Research Article

International Journal of Endocrinology Research and Reviews

Sheppard Siegal Syndrome (Familial Mediterranean Fever) With Homozygous M694v Gene Mutation and Saa1 Amyloidosis Gene Genotype 1.1/1.5: Documenting the Occurrence in An Iraqi Girl, And an Evidence-Based Therapeutic Recommendation

Aamir Jalal Al-Mosawi

Advisor and expert trainer, The National Training and Development Center Iraqi Ministry of Health, Baghdad, Iraq

***Corresponding author**
Aamir Jalal Al-Mosawi, Advisor and expert trainer, The National Training and Development Center, Iraqi Ministry of Health, Baghdad, Iraq. E-mail:almosawiAJ@yahoo.com

Submitted: 11 Jan 2022; **Accepted:** 18 Jan 2022; **Published:** 25 Jan 2022.

Citation: *Aamir Jalal Al-Mosawi (2022) Sheppard Siegal syndrome (Familial Mediterranean fever) with homozygous M694V gene mutation and SAA1 amyloidosis gene genotype 1.1/1.5: Documenting the occurrence in an Iraqi girl, and an evidence-based therapeutic recommendation. International Journal of Endocrinology Research and Reviews 2(1) : 01-04.*

Abstract

Background: *Sheppard Siegal syndrome was first described in 1945 by Sheppard Siegal who described in details an extraordinary syndrome that was often undiagnosed because it was not clearly understood. Siegal suggested that the syndrome are constant is characterized by recurrent paroxysms of severe abdominal pain with fever which can high. Four mutations in the MEFV gene have been reported to account for 86% of the mutations causing Sheppard Siegal syndrome. Nothing is known is known about the genetic mutations causing Sheppard Siegal syndrome in Iraqi children.*

Patients and methods: *An Iraqi girl from Al-Anbar province with Sheppard Siegal syndrome was studied, and the relevant literatures were reviewed with the aim of suggesting an evidence-based therapeutic recommendation.*

Results: *An 11-year old Iraqi girl was having recurrent attacks of fever, abdominal pains, and pains in her limbs. Mutation analysis of MEVF gene covering twelve mutations (E148Q, P369S, F479L, M6801 (G/C), 169del, M694V, M694I, K695, V726A, A744S, R761H) was performed. The analysis showed that the patient was homozygous for M694V gene mutation and also had the serum amyloid A1 (SAA1) gene, genotype 1.1/1.5. Although, polymorphism in the SAA1 gene is not present in this patient, we recommended early treatment with colchicine no just to prevent the recurrence of inflammatory attacks, but also to prevent the development of renal amyloidosis.*

Conclusion: *Nothing is known is known about the genetic mutations causing Sheppard Siegal syndrome in Iraqi children. However, we reported an Iraqi girl with Sheppard Siegal syndrome caused by homozygous M694V gene mutation. In addition, we provided an evidence-based therapeutic recommendation for the patient.*

Keywords: Sheppard Siegal syndrome, Iraq, colchicine.

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

Siegal suggested that the characteristics of the syndrome are constant and distinctive. It is characterized by recurrent paroxysms of severe abdominal pain with fever which can high. Chilliness or a shaking chill can also be associated with the recurrent attacks. Siegal attributed peritoneal involvement to the symptom of abdominal soreness and the presence of widespread, exquisite direct and rebound tenderness [1].

In 1949, Sheppard Siegal described six new patients with the new syndrome which he called "Benign paroxysmal peritonitis" during that time. According to Siegal the syndrome begins in early in life and patients continues to experience attacks for years. The syndrome described by Siegal is characterized by recurrent paroxysms of abdominal pain with clinical evidence of peritoneal irritation. Attacks can be associated with high fever, and leucocytosis and polymorphonucleosis are commonly observed during the attack. Chest pain that is worse on inspiration may occur during the attacks which may recur at a variable intervals ranging from one month years. The patients are generally well between attacks. Siegal thought the symptoms can sometime be similar to acute surgical abdominal conditions such as appendicitis.

Three of the six patients reported by Siegal have been operated upon during an attack, and operative findings included hyperemia or edema of the peritoneum, with or without serous or sero-fibrinous exudate.

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.

Siegal suggested the presence of relation of the syndrome with allergy, as of eleven having the syndrome, two patients were atopic and an other four patients had a definite family history of allergy. Siegal emphasized that neither adrenalin nor the antihistamines could control the attacks of the syndrome [2].

In 1964, Siegal described his 50 personally observed patients (36 males and 14 females) of the syndrome which he called during that time "Familial paroxysmal polyserositis". Three patients died because of renal failure or cardiac failure which was associated with I rheumatic mitral stenosis.

