotic range (13170 mg/dl), hypoproteinemia (3.2 gr/dl), and hypoalbuminemia (1.3 gr/dl); Endocrinology evaluation was done because of non-palpable testes and a micropenis. Baseline luteinizing hormone and follicle-stimulating hormone levels were low however complete evaluation with LHRH test and HCG tests could not be performed.

Abdominal ultrasound performed at 6 weeks of age showed bilateral adrenal calcifications, which had not been diagnosed prenatally. The child died suddenly at the age of 7 weeks. Autopsy was not performed.

Patient 2

The parents of patient 2 were healthy double first cousins and had two healthy children (Figure 1). The mother presented to the genetics clinic in her third pregnancy because of increased nuchal translucency (3.9 mm) at week 11th; She reported that her nephew (patient 1) had died early in infancy (Figure 1); Fetal karyotype and chromosomal microarray analysis (CMA) performed on chorionic villous cells were of a normal male. Second trimester biochemical testing (AFP 0.79 MoM; HCG:1.82 MoM; uE3:0.31 MoM) showed an elevated risk for trisomy 21 of 1:40 with an a priori age-related risk of 1:530. Ultrasound examination at 21 weeks of pregnancy showed bilateral adrenal calcifications (Figure 2), and subsequently pericardial and pleural effusion. Micropenis was not observed. A normal amniotic fluid level of 7-dehydrocholesterol permitted the exclusion of Smith Lemli Opitz syndrome which had been considered because of the borderline maternal serum uE3 level in pregnancies of both patients and the

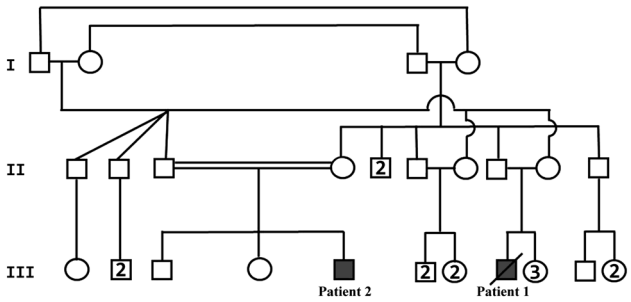

Figure 1 Pedigree of the family

micropenis in patient 1.[2] Maternal serological testing for Toxoplasma, Rubella, CMV and parvovirus did not suggest maternal infection during the pregnancy. The finding of bilateral adrenal calcifications prompted sequencing of the lysosomal acid lipase (LIPA) gene which was normal ruling out Wolman syndrome.[3] Sequencing of the WT1 gene permitted the exclusion of Denys Drash syndrome, type 4 nephrotic syndrome (NPHS4) and Fraser syndrome.[4,5] Patient 2 was born at 38 weeks of gestation with a birth weight of 3500 grams (50-90th percentile) . The placenta was significantly enlarged. The child presented with massive proteinuria in the nephrotic range already at the age of 2 days (1003 mg/dl) . Also thrombocytopenia and a small penis with no palpable testis were detected. Low baseline testosterone levels, lack of testosterone response to HCG test and exaggerated gonadotrophins response to early life luteinizing hormone-releasing hormone test were suggestive of testicular dysfunction. In addition mullerian inhibitory factor level was very low which was compatible with prenatal testicular dysfunction. Ultrasound examination of the abdomen showed bilateral adrenal calcifications with no detectable testes. The child died at the age of 3 months. Autopsy was not performed.

A summary of the clinical findings of both children is presented in Table 1.

DISCUSSION

Prenatal diagnosis of genetic syndromes is challenging in part because of the limitations of prenatal imaging technologies and the difficulties in predicting the postnatal phenotype. However, the presence of specific findings combined with knowledge of a previously recognized condition in a family can sometimes help in guiding the prenatal management and diagnosis. Here we report on a unique prenatal presentation of two fetuses with bilateral adrenal calcifications, increased nuchal translucency\nuchal fold, and micropenis with impalpable testes, which occurred in two pregnancies of first cousins.

The family history and the fact that the adrenal calcifications were bilateral were not suggestive of intrauterine infections, adrenal tumors, or neuroblastoma.[6,7]

Both babies had normal weights, and there was no history of hypoxia nor septicemia, and Addison disease was ruled out. The second child was born with thrombocytopenia, which could have been one risk factor for hemorrhage and adrenal calcifications, although the calcifications were already diagnosed at 22 weeks of pregnancy. Hypercoagulopathy, which is often reported with congenital nephrotic syndrome, might have been present already during the pregnancy, perhaps leading to thromboembolism, which could be the cause for the adrenal calcifications and vanishing testes. One hypothesis for anorchia in XY male patients that has been suggested is that it might be because of a compromise of vascularization during the descent of the testes resulting from torsion, kinking of the vasculature, direct trauma, or spermatic vascular thrombosis.[8] The bilateral adrenal calcifications and the consanguinity suggested the diagnosis of Wolman disease, which was ruled out by molecular analysis. Interestingly, both mothers had an elevated risk for trisomy 21 on maternal serum biochemical screening and a borderline uE3 serum level. This with abnormal nuchal translucency prompted us to rule out chromosomal abnormalities and Smith Lemli Optiz syndrome.[9]

Although both patients had postnatal nephrotic range proteinuria, which was suggestive of congenital nephrotic syndrome, maternal serum levels of alpha-fetoprotein as well as amniotic fluid levels were not elevated.[10,11] Congenital nephrotic syndrome and increased nuchal translucency have been reported previously,[9,12] but to the best of our knowledge, this has not been reported with any disorder including bilateral adrenal calcifications nor anorchia.

