An Algerian Family with TNF Receptor Associated Periodic Syndrome (TRAPS) Associated Amyloidosis and the p.Thr79Met Mutation

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Keywords: TRAPS; Algeria; FMF; AA Amyloidosis

Abbreviations
CRP: C-Reactive Protein; FMF: Familial Mediterranean Fever; IL: Interleukin; MEVF: Mediterranean Fever; SAA: Serum Amyloid A Protein; TNFRSF1A: (TNF) Tumor Necrosis Factor Receptor Super Family 1A; TRAPS: (TNF) Receptor Associated Periodic Syndrome

Abstract
We report the case of a 36-year-old woman of Algerian descent on dialysis for renal AA amyloidosis. She reported since the age of 6 years recurrent episodes of 2 weeks duration characterized by fever, weakness, abdominal pain, myalgias, arthralgias, erythema, and chest pain. Diagnosis of TRAPS was confirmed by the presence of heterozygous p.Thr79Met mutation in TNFRSF1A. Genetic evaluation of all affected members of her family disclosed the p.Thr79Met mutation in TNFRSF1A, including one patient with amyloidosis. Genotype-phenotype correlations revealed variable clinical presentation and incomplete penetrance. TRAPS is a rare Mendelian auto-inflammatory disease that may be observed in populations where familial Mediterranean fever is highly prevalent. In this context, a high level of clinical suspicion is mandatory to evoke the diagnosis of TRAPS and initiate the appropriate treatment in order to prevent AA amyloidosis and its renal consequences.

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Case Description
The proband (II/7 Figure 1) is a 36-year-old woman native of southern Algeria. Her parents were first cousins. She was hospitalized in February 2013 for kidney biopsy in front of nephrotic syndrome and renal insufficiency (creatinine clearance at 45 mL/min). She has a history of recurrent inflammatory attacks since the age of 6 years. These attacks are characterized by fever of more than 15 days and fasciitis affecting the limbs with a typical migrating proximal to acral evolutive pattern during the attack. Other symptoms during attacks are abdominal pain first localized then diffuse at the acme of the fever, arthralgias with no signs of arthritis, headache, periorbital edema, and fatigue. She underwent an appendicectomy at the age of 10 that did not suppress recurrent abdominal attacks. Some attacks were triggered by physical stress and menstruation. At the age of 35 years, the patient presented with a major edematous syndrome and orthostatic hypotension, proteinuria at 3 g/day and hypoalbuminemia at 14 g/L.
Inflammation was present with C-reactive protein (CRP) at 120 mg/L and anemia (hemoglobin 9 g/dL). Immunological workup was unremarkable for autoimmune diseases (normal complement, C3, C4, negative anti-nuclear antibodies, anti-DNA and anti-neutrophil cytoplasm antibodies), while serum protein electrophoresis and immunofixation excluded gammopathies. Kidney biopsy disclosed AA amyloidosis (Figure 2).

Finally genetic study was done after informed consent obtained from the patient and all of her family (Figure 1) that showed no mutation in the MEVF gene and disclosed the p.Thr79Met (formerly T50M) mutation in the TNFRSF1A gene at the heterozygote state. Since August 2013, the patient has been on chronic hemodialysis with many complications: hypotension, recurrent thrombosis of the fistula. Attacks are less frequent, spaced with one each six months, but remain very painful especially when fasciitis occurs on the side of the fistula with hyperleukocytosis, thrombocytosis and CRP at 130 mg/L. Attacks remain responsive to intravenous corticosteroid therapy. Amyloidosis is still evolutive as the patient has developed a probable amyloid goitre.

Her father, (Patient I/2 Figure 1) aged 70 years is on hemodialysis since the age of 52 for chronic renal disease of undetermined cause. He had a long history of recurrent attacks since the age of 12 years with approximately 3 attacks per year. Attacks last 15 days with fever, fasciitis, arthralgias, abdominal pain, unilateral scrotitis, periorbital edema. Edematous syndrome appeared at the age of 38 years and hemodialysis was started at the age of 40. Since he has been on hemodialysis, the patient has remained free of clinical inflammatory attacks; fistula performed at the left radial artery 30 years ago is still functional. He has developed a euthyroid goiter, and his CRP remains normal. Salivary gland biopsy returned in favor of AA amyloidosis (Figure 3).
gradually up to 3 mg/day for one year without any clinico-biological
no overt clinical renal disease and salivary gland biopsy showed no
mutation and is still healthy.

in TNFRSF1A at the heterozygote state. Since 2015 the patient is under
10 mg/day of corticosteroids and remains free of symptoms of TRAPS.

presented with the same symptoms as her elder sister since age 6, with
arthralgias of the large joints, scrotitis and migrating skin lesions of the
limbs. Colchicine was
maximum. His twin (II/12) is also heterozygous for the
mutation found in
TNFRSF1A. Since 2015 the patient is treated with prednisone 10
mg/day. She is since clinically
improvement. Genetic study disclosed the same
mutation of the TNFRSF1A gene.

