The Turkish Journal of Pediatrics 2020; 62: 326-331
https://doi.org/10.24953/turkjped.2020.02.022

Case Report

A rare case of syndromic severe congenital neutropenia: JAGN1 mutation

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ABSTRACT

Background. Neutrophils are essential innate cells to fight bacterial and fungal pathogens. Jagunal homolog 1 (JAGN1) mutations were recently defined as rare genetic defects causing severe congenital neutropenia. JAGN1 participates in the secretory pathway and is required for granulocyte colony-stimulating factor receptor-mediated signalling. This gene is required for normal ultrastructure and granulation of endoplasmic reticulum of myeloid progenitor cells. Its defect is related to increased predisposition to apoptosis. In the literature, a few cases have been reported with congenital anomalies such as cardiac and renal anomalies.

Case. Here we report a patient in which JAGN1 deficiency was found after several years. Apart from syndromic facial appearance we were unable to detect any other systemic malformations.

Conclusion. The causes of multisystemic features of mutations in JAGN1 gene remain unknown. JAGN1 mutations must be considered in patients with severe congenital neutropenia especially with facial dismorphism even in the absence of systemic manifestations.

Key words: severe congenital neutropenia, JAGN1 mutation.

Severe congenital neutropenia is characterized by susceptibility to recurrent life threatening bacterial infections due to maturation arrest of neutrophils. Different studies have shown mutations in ELA 2, HAX 1, G6PC3, WAS, GF11 and VPS45 genes.[1-7] In 2014, Boztug et al.[8] described mutations in Jagunal homolog 1 (JAGN1) gene that play a role in neutrophils differentiation and maintenance. JAGN1 is an endoplasmic reticulum (ER) resident protein responsible for normal ultrastructure of the granules in neutrophils, and also contributes to N-glycosylation of multiple proteins. Mutations of this gene cause absent granules in the neutrophils and increased apoptosis of the neutrophils.[8] Here we report a patient with severe congenital neutropenia that showed homozygous JAGN1 mutation.

Case Report

Our patient is a 10-year-old male born to first cousin parents. He was the first child of the family and was born 1900 grams at 37 weeks of gestation. He was admitted due to neonatal sepsis for a month on the fourth day after birth. He was re-hospitalized because of ulcers and abscesses on the bilateral lower extremities which did not regress with antibiotics at 6 months of age. After these 2 episodes of hospitalizations, severe neutropenia was noticed on the complete blood count analysis.

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Received 13th December 2017, revised 8th January 2018, 2nd March 2018, 24th May 2018, accepted 30th November 2019.

This study was presented at the 4th The Friends of Children Congress, İstanbul, Turkey, 24-26th March 2016.

In initial laboratory tests leukocyte count was 5120/mm^3, while absolute neutrophil count (ANC) was 100/mm^3, hemoglobin was 10.9 g/dl and thrombocyte count was 357000/mm^3. Deep neutropenia was seen in repeated complete blood counts (ANC: 0-200/mm^3). Bone marrow aspiration revealed maturation arrest of the neutrophils. Granulocyte – Colony Stimulating Factor (G-CSF) (5 μg/kg) treatment was started with the presumed diagnosis of Kostmann syndrome. All ANC were 0-200 / mm^3 without G-CSF. After G-CSF, ANCs increased up to just maximum 700 / mm^3. Physical examination was normal except triangular face and ears. His growth and mental development were within normal percentiles. Cardiac and abdominal investigations did not show any accompanying congenital anomalies.

He was treated for recurrent skin ulcers and abscesses until 1.5 years of age. He had recurrent infections including pneumonia, otitis media, sinusitis and skin abscess. At 3 years of age, he was hospitalized due to severe pneumonia and cavernous lesions were seen on thorax computed tomography. As anti-bacterial treatments did not cause any regression, anti-fungal and anti- tuberculosis treatments were given empirically. None of the fungal agents or *M. Tuberculosis* bacillus were revealed by culture. After 6 months of treatment, cavernous lesions regressed and treatment was stopped.

Serum levels of immunoglobulins and lymphocyte subtypes were within normal ranges. Because he had complaints that were suggestive of asthma and allergic conjunctivitis, skin prick test was performed and positive result was found against house dust mites. A summary of laboratory evaluation is shown in Table I.

In the investigation of genetic causes of severe congenital neutropenia, mutation analysis for ELENA, HAX1, G6PC3 and GCSF receptor mutations were found to be negative in 2012. After identification of JAGN1 deficiency in 2014, the relevant gene was sequenced and a homozygous missense mutation was detected in exon 2 of JAGN1 gene (c 130 c>T , p. His 44 Tyr) (Fig. 1).

Table I. Laboratory evaluation of the patient.

