Simple Evaluation of Thyroid Function Leading to the Diagnosis of Allan-Herndon-Dudley Syndrome, a Rare Neurodevelopmental Disorder

Aviv Schupper MD[1,6,7], Galia Barash MD[2], Lilach Benyamini MD[3], Revital Ben-Haim MD[4], Eli Heyman MD[5,7], Eli Lahat MD[4,7], and Haim Bassan MD[4,7]

[1]Department of Pediatrics, [2]Pediatric Endocrinology and Diabetes Unit, [3]Genetics Institute, [4]Pediatric Neurology and Development Center, and [5]Department of Pediatric Neurology and Epilepsy, Shamir Medical Center (Assaf Harofeh), Zerifin, Israel

[6]Department of Military Medicine and Tzameret Program, Faculty of Medicine, Hebrew University of Jerusalem, Israel and Medical Corps, Israel Defense Forces, Israel

[7]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

KEY WORDS: Allan-Herndon-Dudley syndrome, dysthyroidism, global developmental delay (GDD), monogenic disease, neurodevelopmental disorders

IMAJ 2023; 25: 374–376

Global developmental delay (GDD), defined as a significant delay in two or more developmental domains (e.g., gross/fine motor, cognitive, speech/language, personal/social, activities of daily living), affects 1–3% of children. According to the Israeli Ministry of Health, thyroid function studies are not indicated in children with GDD unless there are systemic features suggestive of thyroid dysfunction (https://www.gov.il/he/Departments/policies/mr36-2012). This approach also exists in other countries with newborn screening programs for congenital hypothyroidism.

We present the case of an infant with GDD, who despite normal newborn screening tests, underwent a repeated extended thyroid function analysis (including T3 levels) leading to a diagnosis of Allan-Herndon-Dudley syndrome, a rare genetic neurodevelopmental syndrome.

PATIENT DESCRIPTION

A male infant was born to a non-consanguineous couple of Bukhari Jewish and North African Jewish descent. The mother and grandfather had congenital ptosis. Chromosomal microarray analysis (CMA), obtained from amniocentesis due to elevated maternal alpha-fetoprotein, was normal. Prenatal and perinatal periods were uneventful except for clavicular fracture and failure to pass the hearing screening test. Auditory brainstem response was normal and newborn screening test results, including T_4, were within normal limits.

At 2 months of age, torticollis was diagnosed. At 6 months he failed to achieve developmental milestones and had feeding difficulties. At age 7.5 months, he was admitted to our center due to feeding difficulties, failure to gain weight, irritability, myoclonic episodes, and focal tonic seizures. On physical examination the infant was alert but irritable and made eye contact. His head circumference was 43 cm (25th percentile compared to 60th percentile at birth). He had bilateral temporal narrowing, ptosis, head-lag, axial hypotonia, increased appendicular tone (upper > lower), intermittent dystonic movements, and a persistent Moro response. Funduscopic examination was normal. Development was severely delayed. He could not roll over, was not reaching for objects, and produced monotonic sounds.

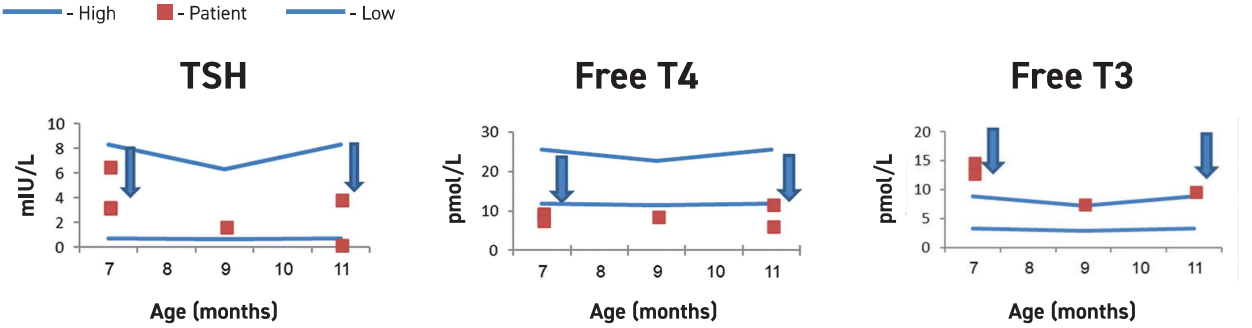
Laboratory investigation, including complete blood count, blood glucose, renal function, liver enzymes, electrolytes, gases, ammonia, lactic acid, amino acids, total and free carnitine, acylcarnitines, biotinidase, very long chain fatty acids, and urinary organic acids, were all within normal limits. Cerebrospinal fluid analysis was normal, including cell count, glucose, protein, lactic acid, culture, and amino acids.