A sister, (Patient II/8 Figure 1) is a 34-year-old patient who
presented with the same symptoms as her elder sister since age 6, with
a periodic biaunal attack of 2 weeks: fever, fasciitis, arthralgias, skin
lesions, appendectomy at the age of 20, but without renal involvement.
Salivary gland biopsy showed no abnormalities. Colchicine was started
ggradually up to 3 mg/day for one year without any clinico-biological
improvement. Genetic study disclosed the same p.Thr79Met mutation in
TNFRSF1A at the heterozygote state. Since 2015 the patient is under
10 mg/day of corticosteroids and remains free of symptoms of TRAPS.
Her CRP remains slightly elevated between 7 and 10 mg/L.

A brother (Patient II/11 Figure 1) aged 30 had similar symptoms in the
pediatric age, with a periodic biaunal attack of 2 weeks: arthralgias of the large joints, scrotitis and migrating skin lesions of the
limbs. Colchicine was inefficient to prevent attack's recurrences. He has
no overt clinical renal disease and salivary gland biopsy showed no
amyloid deposits. No mutation was found in MEFV and further study
disclosed the p.Thr79Met mutation at the heterozygote state in
TNFRSF1A. Since 2015 the patient is treated with prednisone 10
mg/day and has no clinical symptoms. His CRP is measured at 7 mg/L
maximum. His twin (II/12) is also heterozygous for the p.Thr79Met
mutation and is still healthy.

Another brother (II/2 Figure 1) is an asymptomatic man aged 40 in
good general condition with no specific history of inflammatory
attacks and no signs of renal disease. His daughter is a girl aged 15
(Patient III/1 Figure 1) with a history, since age 5 of quarterly
inflammatory attacks of fever, arthralgias, and skin lesions. The patient
had several hospitalizations in pediatric wards and the diagnosis of
untagged rheumatism was made and symptomatic treatment was
started. She was depressed because of prolonged bed rest. In 2014 she
had hemoglobin at 10 g/dl, a CRP at 20 mg/l and no renal disease.
Salivary gland showed no amyloid deposits. She was first treated with
colchicine at 2 mg/day without clinical or biological benefit and after
 genetic results with prednisone at 10 mg/day. She is since clinically
asymptomatic with a CRP at 10 mg/L. Both this patient and her father
harbor the p.Thr79Met mutation of the TNFRSF1A gene.

Discussion

We report a TRAPS family native to the south of Algeria. Clinical
presentation is quite typical of TRAPS phenotype with quarterly or
even semi-annual inflammatory attacks of 15 to 21 days. Symptoms
observed during attacks are: migratory fasciitis, arthralgias of large
joints, abdominal pain simulating a surgical emergency, unilateral
vaginalitis, with a frank acute phase response, all spontaneously
resolving in 15 to 28 days [4-6]. The p.Thr59Met mutation found in
this family has already been described in TRAPS patients belonging to
other populations [1]. Moreover, in our family, it segregates with the
disease as all clinically affected individuals over 3 generations harbour
the mutation. However, two individuals harbour this mutation and
remain currently free of clinical symptoms, thus conveying the
incomplete penetrance of the mutation in this family. Clinical
expression is relatively similar in all patients except for amyloidosis
that occurred in two of them and at a young age in the proband.
Amyloidosis is usually associated with mutations involving cysteine
residues that confer the most severe phenotype in TRAPS. However,
amyloidosis has already been reported with p.Thr59Met [5,6]. These
two characteristics: incomplete penetrance and variable expression of the
disease including the presence of amyloidosis have widely been
described in TRAPS [5,7].

The p.Thr79Met mutation of the TNFRSF1A gene is one of the most
frequent associated with TRAPS. It has been described in a number of
families, mainly of European ancestry [1]. To our knowledge it has not
been described in patients of Algerian origin. Several cases of TRAPS
patients have already been reported among the Arab population from
the Middle East (Iraq, Kuwait) and Maghreb (Mauritania) and in
Africans too, with other mutations (p.Thr66Ile, p.Cys72Tyr,
p.Thr79Lys) [8].

We wish to emphasize the delayed diagnosis of TRAPS in this family. Indeed, in the settings of a history of recurrent inflammatory
attacks and amyloidosis in a family belonging to a population where
FMF is frequent, this latter diagnosis was suspected and colchicine was
thus given to the patients. The mode of inheritance of the disease in
this family with consanguinity is compatible with a pseudo-dominant
mode of inheritance. Consanguinity is frequent in this population and
favours the emergence of recessive diseases such as FMF. In a second
step, the lack of efficacy of colchicine, the absence of MEFV mutations
and a more thorough analysis of the symptoms led to the hypothesis of
TRAPS in this family. The discovery of a mutation in the TNFRSF1A
gene confirmed the diagnosis that allowed a more accurate treatment for
the patient's attacks who were sensitive to steroids.

Conclusion

This family from southern Algeria has a long history of diagnostic
wandering. The strong consanguinity in this family is a deceptive
element since it reinforced the hypothesis of a recessive disease led to the wrong diagnosis of FMF and delayed the diagnosis of TRAPS. This emphasizes the importance of a precise analysis of the clinical symptoms in a context of recurrent familial fever in a country where FMF is highly prevalent as well as the interest of the negative therapeutic test with colchicine in this context. This case also highlights the value of the molecular diagnosis which led to a targeted therapeutic management.

Conflict of Interest

The authors have no conflict of interest to declare.

Consent Obtained

All patients and healthy family members gave written consent for genetic analysis and anonymous publication.

Ethical Approval for this Study

All the patients of this study have given writing consent formal consent is not required. This article does not contain any studies with humans or animals performed by any of the authors.

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