	Patient's result	Normal values
Hemoglobin	10.9 g/dl	12-14 g/dl
Leukocytes	5120 / mm^3	4000-15000 / mm^3
Absolute neutrophil count (ANC)	0-200 / mm^3	1500-6000 / mm^3
Absolute lymphocyte count (ALC)	4200 / mm^3	1500-4000 / mm^3
Absolute eosinophil count (AEC)	500-1800 / mm^3	0-500 / mm^3
Absolute monocyte count (AMC)	300-4000 / mm^3	100-1000 / mm^3
Plateletes	357000/ mm^3	150000-450000 / mm^3
IgG level	898 mg/dl	842-1943 mg/dl
IgA level	67.2 mg/dl	62-390 mg/dl
IgM level	97 mg/dl	54-392 mg/dl
IgE level	17.6 KU/L	<161.3 KU/L
Lymphocyte subtypes (%)	CD3: 72,	55 – 78
	CD4: 38,	27 – 53
	CD8: 18,	19 – 34
	CD16+56: 12,	4 – 26
	CD19: 22,	10 – 31
	CD20:24,	10 – 30
	HLA-DR: 18	2-12
Genetic analysis	JAGN1 gene (c 130 c>T, p. His 44 Tyr	

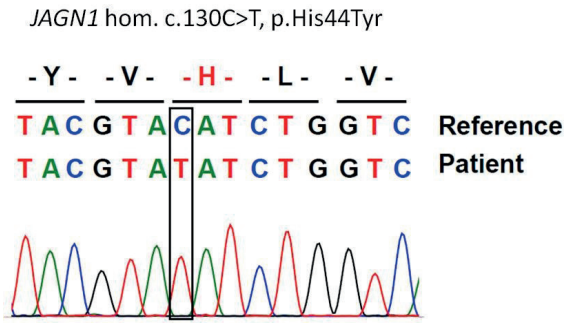

Fig. 1. Mutation analysis of the patient by sanger sequencing.

The patient is still being followed in our immunology department and receiving high doses of G-CSF (10 μg /kg). He requires hospitalization 2-3 times every year due to pneumonias and higher doses of G-CSF during infections, nevertheless, neutrophil counts have not increased adequately. Matched unrelated donor screening continues for bone marrow transplantation because of a lack of a family matched donor.

Informed consent was received from the parents before preperation of manuscript.

Discussion

In an animal study Wirnsberger et al.[9], showed, that JAGN1 deficient mice do not show neutropenia, they are characterized by increased susceptibility to fungal infections due to defective killing capacity of neutrophil granulocytes. In this report, we describe a patient with JAGN 1 mutation with different features which is not defined in the original report[8] and the report of Baris et al.[10] The original report including 14 patients described recurrent respiratory tract infections, sepsis, skin abscess and pancolitis. Multisystemic manifestations such as short stature, convulsion, bone abnormalities (hip dysplasia, amelogenesis imperfecta, osteoporosis, scoliosis), pyloric stenosis, pancreatic insufficiency and coarctation of aorta were also reported in this cohort.[8] Differently, our patient did not show any multisystem abnormalities except facial dysmorphism. Baris et al.[10] described urogenital abnormalities, short stature, learning disorders, hypothyroidism and hypogammaglobulinemia. In our patient no immunologic abnormalities were seen besides neutropenia. Now his main symptoms include cough, rhinorrhea and conjunctivitis, after recovering from serious infections which were frequent during his younger childhood years. They were considered due to a house dust mite allergy. An allergic condition has not been reported before in these patients. We think that it may be seen co-incidentally and needs further investigation.

Like the other patients in the original cohort, our patient did not respond to high dose G-CSF treatment.[8] Interestingly, in the mice study, the authors stated that JAGN1 knock out mice's neutrophils showed increased killing capacity with GM-CSF.[9] We could not try this type of CSF in our patient during his infections.

Homozygous missense mutation in the exon 2 detected in our patient was the same as the Turkish patients in the study of Baris et al.[10] and the original cohort.[8] In the series containing 14 patients, there were 2 Turkish patients carrying the same mutation as our patient. Skull bone thickness due to extramedullary hematopoesis were reported as a different clinical finding. We think that this mutation may be a common mutation in the Turkish population and may be used to screen for the etiology of severe congenital neutropenia in Turkish patients. Because of lack of hypogammaglobulinemia and multisystemic manifestations in our patient as in previous reported Turkish patients, we think that this type of mutation does not cause the same phenotype in all patients. The cause of multisystemic features of mutations in JAGN 1 gene remains unknown. All cases presented previously are summarized in Table II.