In 1964, Siegal suggested that the recurrent febrile syndrome of serosal inflammation may present as paroxysmal peritonitis (with paroxysmal pleuritis) which is the most common manifestation. The second most frequent presentation is intermittent arthralgias, monoarthritis and paroxysmal pyrexia. Cutaneous eruptions are sometimes observed [3].

The syndrome commonly begins during childhood or in youth, and the earliest age at onset reported by Siegal was seven months, while the latest age of onset was forty-three years. Attacks of the syndrome usually last two to three days and, often recur every few weeks.

Siegal emphasized that progressive renal disease is the most serious organ involvement, but in the 50 patients he reported in 1964, 48 patients didn't develop nephropathy. Two patients died because of chronic renal failure, and in one of them, chronic glomerulonephritis was observed at autopsy, while renal amyloidosis was found on biopsy in the second patient.

Siegal 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.

Of 50 patients described by Siegal in 1964, 42 patients were Jewish (35 were definite Ashkenazi, 3 were probable Ashkenazi. 4 Sephardic), seven patients were Armenians, and one patient was Maltese. The 50 cases included 10 familial cases including two families, Ashkenazi Jewish and Armenian, with five members affected.

Siegal also emphasized that treatment of the syndrome was generally not satisfactory, but the use corticosteroids has been definitely useful in terminating attacks in three of fifteen patients [3].
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 (Brik et al, 1999) [4]. Colchicine has been used for the treatment and prevention amyloidosis [4-9]. Nothing is known is known about the genetic mutations causing Sheppard Siegal syndrome in Iraqi children.

Patients and methods

An Iraqi girl from Al-Anbar province with Sheppard Siegal syndrome was studied, and the relevant literatures were reviewed with the aim of suggesting an evidence-based therapeutic recommendation.

Results

An 11-year old Iraqi girl was having recurrent attacks of fever, abdominal pains, and pains in her limbs. Mutation analysis of MEVF gene covering twelve mutations (E148Q, P369S, F479L, M6801 (G/C), 169del, M694V, M694I, K695, V726A, A744S, R761H) was performed.

The analysis showed that the patient was homozygous for M694V gene mutation and also had the serum amyloid A1 (SAA1) gene, genotype 1.1/1.5.

Although, polymorphism in the SAA1 gene is not present in this patient, we recommended early treatment with colchicine no just to prevent the recurrence of inflammatory attacks, but also to prevent the development of renal amyloidosis. Our therapeutic recommendation was based on the evidence provided by Mimouni et al (2000), Ben-Chetrit (2003), Barut et al (2018) [6,7,9].

Discussion

Dewalle et al (1998) suggested that Sheppard Siegal syndrome is a relatively common recessive disease in non-Ashkenazi Jews, and the M694V mutation was found in about 80% of Jewish patients (Iraqi and North African) with Sheppard Siegal syndrome. Dewalle et al studied 109 Jewish patients who had Sheppard Siegal syndrome with 0, 1 or 2 M694V mutations. They found that homozygous for M694V mutation had considerably more severe

disease that started earlier (mean age 6.4 +/- 5 vs. 13.6 +/- 8.9) and developed arthritis and pleuritis twice as in patients with one or no M694V mutation. In addition, all the three patients with amyloidosis displayed had M694V mutations. However, there was no association between homozygous M694V mutation with fever, peritonitis, response to colchicine and erysipeloid eruption [5].

Livneh et al (1999) emphasized that Sheppard Siegal syndrome is an important cause of amyloidosis, 16 mutations in MEFV gene can cause the disease. Livneh et al 178 patients with Sheppard Siegal syndrome including 30 developed amyloidosis. The examined MEFV gene for 4 mutations. Mutations were found in 29 of the patients who had amyloidosis patients, and 27 of them were homozygous for M694V. One patient was homozygous for both V726A and E148Q. In another patient E148Q and V726A were found on one allele, while V726A was found on the second allele. The study of Livneh et al suggested that amyloidosis was much commoner in patients homozygous for M694V than in patients with other mutations ($P < 0.0001$). In three patients homozygous for M694V, amyloidosis was the only expression of the mutation [10].

Brik et al (1999) studied 70 patients with Sheppard Siegal syndrome and performed analysis for four mutations (M694V, M680I, V726A, M694I). M694V mutation was found in 92% of non-Ashkenazi Jewish patients, and in only 30% of the Arab patients. However, the four mutations were found in 94% of the Arab patients, but without particular prevalence for any one.

Brik et al found that patients having homozygous M694V mutation were much more likely to have severe disease with an earlier age of onset, and more frequent attacks. Only patients with the M694V mutation had a family history of amyloidosis. Brik et al didn't find an association between the mutation type and the predominance of fever, abdominal pain, pleuritis, skin eruption, or response to colchicine.

Brik et al thought that Sheppard Siegal syndrome generally has a milder course and a better prognosis in Arab patients than in non-Ashkenazi Jewish patients [4].