An electroencephalographic examination revealed generalized slowing and repeated multifocal and generalized epileptiform activity followed by background attenuations. Brain magnetic resonance imaging (MRI) showed slightly dilated fourth ventricle, enlargement of the subdural spaces, and small subdural hemorrhage that was attributed to brain atrophy and secondary tear of bridging veins. MR spectroscopy, was normal.

His thyroid stimulating hormone (TSH) level was normal (3.21 mIU/L, normal values 0.73–8.35 mIU/L), free T_4 level was slightly decreased (9.25 pmol/L, normal values 11.9–25.6 pmol/L), and free T_3 was elevated (14.6 pmol/L, normal values 3.3–8.9 pmol/L) [Figure 1]. The infant was treated with omperazole, enriched enteral feeding, and levothyroxine. He required combinations of multiple antiepileptic medications with partial seizure control, including levetiracetam, pyridoxine, clobazam, clonazepam, topiramate, vigabatrin, sulthiame, brivaracetam, and valproic acid.

Allan-Herndon-Dudley syndrome was suspected due to a combination of clinical manifestations, elevated T_3, low free T_4, and normal TSH [1]. Next generation sequencing (NGS) whole exome test revealed a new pathogenic hemizygous truncating mutation of a single amino acid substitution in exon number 5, in a crucial

Figure 1. Thyroid function tests along time
Arrows indicate initiation and cessation of levothyroxine treatment. Squares are the patient thyroid function test results. Lines demarcate the normal value borders according to the specific laboratory examining the test



region for protein production (c. 1296C > A) in the SLC16A2 gene. Genetic counseling was provided to the parents.

After diagnosis was made, levothyroxine treatment was stopped, as previously suggested by Zung et al. [1] [Figure 1]. In the year after, the patient was admitted to our medical center several times, mainly due to respiratory illnesses and seizures. His development was significantly delayed (developmental quotient below 50). A gastrostomy tube was inserted, seizures were finally controlled, and follow-up electroencephalogram revealed generalized slowness without epileptiform activity. The family was offered to participate in a clinical trial that investigates the efficacy of tiratricol (a T3 analogue called Triac): Triac Trial II; ClinicalTrials.gov number NCT02396459.

COMMENT

Allan-Herndon-Dudley syndrome, a rare X-linked recessive disease, was first described in 1944 but only in the beginning of this century was it linked to SLC16A2, a gene that encodes monocarboxylate transporter -8 (MCT-8) [1-3]. MCT-8 acts as a transporter of thyroid hormones located in blood-brain barrier, liver, kidney, pituitary, and thyroid gland cells. A variety of mutations have been reported from a single amino acid substitution, deletion, or insertion to large deletions of several exons. Some of these mutations disable the protein while some leave a residual functioning transporter [4]. Without a proper function of MCT-8 the thyroid hormones, and most importantly T3, which is the active form, do not cross the blood-brain barrier and are deficient in the patient's brain, thus influencing neurodevelopment. Cardiac and muscular thyroid hormone activity is preserved or even hyperfunctioning due to other intact thyroid hormones transporters, resulting in a clinical picture of brain hypothyroidism accompanied by peripheral hyperthyroidism. The unique thyroid hormone profile of elevated T3, low T4 and normal or slightly elevated TSH are caused by an improper feedback mechanism at the pituitary and thyroid gland levels due to disturbed thyroid hormones transported into those cells.

Clinical presentation and severity are dictated by mutation type. Approximately two-thirds of the cases are inherited from asymptomatic mothers. Most cases are discovered in infancy following an uneventful perinatal period, initially with hypotonia and GDD. Soon after a combination of neurologic and peripheral signs appears. Neurologic signs include failure to achieve motor milestones (up to 100%), hypotonia (74–100%), muscle weakness (34.5–88%), extrapyramidal sign (up to 75%), seizures (14–29%), late onset pyramidal signs, and spastic paralysis. Peripheral signs include feeding difficulties with poor weight gain (33–66%), scoliosis (21–53%), ptosis, and cryptorchidism (2–33%). Dysmorphic characteristics may accompany and include acquired microcephaly, bitemporal narrowing, and myopathic facies. MRI examination shows general brain atrophy. Although milder phenotypes of hypotonia and GDD were described, the prognosis is poor, and most patients never gain capability of walking or speaking and present with profound intellectual disability (33–80%). Life span is usually shortened due to secondary complications such as respiratory infections or aspiration pneumonia.

