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Research Article

Sheppard Siegal Syndrome (Familial Mediterranean fever): The Value of Serum Amyloid a in the Diagnosis and Treatment Decision

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Abstract:

Background: Sheppard Siegal syndrome was first described in 1945 by Sheppard Siegal. He described in details an extraordinary syndrome that was often undiagnosed because it was not clearly understood. The syndrome described by Siegal is characterized by recurrent attacks of fever, and commonly begins during childhood, and may begin as early as seven months. Attacks of the syndrome usually last two to three days and, often recur every few weeks. Siegal emphasized that progressive renal disease in the form of amyloidosis or chronic glomerulonephritis is the most serious organ involvement. Four mutations in the MEFV gene have been reported to account for 86% of the mutations causing Sheppard Siegal syndrome. Colchicine has been used for the treatment and prevention amyloidosis.

Patients and methods: The father of a 3.5-year Iraqi boy (Born on the 19th of March, 2018) of Kurdish origin living in Dubai consulted us during September, 2021 about the appropriate treatment of his son who was experiencing recurrent attacks of high fever over about one year. He consulted us after consulting few physicians in Dubai who were prescribing oral and injectable acetaminophen for the symptomatic control of fever during the attacks. The case was studied and an evidenced-based recommendation is presented in this paper.

Results: The attacks of fever were persisting for few days and were not generally associated with mo other significant symptoms other than the general ill health and tiredness that can be associate with fevers of various etiologies. Between the attacks, the boy was in good health and had normal activity. The father was unaware of a similar illness in their relatives. Serum amyloid A (EIA) was performed during the last attack of fever during August, 2021, and was very high (517mg/L), as the normal level is less than 6.40517mg/L. Analysis of regions of the MEFV gene showed no pathogenic variants were detected.

Conclusion: We have recommended monitoring serum amyloid A during attack free periods, and initiate colchicine therapy if serum amyloid A was found high to prevent the development of amyloidosis according to the evidence provided by Berkun et al (2007).

Keywords: sheppard siegal syndrome; serum amyloid; diagnosis and treatment; evidence-based medicine

Introduction:

Sheppard Siegal syndrome was first described in 1945 by Sheppard Siegal (Figure-1). He described in details an extraordinary syndrome that was often undiagnosed because it was not clearly understood.

Figure-1: *Dr. Sheppard Siegal, an internist who served as the chief of allergy services at Mount Sinai Medical Center. He graduated from the College of Physicians and Surgeons at Columbia University in 1932, and died at the age of 79 years*

The syndrome described by Siegal is characterized by recurrent attacks of fever which can be high and associated with abdominal pain that is attributed to peritoneal irritation. Leucocytosis and polymorphonucleosis are commonly observed during the attack. In 1949, Siegal emphasized that the occurrence of the syndrome in five male members of a one family confirmed the familial nature and suggested a genetic factor. Siegal also emphasized that all patients reported during the 1940s were Jewish or Armenian.

The syndrome described by Siegal commonly begins during childhood, and may begin as early as seven months. Attacks of the syndrome usually last two to three days and, often recur every few weeks

Siegal emphasized that progressive renal disease in the form of amyloidosis or chronic glomerulonephritis is the most serious organ involvement, but in the 50 patients he reported in 1964, 48 patients didn't develop nephropathy.

Siegal also emphasized the familial nature of the syndrome and that it commonly affects patients of Mediterranean origin including Jews (Ashkenazi and non-Ashkenazi), Armenians and Arabs and, less commonly, Italians, Maltese and Greeks [1].

Four mutations in the MEFV [MEditerranean FeVer] gene (a gene on 16p13.3, composed of 10 exons and spans about 14 Kb of genomic DNA, it encodes a protein whose function is not clearly known,) have been reported to account for 86% of the mutations causing Sheppard Siegal syndrome [1,2]. Colchicine has been used for the treatment and prevention amyloidosis [1, 2].

