case of a 16 year old boy with histologically defined angiokeratoma circumscriptum on the ventral aspect of the tongue [3]. Another 12 year old boy with angiokeratoma circumscriptum isolated to the ventral tongue was reported [2]. The third patient was a 6-year old male who presented with a 2 year history of recurrent mass on the dorsal tongue [4]. Our case of lingual angiokeratoma circumscriptum involved both the dorsal and ventral surfaces of the tongue. Another interesting point to be noted is that all four patients including ours were male patients.

The pathogenesis of angiokeratomas is still unknown. It has been reported to develop overlying an arteriovenous fistula and in areas of lymphangioma circumscriptum after local injuries [7,8]. Angikeratomas may be treated with complete surgical excision, cryotherapy and laser ablation including copper vapour, potassium tritanyl phosphate, and argon lasers.

Contributors: All the authors have participated equally in the preparation of the article.
Funding: None; *Competing interests:* None stated.

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Aldosterone Synthase Deficiency Type II with Hypospadias

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Received: February 11, 2011; Initial review: March 21, 2011; Accepted: May 14, 2011.

Aldosterone synthase deficiency (ASD) type II was diagnosed in a 3 week old boy with severe dehydration. Elevated plasma renin activity, low-normal aldosterone, increased levels for 18-OH corticosterone (18-OHB) and 18-OH-deoxycorticosterone were measured. Sequencing revealed a homozygous mutation for c554C>T in exon 3 (p.T185I) (*CYP11B2)*. Hypospadias has so far not been reported in ASD.

Key words: *Aldosterone synthase deficiency type II, Hypospadias.*

Two types of aldosterone synthase deficiency (ASD) are described at the hormonal level: type 1 (ASD1), with undetectable aldosterone levels, while the levels of 18-hydroxy-11-deoxycorticosterone (18-OHDOC) are increased, levels of 18-OHB are reduced, and the ratio B/18-OHB is increased. Type 2 ASD (ASD2) is characterized by low aldosterone levels, increased 18-OHB and 18-OHDOC levels, as well as an increased 18-OHB/aldosterone ratio.

Clinical signs for ASD are failure to thrive, vomiting, and severe dehydration [1,2]. Hyperkalemia, hyponatremia, metabolic acidosis, elevated plasma renin activity and low or undetectable aldosterone levels are the main laboratory characteristics of ASD [1, 3]. Both types of ASD have not been described to have genital anomalies. Herein we describe a one year old boy with ASD2 and penile hypospadias.

CASE REPORT

The boy was born after uneventfull pregnancy and delivered at 39 wk gestation with a birth weight of 3400 g, and a length of 51 cm. The parents were young,

nonconsanguineous Macedonian Albanians. At the age of 4 weeks, he was admitted to hospital for vomiting and failure to thrive.

He had blue sclera and penile hypospadias. The blood pressure was 80/40 mm Hg. He had hyponatremia (serum sodium, 131mmol/L), hyperkalemia (serum potassium varied between 6.0-6.8 mmol/L), and no metabolic acidosis. Urine osmolality was normal. Magnesium, chloride, creatinine, urea, uric acid, liver enzymes, and proteins levels were normal. There were no signs of salt-wasting nephropathy or enteropathy, urinary tract infection, or obstruction.

The karyotype was 46, XY. Plasma steroid hormones were measured by liquid chromatography- tandem mass spectrometry. Unstimulated progesterone was 0.06 (normal 0.03-0.25ng/mL), 11-desoxycorticosterone 0.06 (0.03-0.63 ng/mL), corticosterone 3.2 (0.03-2.98 ng/mL), 18-OHB 22.0 ng/mL (0.20-0.53), 18-OH-DOC 0.4 ng/mL (0.05-0.56), aldosterone <0.03 (0.03-0.82 ng/mL), 17-OH-progesterone <0,03 (0.2-0.63 ng/mL), 11-desoxycortisol 0.58 (0.66-2.46ng/mL), cortisol 62 (47.6-105.7 ng/mL), cortisone 16 (14-28.9 ng/mL). ACTH stimulation test results were within normal range for 17OH progesterone and 17OH pregnenolone. The baseline/HCG stimulated testosterone, DHT and androstenedione levels were done before and after administration of 3 doses of hCG (1500 ie). Results before stimulation: DHEA-S 31 (15-39) ng/mL, 17-OH-Pregnenolon 0,3 ng/mL, androstendion 3 (2.9- 23) ng/dL, testosteron <2,9 (2,9-20) ng/dL, DHT <2,9 (2,9-38) ng/dL. After hCG administration: androstendion 15 ng/dL, testosteron 325 ng/dL, DHT 29 ng/dL. DHEA, DHEA-S and 17-OH-Pregnenolone within the normal range. Baseline androgens were within the normal limits and there was a typical rise after hCG. Ratio A/T<1 (normal), T/DHT 11 (normal). No evidence was found for Leydig cell insufficiency, disorder of androgen biosythesis or action.

