A CHILD WITH LARON SYNDROME ASSOCIATED WITH VASCULITIS

R. Unsal Sac^{1,*}, M.A. Tasar¹, U. Tiras², S. Savas Erdevi³, Y. Dallar Bilge¹

¹Ministry of Health Ankara Training and Research Hospital, Dept. of Pediatrics, ²Acibadem Maslak Hospital - Pediatrics Clinics, ³“Dr. Sami Ulus” Maternity and Children’s Training and Research Hospital, Dept. of Pediatric Endocrinology, Ankara, Turkey

Abstract

Background and Objectives. Levels of insulin-like growth factor-I are characteristically low in Laron syndrome which is a factor that has important roles on vascular health and development. Congenital insulin-like growth factor-I deficiency was reported to be associated with some vascular disorders. However, vasculitis diseases and Laron Syndrome association has not been reported in English literature up to date.

Patient. We report the case of a two and a half years old Turkish girl, who was diagnosed as Laron syndrome when she was 12 months old. She presented with acute vasculitis lesions. Her physical examination and laboratory studies did not reveal a specific infectious agent or also an autoimmune disease was not detected. Her lesions disappeared during hospitalization without a complication.

Conclusion. Since insulin-like growth factor-I reduces endothelial cell oxidative stress and maintains the structural integrity of vessels, some common mechanisms might be responsible for the occurrence of vasculitis in this patient with Laron syndrome. The role of insulin-like growth factor-I and recombinant human insulin-like growth factor-I treatment choice in vasculitis diseases is a matter of investigation.

Key words: Child, Growth hormone, Insulin-like growth factor, Laron syndrome, vasculitis.

INTRODUCTION

Laron syndrome (LS) is a primary growth hormone (GH) resistance or insensitivity syndrome (GHIS) characterized with low insulin-like growth factor-I (IGF-1) and high GH levels. The mitogenic actions of GH are mediated through increases in the synthesis of IGF-1, a single chain peptide with 70 amino acids coded for by a gene on the long arm of chromosome 12. The pathogenesis of this syndrome is due to various molecular defects from exon deletion to

nonsense, frame shift, splice and missense mutations in the GH receptor gene or in its post-receptor pathways (1). Main diagnostic features are severe growth retardation, acromicria, small gonads, genitalia, and obesity.

Insulin-like growth factor-I promotes vascular health by activating nitric oxide syntheses on vascular endothelium, and it up-regulates the activity of glutathione peroxidase expression, which is thought to play an important role in the ability of IGF-1 to reduce endothelial cell oxidative stress and premature senescence (2, 3).

In hypersensitivity vasculitis the small vessels are involved and characteristic leukocytoclasia is seen, which refers to the nuclear debris remaining from the neutrophils, infiltrating in and around the vessels during the acute stages. A hypersensitivity vasculitis occurs after exposure to endogenous self proteins like immunoglobulin, tumor antigens, exogenous drugs or infectious agents as an antigen. Generally predominating clinical picture is the skin involvement, but other organ systems may also be involved to varying degrees (4).

Since IGF-1 promotes vascular health, in GHIS, which is characterized with IGF-1 deficiency, we wonder if there is a predisposition to vasculitis. After presentation of the patient, bound to the role of IGF-1 in vascular disorders, it is argued if the association of vasculitis and GHIS is meaningful, or whether the patient we present here is an isolated one. To the best of our knowledge, this is the first report of a patient of GHIS associated with vasculitis, in English literature.

Presentation of the patient

A two and a half years old Turkish girl was admitted to hospital with the complaint of rash (Figs 1 and 2). Rash appeared a few days ago, mainly on buttocks and lower extremities, and a notable

*Correspondence to: Rukiye Unsal Sac MD, Ministry of Health Ankara Training and Research Hospital, Dept. of Pediatrics, Şükriye mah., Altundağ, Ankara, 06340, Turkey, E-mail: rukiyeunsal@hotmail.com

coalescence occurred at the day of admission.

At her past medical history, she was diagnosed as GHIS, when she was admitted to Pediatric Endocrinology, due to short stature, at the age of twelve months. Her birth weight and birth height were 3950 gram and 45 cm, respectively. Although birth weight was more than 2500 g in most newborns with GHIS, some babies can weigh less than 2100 g (REF). The birth weight of her brother was 5 kg, and he had also been diagnosed as GHIS at 4 years age. It was thought that the high birth weights of these siblings were relevant to the presence of type 2 diabetes in both of their parents. Parents had consanguinity, being the grandchildren of siblings. The mother was 151 cm tall and her father was 160 cm tall.