Cazeneuve et al (2000) studied 137 Armenian patients with Sheppard Siegal syndrome from 127 families living in Armenia. They found that SAA1alpha/alpha genotype was associated with 7 times higher risk for developing renal amyloidosis, compared with other SAA1 genotypes. This association, which was present whatever the MEFV genotype, and the risk was much more in patients homozygous for M694V (11/11). Polymorphisms in the SAA2 or APOE gene were not associated with susceptibility to renal amyloidosis [11].

Delibaş et al (2005) studied 50 patients with Sheppard Siegal syndrome, and found that the most common MEFV mutation and SAA1 genotype were M694V/M694V in 26 of 50 patients and SAA1 alpha/alpha in 26 of 50 patients [12].

Atoyan et al (2016) studied 1017 patients with familial Sheppard Siegal syndrome from the database of the Center of Medical Genetics in Yerevan. They found that patients with homozygous M694V mutation were greatly associated with the clinical features of Sheppard Siegal syndrome and renal amyloidosis. None of the SAA1 polymorphisms had any correlation with Sheppard Siegal syndrome clinical features. However, homozygosity for SAA1 α/α polymorphism was associated with development of renal amyloidosis while the β/β polymorphism was protective against amyloidosis [13].

Mimouni et al (2000) studied 382 patients with Sheppard Siegal syndrome including North African Jews, other Jews, Turks, Armenians living in the United States, and Armenians from Yerevan in Armenia. They found an important association between M694V homozygosity and the development of amyloidosis. Amyloidosis developed in 44 of 171 M694V homozygous patients (25.7%), but in 22 of 143 compound M694V heterozygous patients (15.4%), and in 7 of 57 patients with other mutations (12.3%).

According to Mimouni et al, M694V homozygous patients not treated with colchicine before the age of 20 years had a 61.0% risk of developing amyloidosis before the age of 20. Therefore, Mimouni et al recommended that M694V homozygous patients receive colchicine irrespective of the severity of the periodic inflammation with the aim of preventing the development of amyloidosis [6].

Ben-Chetrit (2003) suggested that the risk of amyloidosis is higher in male patients with Sheppard Siegal syndrome and in patients having polymorphism a/a in the SAA1 gene. Ben-Chetrit emphasized that colchicine is the treatment of choice and it can prevent the development of amyloidosis [7].

Sarkisian et al (2008) reported that of the 12 MEFV mutations found in 7000 Armenian patients with Sheppard Siegal syndrome, in the heterozygote state the most severe disease was associated with a single M694V mutation [14].

Inal et al (2009) followed 124 children with Sheppard Siegal syndrome for 18 years. 105 patients had at least one MEFV gene mutation. M694V homozygosity was the most common mutation, followed by M694V heterozygotes and M694V-M680I compound heterozygotes. The findings of Inal et al supported the previously published data that M694V homozygote and compound heterozygote states for M694V were associated with a more severe disease [15].

Başaran et al (2015) reported their experience with the treatment of 8 children(6 males, 2 females) with Sheppard Siegal syndrome refractory or unresponsive to colchicine, who continue to experience severe and frequent attacks and/or having high acute phase reactance levels despite treatment with the maximum dose of colchicine (2 mg/daily). Six patients had homozygous M694V mutations, one patient had heterozygote M694V mutation, and one patient had no mutation. The patients were treated successfully with anakinra and/or canakinumab, and no patients developed any severe adverse effects [8].

Barut et al (2018) reported 708 patients (362 males and 346 females) with Sheppard Siegal syndrome treated with colchicine for a minimal of six months. Abdominal pain was present in 634 patients (89.5%), and was the commonest manifestation. Fever was

present in 629 patients (88.8%), while arthritis was present in 288 (40.7%). In 23 patients with arthritis, an additional diagnosis of juvenile idiopathic arthritis was also made.

M694V mutation (Homozygote or heterozygote) was commoner in patients with arthritis .Erythrocyte sedimentation rate and CRP level were in high levels even during attack-free period in 97 of 697 patients (13.9%) and in 78 of 670 patients (11%) respectively.

Proteinuria was observed in ten patients (1.4%), and renal amyloidosis was diagnosed by renal biopsy in only two patients who had homozygous M694V mutation or compound heterozygous M694V/M680I mutation. 47 patients (6.6%) were resistant to colchicine therapy including 30 patients with homozygote M694V mutation.

Barut et al supported the previously published data suggesting that homozygous M694V mutation is the most likely mutation to be associated with more severe disease.

Barut et al emphasize that treatment of Sheppard Siegal syndrome which include prevention of renal amyloidosis require strict compliance to colchicine therapy [9].

Conclusion

Nothing is known is known about the genetic mutations causing Sheppard Siegal syndrome in Iraqi children. However, we reported an Iraqi girl with Sheppard Siegal syndrome caused by homozygous M694V gene mutation. In addition, we provided an evidence-based therapeutic recommendation for the patient.