Treatment and surveillance are multidisciplinary and may include developmental interventions, anti-epileptic drugs, medications to control extrapyramidal movements, anti-gastroesophageal reflux medications, gastrostomy, and orthopedic interventions. Levothyroxine treatment might aggravate the clinical condition because the given analogue cannot enter the central nervous system, while peripherally there is an excess. Recently, a study of patients diagnosed with Allan-Herndon-Dudley syndrome introduced a T3 analogue named Triac (3,3',5-tri-iodothyroacetic acid; also known as tiratricol), which is known for its ability to cross the blood-brain barrier without MCT-8, resulted in reduction in serum T3 concentrations, less deterioration of body weight, reduction in prevalence of tachycardia, and amelioration of peripheral thyrotoxicosis signs [5].

The influence of this treatment on neurodevelopmental is still under investigation.

CONCLUSIONS

Extended thyroid function screening (T3, T4, TSH) are not indicated in children with GDD in Israel unless there are systemic features suggestive of thyroid dysfunction. We present a case of an infant with GDD, diagnosed with Allan-Herndon-Dudley syndrome due to T3 level testing. This simple test can lead to early diagnosis of this rare syndrome, thus avoiding expensive unnecessary laboratory investigations, allowing genetic counselling and pre-implantation genetic diagnosis, and enabling early participation in clinical trials for emerging therapies. Clinicians should be aware of this rare diagnosis and consider adding T3 level to the workup algorithm of GDD, not only in cases with the classic phenotype of this syndrome, but also in GDD in general.

Correspondence

Dr. H. Bassan
Pediatric Neurology and Development Center, Shamir (Assaf Harofeh) Medical Center, Zerifin 70300, Israel
Fax: (972-8) 977-9945
Email: bassan@tauex.tau.ac.il

References

1. Zung A, Visser TJ, Uitterlinden AG, Rivadeneira F, Friesema EC. A child with a deletion in the monocarboxylate transporter 8 gene: 7-year follow-up and effects of thyroid hormone treatment. *Eur J Endocrinol* 2011; 165 (5): 823-30.
2. Dumitrescu AM, Liao XH, Best TB, Brockmann K, Refetoff S. A novel syndrome combining thyroid and neurological abnormalities is associated with mutations in a monocarboxylate transporter gene. *Am J Hum Genet* 2004; 74 (1): 168-75. [published correction appears in *Am J Hum Genet* 2004; 74 (3): 598].
3. Friesema EC, Grueters A, Biebermann H, et al. Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation. *Lancet* 2004; 364 (9443): 1435-7.
4. Groeneweg S, van Geest FS, Peeters RP, Heuer H, Visser WE. Thyroidhormone transporters. *Endocr Rev* 2020; 41 (2): bnz008.
5. van Geest FS, Groeneweg S, van den Akker ELT, et al. Long-term efficacy of T3 analogue triac in children and adults with MCT8 deficiency: a real-life retrospective cohort study. *J Clin Endocrinol Metab* 2022; 107 (3): e1136-47.

I like not only to be loved, but to be told that I am loved; the realm of silence is large enough beyond the grave.

George Eliot (Mary Ann Evans) (1819–1880), English novelist, poet, journalist, translator

There are conditions of blindness so voluntary that they become complicity.

Paul Bourget (1852–1935), French novelist and critic

Capsule

A non-antibiotic-disrupted gut microbiome is associated with clinical responses to CD19-CAR-T cell cancer immunotherapy

Increasing evidence suggests that the gut microbiome may modulate the efficacy of cancer immunotherapy. In a B cell lymphoma patient cohort from five centers in Germany and the United States (Germany, n=66; United States, n=106; total, n=172), **Stein-Thoeringer** and colleagues demonstrated that wide-spectrum antibiotics treatment (high-risk antibiotics) prior to CD19-targeted chimeric antigen receptor (CAR)-T cell therapy is associated with adverse outcomes, but this effect is likely to be confounded by an increased pretreatment tumor burden and systemic inflammation in patients pretreated with high-risk antibiotics. To resolve this confounding effect and gain insights into antibiotics-masked microbiome signals impacting CAR-T efficacy, the authors focused on the high-risk antibiotics non-exposed patient population. Indeed, in these patients, significant correlations were noted between pre-CAR-T infusion *Bifidobacterium longum* and microbiome-encoded peptidoglycan biosynthesis, and CAR-T treatment-associated 6-month survival or lymphoma progression. Furthermore, predictive pre-CAR-T treatment microbiome-based machine learning algorithms trained on the high-risk antibiotics non-exposed German cohort and validated by the respective US cohort robustly segregated long-term responders from non-responders. *Bacteroides*, *Ruminococcus*, *Eubacterium*, and *Akkermansia* were most important in determining CAR-T responsiveness, with *Akkermansia* also being associated with pre-infusion peripheral T cell levels in these patients. Collectively, the authors identify conserved microbiome features across clinical and geographical variations, which may enable cross-cohort microbiome-based predictions of outcomes in CAR-T cell immunotherapy.

Nature Med 2023; 29: 906
Eitan Israeli