At the age of twelve months, her bone age was compatible with three months. Serum levels of GH were 32.2 ng/mL, and IGF-1 was 18 ng/mL measured. When L-3, 4-dihydroxyphenylalanine (L-DOPA) test was performed serum GH levels at 0, 40, 60, 90 and 120. minutes were determined as 15, 2.5, 1.5, 14 and 9.5 ng/mL. After L-DOPA test, IGF-1 level was detected as 27 ng/mL. In the protocol for the generation test we used, recombinant human GH was administered with the dose of 33 mcg/kg/day, for four days, total dose was 132 mcg/kg.

Serum IGF-1 levels were measured as 17 ng/mL before and 32 ng/mL after IGF generation test. IGF-binding protein-3 level before and after IGF generation test was determined as 163 ng/mL and 216 ng/mL, respectively. Basal IGF-1 level of her brother was 30 ng/mL. After the IGF-1 generation test an increase to 53 ng/mL was seen and Δ IGF was determined as 23 ng/mL. Method used in determining GH, IGF-1 and IGFBP-3 was Electro-chemiluminescence immunoassay (ECLIA), immulite xpi 2000 Siemens, Deutschland.

Diagnosis of GHIS was based on clinical features along with high concentrations of basal GH and poor response to IGF generation test; we used the scoring system described by Savage *et al.* at a multicentre study based on genetically heterogeneous 27 patients (5). According this scoring system, it is recommended that 5 clinical and biochemical parameters are diagnostic for GHIS.

Scoring involved assessment of the following 7 parameters (5):

Our patient's height SDS<-3SDS+basal GH>2.5 ng/mL+basal IGF1<50 ng/mL, basal IGFBP3<-2 SDS, delta IGFBP3< 400 ng/mL: Total score: 5.

Test	Parameter	Criteria	Score
Auxology	Height	<-3 SDS	1
Basal GH	GH	>2.5 ng/mL	1
Basal IGF1	IGF1	≤ 50 ng/mL	1
	IGFBP3	<-2 SDS	1
IGF1 generation	Δ IGF1	<15 ng/mL	1
	Δ IGFBP3	< 400 ng/mL	1
GH binding	%GH bound	< %10	1

The diagnosis is made if 5 of the 7 parameters are positive.

At her hospitalization because of these vasculitis lesions, her vital signs including, fever, blood pressure, respiratory and heart rate were within normal limits for her age. Respiratory, cardiac, abdomen and genitourinary examination were normal. Her weight (7500 gram), height (67 cm) and head circumference were (43.5 cm) all below 3 percentiles. Height standard deviation score was -6.13 SD. Head circumference according to height was normal. The ratio of head-pubis to pubis-heel was 1.2 and shoulder-elbow to elbow-hand was 12/13. Her face's appearance was atypical with prominent forehead, depressed nose and long filthrum. Bilateral purple, lots of purpuric and confluent rash, some of them hemorrhagic and bullous were detected on lower extremities (Fig. 1). Fewer petechial lesions also existed on body and upper extremities.

Laboratory examination of the patient revealed thyroid functions, serum chemistry, coagulation parameters, zinc level and urinalysis as normal. Antigliadin and antiendomysium antibodies were negative. Autoimmune markers were negative including antinuclear antibody, perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) and cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA). Serum immunoglobulin (Ig) of A, G, M and E, and also C complement 3 and 4 values were in normal limits. Hepatitis A, B, C, human immune deficiency virus, toxoplasmosis, ebstein-barr virus and herpes simplex virus serologies were negative. Cytomegalovirus IgG was positive, but IgM was negative. Occult blood in gaita was negative.

Her hemoglobin value was 11.5 gram/dL, thrombocytes 125.000/mm³, and white blood cells 15.600/mm³. Peripheral blood smear revealed mild burr cells, hypochromia, lymphocytes accounted 50% of counted white blood cells; the other findings were normal. These abnormalities returned to normal after days, with the evanescent vasculitis lesions. Skin biopsy was reported as leukocytoclastic vasculitis.

The patient was observed without giving any medication. Vital signs remained stable and rash began to disappear by the second day of hospitalization. By the

Figure 1. Child diagnosed as Laron Syndrome, presented with bilateral lots of confluent, purple, vasculitis lesions on lower extremities. Some of these lesions were hemorrhagic and bullous in appearance. Fewer petechial lesions also existed on buttocks.

eight day of hospitalization, the patient was discharged.

The patient was followed-up in our hospital for a period of one year. Next monitoring was carried out at another centre, and it was learned that IGF-1 treatment was initiated to her. Autoimmune disease and recurrent pneumonia did not develop at her, during monitoring. It was learned from the patient's father that genetic analysis was sent from the patient, but the result is not available, yet. When we obtain the result we will notify.