Acknowledgement

Conflict of interest: None.

References

1. Siegal S. Benign paroxysmal peritonitis: Second Series.Gastroenterology1949 Feb; 12(2):234-47. Doi: 10.1016/S0016-5085(49)80034-5
2. Siegal S. Benign paroxysmal peritonitis. Ann Int Med Jul 1945; 22: 1. Doi: 10.7326/ 0003-4819-23-1-1.
3. Siegal S. Familial paroxysmal polyserositis: Analysis of fifty cases. The American Journal of Medicine Jun 1964; 36 (6): 893-918. Doi: 10.1016/0002-9343(64)90119-6
4. Brik R, Shinawi M, Kepten I, Berant M, Gershoni-Baruch R. Familial Mediterranean fever: clinical and genetic characterization in a mixed pediatric population of Jewish and Arab patients. Pediatrics 1999 May; 103(5):e70. Doi: 10.1542/peds.103.5.e70
5. Dewalle M, Domingo C, Rozenbaum M, Ben-Chétrit E, Cattan D, Bernot A, Dross C, Dupont M, Notarnicola C, Levy M, Rosner I, Demaille J, Touitou I. Phenotype-genotype correlation in Jewish patients suffering from familial Mediterranean fever (FMF). Eur J Hum Genet 1998 Jan; 6(1):95-7. Doi: 10.1038/sj.ejhg.5200170.
6. Mimouni A, Magal N, Stoffman N, Shohat T, Minasian A, Krasnov M, Halpern GJ, Rotter JI, Fischel-Ghodsian N, Danon YL, Shohat M. Familial Mediterranean fever: effects of genotype and ethnicity on inflammatory attacks and amyloidosis. Pediatrics 2000 May; 105(5):E70. Doi: 10.1542/peds.105.5.e70. PMID: 10799634.
7. Ben-Chetrit E. Familial Mediterranean fever (FMF) and renal AA amyloidosis--phenotype-genotype correlation, treatment and prognosis. J Nephrol 2003 May-Jun; 16(3):431-4. PMID: 12832747.
8. Başaran Ö, Uncu N, Çelikel BA, Taktak A, Gür G, Cakar N. Interleukin-1 targeting treatment in familial Mediterranean fever: an experience of pediatric patients. Mod Rheumatol 2015 Jul; 25(4):621-4.Doi:10.3109/14397595.2014.987437. PMID:25528863.
9. Barut K, Sahin S, Adrovic A, Sinoplu AB, Yucel G, Pamuk G, Aydın AK, Dasdemir S, Turanlı ET, Buyru N, Kasapcopur O. Familial Mediterranean fever in childhood: a single-center experience. Rheumatol Int 2018 Jan; 38(1):67-74.Doi: 10.1007/s00296-017-3796-0. PMID: 28828621.
10. Livneh A, Langevitz P, Shinar Y, Zaks N, Kastner DL, Pras M, Pras E. MEFV mutation analysis in patients suffering from amyloidosis of familial Mediterranean fever. Amyloid 1999 Mar; 6(1):1-6. Doi: 10.3109/13506129908993281. PMID: 10211405.
11. Cazeneuve C, Ajrapetyan H, Papin S, et al. Identification of MEFV-independent modifying genetic factors for familial Mediterranean fever. Am J Hum Genet. 2000 Nov; 67(5):1136-43.Doi: 10.1016/S0002-9297(07)62944-9. PMID: 11017802.
12. Delibaş A, Oner A, Balci B, Demircin G, Bulbul M, Bek K, Erdoğan O, Baysun S, Yilmaz E. Genetic risk factors of amyloidogenesis in familial Mediterranean fever. Am J Nephrol. 2005 Sep-Oct; 25(5):434-40. Doi: 10.1159/000087824. PMID: 16118480.
13. Atoyan S, Hayrapetyan H, Sarkisian T, Ben-Chetrit E. MEFV and SAA1 genotype associations with clinical features of familial Mediterranean fever and amyloidosis in Armenia. Clin Exp Rheumatol 2016 Sep-Oct; 34(6 Suppl 102):72-76. PMID: 27791951.
14. Sarkisian T, Ajrapetian H, Beglarian A, Shahsuvarian G, Egiazarian A. Familial Mediterranean Fever in Armenian population. Georgian Med News 2008 Mar ;(156):105-11. PMID: 18403822.
15. Inal A, Yilmaz M, Kendirli SG, Altintas DU, Karakoc GB. The clinical and genetical features of 124 children with Familial Mediterranean fever: experience of a single tertiary center. Rheumatol Int. 2009 Sep; 29(11):1279-85.Doi: 10.1007/s00296-008-0831-1. PMID: 19115056.