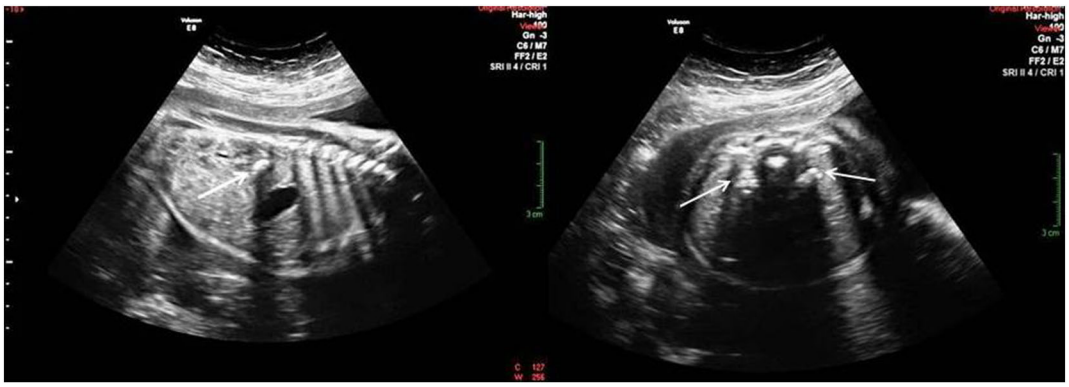

Figure 2 Sagittal view of the left kidney and axial view of the upper abdomen with adrenal calcifications indicated by arrows

Table 1 **Descriptions of the patients' clinical findings and the patients from the literature**

	Patient 1	Patient 2	Indumathi *et al.*[14]	Powers *et al.*[13]
Origin	Arab Muslim	Arab Muslim	Indian (1 patient)	American Indian (3 patients)
Consanguinity	+	+	NA	NA
Third trimester biochemical screening: increased risk for trisomy 21	+	+	NA	NA
Bilateral adrenal calcifications	+ (postnatal)	+ (prenatal & postnatal)	+	+
Increased nuchal translucency\nuchal fold	+	+	NA	NA
Congenital nephrotic syndrome	+	+	+	+
Other	Hypogonadism (prenatal & postnatal)	Hypogonadism (prenatal & postnatal)	Cardiac malformation	NA
Normal karyotype	+	+	NA	NA
Normal CMA	NA	+	NA	NA
7 dehydrocholesterol in amniotic fluid	NA	Normal	NA	NA
Wolman and WT1 sequencing	NA	Normal	NA	NA

+, present; NA, not applicable.

The association of congenital proteinuria and adrenal calcifications was first reported in three patients of American Indian origin.[13] Later, Indumathi *et al.* reported an additional patient with congenital nephrotic syndrome, adrenal calcifications, and a cardiac malformation.[14] In both reports, the etiology of the adrenal calcifications was not known and hypogonadism was not reported (Table 1). The resemblance of the perinatal presentation of these two patients and the consanguinity (Table 1) were suggestive that the fetuses were affected with the same disease. Increased fetal nuchal translucency and congenital nephrotic syndrome have been reported but not in association with bilateral adrenal calcifications and micropenis as presented by these two children.

Bilateral adrenal calcifications and congenital nephrotic syndrome with other clinical findings such as hypogonadism (as reported herein) and cardiac malformations (as previously reported[13,14]) suggest a new clinical entity of autosomal recessive inheritance. This entity should be added to the short list of potential etiologies of prenatal adrenal calcifications. Further molecular studies are needed to identify the genetic basis of this new entity.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Prenatal bilateral adrenal calcifications are a rare prenatal finding.
- Adrenal calcifications may be seen with intrauterine infections, tumor, or in Wolman disease. Risk factors for adrenal calcifications include large birth weight, hypoxia, septicemia, coagulation defects, and thromboembolism.
- The association of adrenal calcifications and proteinuria has been published in two reports of four different patients.

WHAT DOES THIS STUDY ADD?

- We propose that the constellation of bilateral adrenal calcifications, micropenis, testicular dysfunction, increased fetal nuchal translucency, and congenital nephrotic syndrome represents a new clinical entity.
- The consanguinity in this family suggests an autosomal recessive inheritance of this disease.
- This entity should be considered in the differential diagnosis of bilateral adrenal calcifications.

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