DISCUSSION

Insulin-like growth factor-I has a fundamental role in both prenatal and postnatal vascular health and development (6, 7). In mice and in humans, IGF-1 is a necessary growth factor for normal development of retinal blood vessels (8, 9). Even that, the degree of retinal vasculopathy was indicated to show positive correlation with serum IGF-1 levels (10). Hellstrom *et al.* (8) indicated that persistent low serum concentrations of IGF-1 were associated with later development of retinopathy of prematurity. Insulin-like growth factor-I also has a role in diabetic retinopathy (11). Adolescents with type 1 diabetes mellitus (T1DM) had lower IGF-1 than healthy controls. Within the T1DM patients, those with poor glycemic control had lower IGF-1 than those with good glycemic control, as well (12). The evidence for the role of IGF-1 in other vascular diseases like atherosclerosis, hypertension, restenosis, angiogenesis, and diabetic vascular disease is accumulating and the IGFs have become the focus of research by an

increasing number of investigators (13, 14). In a study, knockdown of the IGF-1 gene in mouse was associated with endothelial dysfunction, increased oxidative stress, and apoptosis (15).

The evidence obtained in patients with endocrine IGF-1 deficiencies, show that low IGF-1 levels associates some vascular disorders. Death of Laron dwarfs in Ecuador was mainly related to stroke and cardiovascular disease (16). Low circulating IGF-1 was associated with angiographically documented coronary artery disease (17). In a cross-sectional study, an inverse correlation was documented between circulating IGF-1 levels and carotid arterial intima media thickness (18). Normal levels of GH and IGF-1 are needed for the maintenance of a healthy endothelial function (16).

Excessive GH secretion induces diabetes and promotes the micro vascular complications of diabetes (19). In never-IGF-1-treated two patients of Laron dwarfs with type 2 diabetes, proliferative diabetic retinopathy, nephropathy, and ischemic heart disease were seen as associated complications (11).

In IGF-1 deficient animals, vessel glutathione, ascorbate and eNOS contents are reduced, oxidative stress is increased, inflammation is upregulated, endothelial dysfunction and apoptosis are more pronounced. It has been repeatedly shown that IGF-1 regulates angiogenic processes and, IGF-1 deficiency was associated with abnormal micro vascular development (16).

Recent studies demonstrate that the locally derived (paracrine) IGF-1 system confers vasoprotection, cardio protection, and maintenance of the structural and functional integrity of the microvasculature (16).

It was reported that recombinant human IGF-1 (rhIGF-1) replacement treatment causes significant reduction of serum lipoprotein (a), a coronary artery disease risk factor (20). The potential impact of rhIGF-1 on diabetic complications, like retinopathy, was also investigated (21).

The role of IGF-1 in vasculitis syndromes is a matter of investigation if we consider that low IGF-1 is associated with vasculitis (3).

Although congenital IGF-1 deficiency has been shown to be in relation with some vascular disorders, our report is the first in English literature presented as a patient with GHIS and vasculitis association. So, we intend to remark if there is a meaningful association between GHIS and vasculitis in our patient. It is possible that common mechanisms may be responsible for the occurrence of vasculitis in this patient.

In conclusion, since rhIGF-1 treatment is available, it can be investigated as a choice in treatment of vasculitis diseases.

Conflict of interest

Written informed consent was obtained from the patient for publication of this case report and accompanying images. The authors declare that they have no competing interests.