In conclusion, 3 patients were reported with the same JAGN 1 mutations and all were Turkish worldwide, all of them manifested with multisystemic congenital anomalies and neutropenia. We suggest that JAGN 1 gene mutation must be considered in patients with

Table II. The summary of all reported patients.[8,10]

	Gender	Country	Mutation	Beginning symptoms	Extrahematopoetic manifastations	Treatment and Clinical status
Patient 1	F	Algeria	c.3G>A; p.Met1Ile	ENT infections, aphtosis, perianal cellulitis, skin abscesses	None	Alive without treatment
Patient 2	F	Algeria	c.3G>A; p.Met1Ile	ENT infections,	Short stature (height of 1.46 m)	Alive without treatment
Patient 3	M	Algeria	c.3G>A; p.Met1Ile	Aphtosis, skin abscesses, balanitis, pneumonitis, lung abscess, osteitis perianal cellulitis	Pyloric stenosis	Alive without treatment
Patient 4	F	Algeria	c.3G>A; p.Met1Ile	Otitis, paraodontopathy	Scoliosis, dental malformations	Alive without treatment
Patient 5	M	Algeria	c.3G>A; p.Met1Ile	ENT infections, aphtosis, skin abscesses, pneumonitis, lung abscess, perianal cellulitis	None	Alive without treatment
Patient 6	F	Iran	c.59G>A; p.Arg20Glu	Upper respiratory tract infections, pneumonia, skin abscesses	Febrile convulsion, focal epilepsy	Alive without treatment
Patient 7	M	Turkey	c.130C>T; p.His44Tyr	Upper respiratory tract infections, pneumonia, skin and perianal abscesses, sepsis (Haemophilus influenza)	Extramedullary hematopoiesis with thickening of skull bones	Alive without treatment
Patient 8	F	Turkey	c.130C>T; p.His44Tyr	Upper respiratory tract infections, skin abscess	Bilateral hip dysplasia, extramedullary hematopoiesis with thickening of skull bones	Alive without treatment
Patient 9	F	Iran	c.40G>A; p.Gly14Ser	Skin abscesses, onycholysis	None	Alive without treatment
Patient 10	M	Israel	c.297C>G; p.Tyr99	Aspergillosis (none after HSCT)	Severe osteoporosis and repeated bone fractures (continuing after HSCT)	Alive with HSCT
Patient 11	F	Morocco	c.485A>G; p.Gln162Arg	Skin abscesses, omphalitis, pancolitis	Lipomatosis, pancreatic insufficiency, bone abnormalities, dental malformations	Died at age 5 years owing to pancolitis and septicemia
Patient 12	F	Albenia	c.63G>T; p.Glu21Asp	Upper respiratory tract infections, pneumonia, skin abscess	Short stature (5 cm below third percentile), amelogenesis imperfecta, neurodevelopmental delay	Alive without treatment

Table II. Continue.

	Gender	Country	Mutation	Beginning symptoms	Extrahematopoetic manifastations	Treatment and Clinical status
Patient 13	F	Pakistan	c.485A>G; p.Gln162Arg	ENT infections, upper respiratory tract infections, pneumonia, sepsis (Escherichia coli)	Failure to thrive (height 5 cm below third percentile, weight 3.8 kg below third percentile), coarctation of the aorta, mild developmental delay	Alive, awaiting HSCT
Patient 14	F	Germany	c.35_43del CCGACGGCA; p.Thr12_ Gly14del	Pneumonia (none after HSCT), bronchiectasis	None	Alive with HSCT
Patient 15	M	Turkey	c.130C>T, p. His44Tyr	Gluteal abscess, cervical lymphadenopathies, pneumonia, bronchiectasis, diarrhea, otitis and gingivitis	Failure to thrive, dysmorphic face, hypothyroidism, hypospadias and left undescended testis, hypogammaglobulinemia	Alive without treatment
Patient 16	F	Turkey	c.130C>T, p. His44Tyr	Recurrent skin abscesses, otitis and pneumonia	Learning disability, for triangular face, amelogenesis imperfecta, gingival hypertrophy and short stature, hypogammaglobulinemia	Alive without treatment
Our Patient	M	Turkey	c.130C>T, p. His44Tyr	Neonatal sepsis, ulcers and abscesses on lower extremities, recurrent pneumonia, otitis media and sinusitis	Triangular face, extrovert ears, allergic rhinoconjuntivitis with sensitization against house dust mites	Alive without treatment

ENT: Ear nose throat, HSCT: Hemopoetic stem cell transplantation.

severe congenital neutropenia especially those with facial dysmorphism even in the absence of multisystemic manifestations like our patient.

Acknowledgement

All Turkish authors are primary clinicians of the patient and wrote the manuscript. The authors from Austria performed genetic analysis of the patient. We thank all contributors and the patient's family as well as the patient.

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