Pediatric Endocrinology

PMON193

Reactive oxygen species in the development of gonadal failure in late-onset transaldolase deficiency

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Background: Deficiency in Transaldolase, an essential enzyme in regulating NADPH and ribose 5-phosphate production, has been reported in only 39 patients to date. Most patients present already prenatally/neonatally with intrauterine growth retardation, hepatospleno-megaly and consequent liver failure, anemia, thrombocytopenia, dysmorphic facial features, cardiac and skin abnormalities and hypergonadotropic hypogonadism in cases of late-onset presentation. The mechanism underlying gonadal dysfunction is not fully understood.

Clinical case, methods and results
A 15y old male from an Indian-Jewish background, with atrial-septal-defect, renal tubulopathy, mild facial dysmorphism and transient liver enzymes abnormalities presented with absence of pubertal development. His gonadotropins levels were elevated (LH – 22 IU/L, FSH 103 IU/L) while testosterone was low. Whole exome sequencing revealed homozygous variant in a novel T167M missense mutation in TALDO1 (transaldolase) gene whereas both parents were heterozygote carriers. Protein structure analysis indicate that Threonine 167 is part of transaldolase catalytic site and critical for its function. As transaldolase activity is required for nucleic acids production, NADPH synthesis and reduction of cellular Reactive Oxygen Species (ROS) we measured the ROS accumulation using 2′,7′-dichlorodihydrofluorescein diacetate, in fibroblasts derived from the patient and normal controls. The affected patient’s fibroblasts showed a significantly increased accumulation of ROS (207%, P=0.007), compared to controls indicating an increased susceptibility to oxidative stress.

Conclusion: The novel T167M missense mutation in the transaldolase (TALDO1) gene causes a unique clinical presentation including a relative mild liver involvement and hypergonadotropic hypogonadism. The compromised TALDO1 activity in preventing cellular ROS accumulation in actual patient’s fibroblasts is shown here for the first time and may indicate the therapeutic use of antioxidants in all patients with TALDO1 dysfunction. The high expression of TALDO1 in the testis and the gonadal failure suggests its tissue specific requirement in preventing the accumulation of ROS during steroidogenesis.

Presentation: Monday, June 13, 2022 12:30 p.m. - 2:30 p.m.