References

1. Parks JS, Feiner EI. Hypopituitarism. In: Kliegman RM, Stanton BF, St.Geme JW, Schor NF, Behrman RE, eds. *Nelson Textbook of Pediatrics*. Philadelphia: Saunders, 2011:1876-1881.
2. McCarty MF. IGF-I activity may be a key determinant of stroke risk-a cautionary lesson for vegans. *Med Hypotheses* 2003; 61(3):323-334.
3. Higashi Y, Pandey A, Goodwin B, Delafontaine P. Insulin-like growth factor-1 regulates glutathione peroxidase expression and activity in vascular endothelial cells: Implications for atheroprotective actions of insulin-like growth factor. *Biochim Biophys Acta* 2013; 1832(3):391-399.
4. Langford CA, Fauci AS. The vasculitis syndromes. In: Longo DL, Fauci A, Kasper D, Hauser S, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 17th edition, 2, 2008. (Accessed June 16, 2015, at site <http://highered.mheducation.com/sites/0071466339/information_center_view0/table_of_contents.html>)
5. Savage MO, Blum WF, Ranke MB, Postel-Vinay MC, Cotterill AM, Hall K, Chatelain PG, Preece MA, Rosenfeld RG. *Clin Endocrinol Metab*. Clinical features and endocrine status in patients with growth hormone insensitivity (Laron syndrome). 1993; 77(6):1465-1471.
6. Laron Z. The essential role of IGF-I: lessons from the long-term study and treatment of children and adults with Laron syndrome. *J Clin Endocrinol Metab* 1999; 84(12):4397-4404.
7. Delafontaine P, Song YH, Li Y. Expression, regulation, and function of IGF-1, IGF-1R, and IGF-1 binding proteins in blood vessels. *Arterioscler Thromb Vasc Biol* 2004; 24(3):435-444.
8. Hellstrom A, Engstrom E, Hard AL, Albertsson-Wikland K, Carlsson B, Niklasson A, Löfqvist C, Svensson E, Holm S, Ewald U, Holmström G, Smith LE. Postnatal serum insulin-like growth factor I deficiency is associated with retinopathy of prematurity and other complications of premature birth. *Pediatrics* 2003; 112(5):1016-1020.
9. Hard AL, Smith LE, Hellström A. Nutrition, insulin-like growth factor-1 and retinopathy of prematurity. *Semin Fetal Neonatal Med* 2013; 18:136-142.
10. Löfqvist C, Engström E, Sigurdsson J, Hard AL, Niklasson A, Ewald U, Holmström G, Smith LE, Hellström A. Postnatal head growth deficit among premature infants parallels retinopathy of prematurity and insulin-like growth factor-1 deficit. *Pediatrics* 2006; 117(6):1930-1938.
11. Laron Z, Weinberg D. Diabetic retinopathy in two patients with congenital IGF-I deficiency (Laron syndrome). *Eur J Endocrinol* 2004; 151(1):103-106.
12. AboElAsrar MA, Elbarbary NS, Elshennawy DE, Omar AM. Insulin-like growth factor-1 cytokines cross-talk in type 1 diabetes mellitus: relationship to microvascular complications and bone mineral density. *Cytokine* 2012; 59(1):86-93.
13. Higashi Y, Sukhanov S, Anwar A, Shai SY, Delafontaine PJ. Aging, atherosclerosis, and IGF-1. *Gerontol A Biol Sci Med Sci* 2012; 67(6):626-639.
14. Back K, Islam R, Johansson GS, Chisalita SI, Arnqvist HJ. Insulin and IGF1 receptors in human cardiac microvascular endothelial cells: metabolic, mitogenic and anti-inflammatory effects. *J Endocrinol* 2012; 215(1):89-96.
15. Bailey-Downs LC, Mitschelen M, Sosnowska D, Toth P, Pinto JT, Ballabh P, Valcarcel-Ares MN, Farley J, Koller A, Henthorn J, Bass C, Sonntag WE, Ungvari Z, Csiszar A. Liver-Specific Knockdown of IGF-1 Decreases Vascular Oxidative Stress Resistance by Impairing the Nrf2-Dependent Antioxidant Response: A Novel Model of Vascular Aging. *J Gerontol A Biol Sci Med Sci* 2012; 67(4):313-329.
16. Ungvari Z, Csiszar A. The emerging role of IGF-1 deficiency in cardiovascular aging: recent advances. *J Gerontol A Biol Sci Med Sci* 2012; 67(6):599-610.
17. Spallarossa P, Brunelli C, Minuto F, Caruso D, Battistini M, Caponnetto S, Cordera R. Insulin-like growth factor-I and angiographically documented coronary artery disease. *Am J Cardiol* 1996; 77(2):200-202.
18. van den Beld AW, Bots ML, Janssen JA, Pols HA, Lamberts SW, Grobbee DE. Endogenous hormones and carotid atherosclerosis in elderly men. *Am J Epidemiol* 2003; 157(1):25-31.
19. Tran HA, Petrovsky N, Field AJ. Severe diabetic retinopathy: a rare complication of acromegaly. *Intern Med J* 2002; 32(1-2):52-54.
20. Laron Z, Wang XL, Klinger B, Silbergeld A, Wilcken DE. Insulin-like growth factor-I decreases serum lipoprotein (a) during long-term treatment of patients with Laron syndrome. *Metabolism* 1996; 45(10):1263-1266.
21. Thrailkill KM, Quattrin T, Baker L, Kuntze JE, Compton PG, Martha PM Jr. Co therapy with recombinant human insulin-like growth factor I and insulin improves glycemic control in type I diabetes. RhIGF-I in IDDM Study Group. *Diabetes Care* 1999; 22(4):585-592.