Plasma active renin and direct renin were measured by RIA. Urine renin was 3760 (LIA normal 1.7-23. ng/L), and plasma renin activity >50 ng/mL/h (RIA <3.5 ng/mL/h). ACTH and cortisol had normal values on repeated measurements. The highly elevated 18-OH-B, normal levels of 18-OH DOC and absent aldosterone confirmed the diagnosis of ASD 2.

Treatment with fludrocortisone (0.1 mg/d) corrected the failure to thrive.

Karyotype: Karyotype standardized G-banding was performed. Genomic DNA was extracted and all nine exons of *CYP11B2* of the patient were specifically amplified by PCR in two fragments (exons 1-5 and exons 6-9). Direct sequencing on an ABI PRISM 310 DNA sequencer (PE Applied Biosystems, Foster City, CA) was performed. Informed consent was obtained from the parents. The amplification of the 9 exons of the *CYP11B2* gene by PCR and direct sequencing identified a homozygous missense mutation c.554C>T in exon 3 coding for an aminoacid substitution p.T185I in the index patient.

Informed consent was obtained from the parents.

DISCUSSION

We describe a previously unreported association of ASD2 and penile hypospadias in a Macedonian infant. ASD can be found in congenital adrenal hyperplasia due to 21-hydroxylase or 3β-hydroxysteroid dehydrogenase deficiency, congenital adrenal hypoplasia due to a deficiency of the steroidogenic acute regulatory (StAR) protein and other forms of primary adrenocortical insufficiency. Basal and ACTH stimulated steroid levels can differentiate between ASD and other types of aldosterone deficiency. It is of note that in ASD genitalia are normal, while congenital adrenal hyperplasia has various degrees of virilization or undervirilization.

There are two forms of aldosterone synthase (also termed: corticosterone methyloxidase) deficiency. They both have identical clinical features but differ in profiles of secreted steroids: excretion of 18-hydroxycorticosterone is mildly decreased in type I deficiency, urinary and serum levels of this steroid are markedly increased in patients with type II deficiency.

Genetic alterations that encode CYP11B2 enzymes are found to cause ASD2. Consequentely, patients with ASD2 have efficient 11β-hydroxylase activity, but markedly reduced or ablated 18-hydroxylase and oxidase activities *in vitro*. The excess B is converted to 18OHB by the 11β-hydroxylase activity of the CYP11B2 enzyme [4, 5], therefore increasing the 18OHB/aldosterone ratio and a decreasing the B/18OHB ratio. Absent aldosterone, increased 18OHB and 18OHDOC levels, and an increased 18OHB/aldosterone ratio classified our patient as type 2 ASD.

In contrast to ASD2, ASD-1 is caused by mutations in CYP11B2 that result in a complete loss or total inactivation of aldosterone synthase activity [5]. Both the 18-hydroxylase and oxidase activities are impaired, but the 11β-hydroxylase activity is retained [5-7]. Consequently, the production of 18OHB is lower and B/18OHB ratio is increased.

The p.T185I substitution found in our patient has

previously been reported in association with type II aldosterone synthase deficiency [8] in a consanguineous family of Middle Eastern European origin [8,9]. In addition, a compound heterozygous patient (T185I and a T498A substitution) has been also reported [6]. Interestingly, Macedonian nonconsanguinous immigrants in Australia were found to have the same genetic alteration [6]. A compound heterozygote showed a clinical phenotype of type II deficiency, with both detectable serum aldosterone and elevated 18-hydroxycorticosterone, but *invitro* no residual aldosterone synthase activity [7].

In summary, the hormonal analysis classified the infant as ASD2. The penile hypoplasia can not, at this time be linked to any known cause. A coincidental occurrence cannot be excluded.

Contributors: All authors contributed to reporting and writing the manuscript.
Competing interests: None stated; *Funding:* None.

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Novel Biochemical Abnormalities and Genotype in Farber Disease

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Received: April 27, 2011;
Initial review: May 10, 2011;
Accepted: June 27, 2011.

Farber disease caused by acid ceramidase deficiency is characterised by a triad of painful and swollen joints, subcutaneous nodules, and laryngeal involvement. A one year old female with overlapping features of the classical and type 5 variants is reported. Sialuria and elevated plasma chitotriosidase were unusual findings. A novel mutation of the *ASAH* 1 gene was detected from DNA extracted from the umbilical stump.

Key words: *ASAH 1 gene, Acid ceramidase, Sialic acid, Chitotriosidase, Lysosomal storage disorders.*

Farber disease (FD) (OMIM 228000) is a rare autosomal recessive disorder caused by acid ceramidase deficiency. This enzyme catalyzes the terminal step in glycosphingolipid metabolism, where ceramide is degraded to sphingosine and fatty acid. Less than 100 cases have been reported worldwide [1]. Present case had several unique biochemical findings and a novel mutation, and confirmation of diagnosis was done after death from preserved umbilical cord DNA.