Patients and Methods

The father of a 3.5-year Iraqi boy (Born on the 19th of March, 2018) of Kurdish origin living in Dubai consulted us during September, 2021 about the appropriate treatment of his son who was experiencing recurrent attacks of high fever over about one year. He consulted us after consulting few physicians in Dubai who were prescribing oral and injectable acetaminophen for the symptomatic control of fever during the attacks. The case was studied and an evidenced-based recommendation is presented in this paper.

Results

The attacks of fever were persisting for few days and were not generally associated with mo other significant symptoms other than the general ill health and tiredness that can be associate with fevers of various etiologies. Between the attacks, the boy was in good health and had normal activity (Figure-2). The father was unaware of a similar illness in their relatives.

Figure-2: *Between the attacks, the boy was in good health*

A previous attack of fever which occurred early during July, 2021, was associated with abdominal pain. Urinalysis and abdominal ultrasound showed normal findings.

Laboratory tests (Table-1) showed normal blood sugar, renal and liver function tests, and normal serum electrolytes. However, C-reactive protein was high, while serum alkaline phosphatase was low. Blood counts showed monocytosis and low eosinophil count.

Laboratory Tests performed		
Test	**Value**	**Normal value**
Hemoglobin	10.9 g/dL	10-14 g/dL
RBC	4.37 $x10^{12}$/L	4.2-5 $x10^{12}$/L
MCV	73.9 fL	73-86 fL
MCH	24.9 pg/cell	23-31 pg/cell
MCHC	33.7 g/dL	30-35 g/dL
RDW-CV	12.9 %	11.6-14.6%
Platelet	188 $x10^9$/L	150-450 $x10^9$/L
WBC	7.97 $x10^9$/L	4.9-15.5 $x10^9$/L
Neutrophils	4.79 $x10^9$/L (60.1%)	1.8-8$x10^9$/L (40-75 %)
Lymphocytes	1.85 $x10^9$/L (23.2 %)	1.7-5.5$x10^9$/L (20-50 %)
Eosinophils	0.01 $x10^9$/L (0.1%) (**Low)**	0.09-1.04 $x10^9$/L (1-8%)
Monocytes	1.28$x10^9$/L (16.1%) (**High)**	0.15-1.28 $x10^9$/L (2-10%)
Basophils	0.04 $x10^9$/L (0.5%)	0.02-0.12 $x10^9$/L (0-2%)
Serum urea	17 mg/dL	15-36 mg/dL
Serum creatinine	0.41 mg/dl	0.3-1mg/dL
Serum C-reactive protein	193.2 mg/L **(High)**	0-5 mg/L
Serum random blood sugar	95.86 mg/dL	80-110 mg/dL
Serum SGOT	34 unit/L	21-44 unit/L
Serum SGPT	18 unit/L	0-30 unit/L
Serum alkaline phosphatase	136 unit/L **(Low)**	156-369 unit/L
Serum bilirubin	0.3 mg/dL	0.2-1.2 mg/dL
Direct serum bilirubin	0.15 mg/dL	0-0.5 mg/dL
Serum albumin	3.6 g/dL	3.5-5 g/dL
Serum sodium	137 mmol/L	136-145 mmol/L
Serum potassium	3.9 mmol/L	3.5-5.1 mmol/L
Serum chloride	101 mmol/L	98-107 mmol/L
Serum bicarbonate	22 meq/l	14-24 meq/l

Table 1: *Laboratory tests performed during a previous attack of fever (July, 2021)*

Serum amyloid A (EIA) was performed during the last attack of fever during August, 2021, and was very high (517mg/L), as the normal level is less than 6.40517mg/L.

Analysis of regions of the MEFV gene was performed during September, 2021. PCR amplification and Sanger sequencing analysis of a segment of exon 2, exon 3 and exon 10 and exon-intron boundaries (±8 bp) of the MEFV gene (NM_000243.2; chr.16). The performed analysis was expected to detect most frequent mutations, present in approximately 70-90% of the cases of familial Mediterranean fever, according to the geographical distribution. Variant classification and reporting are performed according to international recommendations [3].

The performed analysis cannot exclude variants outside analyzed regions or not detected by this methodology (for example, gross deletions or duplications, triplet repeat expansions, epigenetic modifications, variants with low level mosaicism). Primer design was performed in order to guarantee specificity and in regions without known genetic variability.

