

A Novel *CYP21A2* Gene Mutation in Classic Congenital Adrenal Hyperplasia

A 3-month-old boy presented with failure to thrive since birth, and poor feeding, lethargy and vomiting for one month. He was born to consanguineous parents and weighed 3.0 kg at birth. There was no family history of previous similarly affected member or early deaths. On examination, his weight and length were 3.25 kg (-4.5 Z-score) and 57.0 cm (-1.35 Z-score), respectively. Genital hyperpigmentation was noted, but there was no ambiguity. Laboratory investigations showed low serum sodium (126 mEq/L), high serum potassium (6.7 mEq/L), and low blood pH (7.09). The 17-hydroxyprogesterone (17-OHP) level was 38.7 ng/mL. Ultrasonography showed enlarged adrenals. A diagnosis of classic Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase (21-OH) deficiency was considered and replacement steroid therapy was initiated. Synacthen test was performed in follow-up after withholding steroids. The baseline serum cortisol and 17-OHP values were 4.60 nmol/L and 22.4 ng/mL and peak stimulated values were 4.87 nmol/L and 54.7 ng/mL, respectively.

Paired-end custom amplicon Next generation sequencing (NGS) carried out on the DNA extracted from peripheral blood of the child revealed the presence of a homozygous variant c.725T>C(p.Leu242Pro) in the *CYP21A2* gene. This is a novel variant, which has never been reported in literature, including large previous Indian CAH patient cohorts [1-3]. The T>C mutation at nucleotide 725 resulting in the substitution of proline for leucine at codon 242 is predicted as pathogenic according

to *in silico* mutation analysis tools (Sift, Polyphen and Mutation Taster) if clinical diagnosis of CAH is certain. However, functional characterization of mutant gene and the parents' carrier status could not be performed.

21-hydroxylase (21-OH) deficiency caused by the defective *CYP21A2* gene results in varying impairment in the secretion of cortisol and aldosterone and accounts for almost 95% of all patients with CAH [1]. The disease manifests as classic salt-wasting, classic simple virilizing and non-classic forms depending on the residual 21-OH enzymatic activity. The number of disease causing mutations in the *CYP21A2* gene has almost doubled to 212 over the past decade [1]. The identification of the mutation allows confirmation of diagnosis and early initiation of steroid therapy.

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A New Interface for Better Throat Examination

Evaluation of ear, nose and throat is an integral part of physical examination of children, both in office practice and inpatient setting. A meticulous screening of these areas can give vital clues, or sometimes the diagnosis *per*

se, especially in the context of a child with fever. Congested throat, follicles on the tonsils, petechiae on the palate, mucosal ulcers and quinsy are some of the common findings picked up on throat examination of a child in a tropical country where infections are common. Usually older children open their mouth on request and a good flashlight would be enough for throat examination. However, when the child is younger, he or she needs to be restrained by the caregiver and sometimes a tongue

depressor may be needed in addition to the flashlight for examining the throat. The visual acuity and skill of the examining physician are also important as the examination has to be quick with minimal discomfort to the child. When it becomes a difficult task for the child as well as the pediatrician, the throat examination is conveniently forgotten.

When examining children, when a conventional flashlight is not available, it is a common practice to use this facility in the mobile phone. We have been using a mobile phone where the flashlight option comes with the Optical Reader application. This application (app) captures visual information and translates the image into digital information the mobile phone is capable of understanding and displaying. Though we initially used

the light source alone for throat examination, we became comfortable using the optical reader as an interface as it served like a flashlight cum magnifying glass. The auto adjustment facility with the app helps in visualizing the throat with more clarity and in quick time. Older physicians with lesser visual acuity may find this method more useful. The image can also be captured and used for teaching. As mobile phones are commonly used, a mobile phone with an optical reader can serve as a useful interface for better throat examination in children.

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Lead Toxicity due to Use of Traditional Medicines in a Child with Type 1 Diabetes Mellitus

The management of Type 1 Diabetes Mellitus (T1DM) in children is a challenging process for the parents that involves understanding the complexities of insulin therapy, monitoring blood glucose, and following a nutritional and exercise plan. Due to the need of lifelong injections, parents often resort to the use of Complementary and alternative medicine (CAM) [1].

An 8-year-old boy was diagnosed elsewhere with T1DM, and initiated on premixed insulin therapy two months before presentation. However, parents started using ayurvedic drugs (Tablet Debix, Sandu Pharmaceuticals Ltd, Goa, and Tablet Chandraprabha Vati, Divya Pharmacy, Uttarakhand) bought over the counter along with insulin. Each tablet was given twice daily. Ten days prior to presentation at our hospital, he developed pain abdomen and non-bilious vomiting. There was history of constipation but no abdominal distension, fever or altered sensorium. There was no history of pica or environmental exposure to chemicals. He was operated for ileoileal intussusception elsewhere but pain abdomen persisted. Lead toxicity was suspected in view of ayurvedic medication use. Blood lead level (BLL) was 73 µg/dL (normal <5 µg/dL). He was then referred to our hospital. The general physical examination was unremarkable, except for pallor. The repeat BLL was 63 µg/dL. A conservative plan was

followed as he showed symptomatic improvement. Chemical analysis of Debix and Chandraprabha Vati tablets revealed lead content of 2.87 and 2.29 µg/g, respectively; the total lead intake amounted to 6.1 µg/day. On day-9 of hospitalization, BLL was 20 µg/dL. Other laboratory investigations showed hemoglobin of 7.8 g/dL, HbA1c 11.8% and positive GAD-65 autoantibodies. He was discharged on basal bolus insulin regimen after two weeks of hospital stay. At follow up 3 months later, the BLL was 2 µg/dL and HbA1c was 8.2%.

The use of CAM is common (18% and 56% in different studies) in children with T1DM [1]. Such products are often promoted as 'natural' or 'safe', and relatively inexpensive 'cure' [2]. However, several CAM including ayurvedic products available over the counter or on the internet contain lead, mercury, or arsenic much above their acceptable levels, and their use may result in potentially serious complications [2]. There are several reports of lead toxicity after the use of ayurvedic drugs in adults with diabetes [2-5]. The usual gastrointestinal manifestations of lead toxicity are abdominal pain, nausea, vomiting and constipation.

The use of CAM is largely unregulated in India [2]. There is an urgent need for rigorous pharmacological and toxicological studies to ensure purity, safety and efficacy of these widely available products.

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