Nevertheless, it cannot be excluded that pseudogene sequences or highly homologous sequences interfere with the technical ability to identify the variants present in this analysis. Additionally, allele dropout cannot be excluded due to the occurrence of rare polymorphisms that might interfere with primer annealing.

Analysis of regions of the MEFV gene showed no pathogenic variants were detected.

We have recommended monitoring serum amyloid A during attack free periods, and initiate colchicine therapy if serum amyloid A was found high to prevent the development of amyloidosis according to the evidence provided by Berkun et al (2007) [8].

Discussion

The patient in this report had markedly elevated C-reactive protein and serum amyloid A, and monocytosis.

Drenth et al (1995) emphasized that the pathogenesis of Sheppard Siegal Syndrome remained unknown, but the attacks are generally associated with an acute-phase response including an increase of serum C-reactive protein during attacks, but it is lowered between attacks [4].

Gunes et al (2017) emphasized the diagnostic value of the association of attacks of Sheppard Siegal syndrome with elevated levels of C-reactive protein, and serum amyloid and monocytosis [5].

Ben-Zvi et al (2015) emphasized that in 10-20% of Sheppard Siegal syndrome patients have no FMF gene (MEFV) mutations.

They compared 47 mutation free patients with 60 patients who were genetically heterogeneous and 57 patients who had homozygous M694V mutation. MEFV-mutation negative FMF patients showed a very similar disease to that of the other 2 groups. However, patients having homozygous M694V had a more severe disease and experienced less chest and erysipelas like attacks, less chronic manifestations, older age of disease onset, and lower colchicine dose [6].

Padeh et al (2010) studied 254 patients who experienced the first attack of Sheppard Siegal syndrome at < or =2 years of age (Mean age at onset of 1.1 +/- 0.8 years), and compared them with 242 patients who experienced the first attack of syndrome between 2 to 16 years. Patients in the two groups had similar manifestations, but the delay in diagnosis was longer in patients having early onset. Sixty of 254 patients who received the diagnosis of the Sheppard Siegal syndrome at < or =2 years had the highest rate of attacks of fever alone as their sole manifestation (40.0% vs. 8.4%, P < .05), and less peritonitis (45% vs. 86.1%, P < .05) and pleuritis (3.4% vs. 32.9%, P < .05).

Padeh et al emphasized that in early life, Sheppard Siegal syndrome often begins with an atypical presentation, characterized by attacks of fever alone, and diagnosis and treatment can be delayed for long time [7].

Berkun et al (2007) emphasized that many patients with Sheppard Siegal syndrome have increased serum amyloid A even during attack-free intervals, and therefore have higher risk of developing amyloidosis [8]. They reviewed 204 patients who had serum amyloid A measurements, including 29% for diagnostic purposes, and 71% for adjustment of colchicine dose.

Elevated serum amyloid A levels were found in a third of patients with Sheppard Siegal syndrome during an attack-free period. The highest rate of elevated serum amyloid A levels was found in patients with proteinuria (60% of this patient group), followed by noncompliant (40%) and genetically positive asymptomatic patients (38%).

Elevated serum amyloid A levels during remission were associated with family history of Sheppard Siegal syndrome, M694V homozygosity, and elevated C-reactive protein (P<0.05 for each).

Patients homozygous for the M694V mutation had the highest level of serum amyloid A. Serum amyloid a measurement led to a change in colchicine dose in 30% of the patients, predominantly in noncompliant patients and patients with proteinuria or with atypical manifestations.

Berkun et al emphasized the diagnostic value of increased serum amyloid level in patients with Sheppard Siegal syndrome and its assessment can help in the adjustment of the colchicine dose [8].

Conclusion:

We have recommended monitoring serum amyloid A during attack free periods, and initiate colchicine therapy if serum amyloid A was found high to prevent the development of amyloidosis according to the evidence provided by Berkun et al (2007) [8].

Acknowledgment

The author is grateful for the father who kindly accepted publishing the boy's photo.
Figure-1 was included in author's previous publications, but the author has its copyright.

Conflict of interest: None.

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