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An Algerian Family with TNF Receptor Associated Periodic Syndrome (TRAPS) Associated Amyloidosis and the p.Thr79Met Mutation: Long-Term Follow-Up and Therapeutic Challenges in a Resource-Limited Setting

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Abstract

We report the long-term follow-up of an Algerian family from the south of the country with TNF Receptor Associated Periodic Syndrome (TRAPS) associated with AA amyloidosis, carrying the heterozygous p.Thr79Met mutation in the *TNFRSF1A* gene. The proband, a 36-year-old woman, and her affected father (I/2) both died from complications of end-stage renal disease related to AA amyloidosis. Two other affected siblings (II/8 and II/11) developed AA amyloidosis with preserved renal function (creatinine clearance 60 and 78 mL/min, respectively) while on long-term corticosteroid therapy. A young niece (III/1) remains free of amyloidosis to date. Although anakinra, an

anti-IL-1 inhibitor, has been available in Algeria since 2020, all living patients have declined this treatment due to major logistical barriers: they reside in remote provinces, have limited financial resources, and are unable to travel monthly to Algiers to collect the syringes. They have thus opted to continue long-term corticosteroid therapy despite its potential limitations in preventing amyloid progression. This case series highlights the therapeutic challenges faced by TRAPS patients in resource-limited settings and emphasizes the need for decentralized access to biologic therapies to improve long-term outcomes.

Keywords: TRAPS, Algeria, FMF, AA Amyloidosis, p.Thr79Met, Corticosteroids, Anakinra, Therapeutic Challenges, Resource-Limited Setting

1. Introduction

TNF Receptor Associated Periodic Syndrome (TRAPS) is an autoinflammatory disorder characterized by recurrent attacks of fever associated with abdominal pain, myalgias, migratory erythematous skin rash, conjunctivitis, and periorbital edema [1]. In contrast to patients with familial Mediterranean fever (FMF), patients with TRAPS usually have a poor response to colchicine but a favourable response to corticosteroids and to interleukin (IL)-1 inhibitors. TRAPS has been described mostly in families of northern European descent; the most thoroughly characterized was a large pedigree of Irish and Scottish ancestry ascertained in Nottingham, England, whose illness was denoted familial Hibernian fever [2]. TRAPS is a very rare disease with an estimated prevalence of about one per million [3]. It has rarely been reported in Arabic populations, where FMF is in contrast highly prevalent. We report the first cases of TRAPS complicated by amyloidosis in a family from the south of Algeria, which was diagnosed late in the course of the disease. We herein present the long-term evolution of this family, highlighting the progressive nature of amyloid deposition even under corticosteroid treatment, as well as the significant therapeutic challenges imposed by geographical and socioeconomic barriers to accessing biologic therapies.

2. Case Description and Long-Term Follow-Up

2.1 Family pedigree (Fig 1)

The proband (II/7, Fig 1) was a 36-year-old woman native of southern Algeria. Her parents were first cousins. She was hospitalized in February 2013 for kidney biopsy in the setting of nephrotic syndrome and renal insufficiency (creatinine clearance 45 mL/min). She had a history of recurrent inflammatory attacks since the age of 6 years. These attacks were characterized by fever lasting 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 included abdominal pain, initially localized then diffuse at the acme of the fever, arthralgias with no signs of arthritis, headache, periorbital edema, and fatigue. She underwent an appendectomy 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.

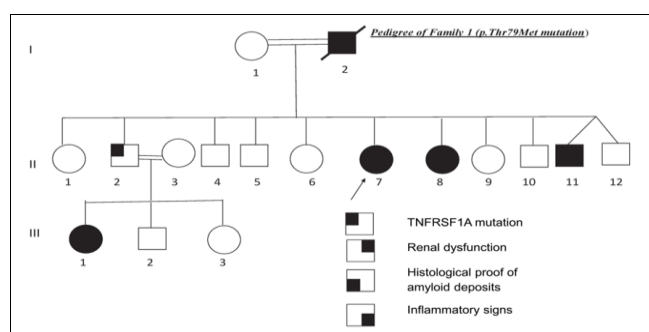
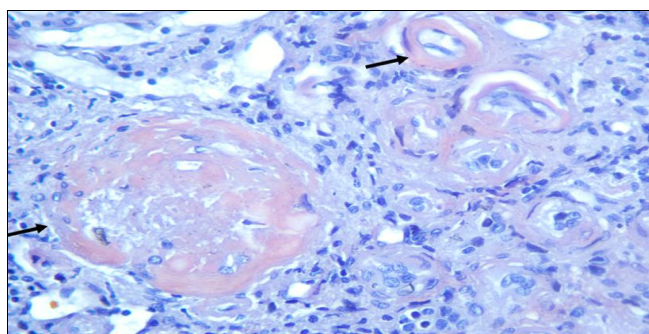
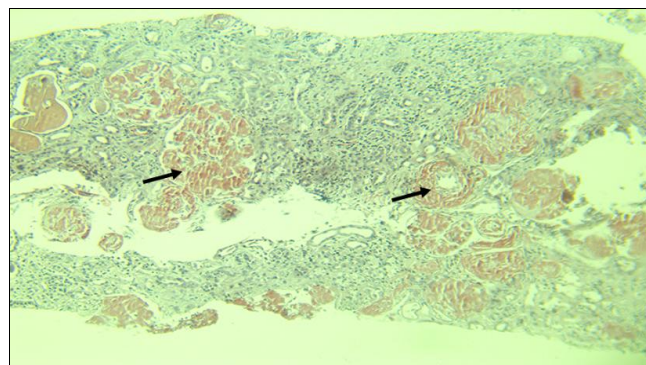


Fig 1: Pedigree of an Arabic Algerian family with TRAPS and AA amyloidosis. The p.Thr79Met mutation is present in Patients (I/2, II/2, II/7, II/8, II/11, II/12, and III/1). * indicates deceased patients. AA+ indicates patients with proven amyloidosis

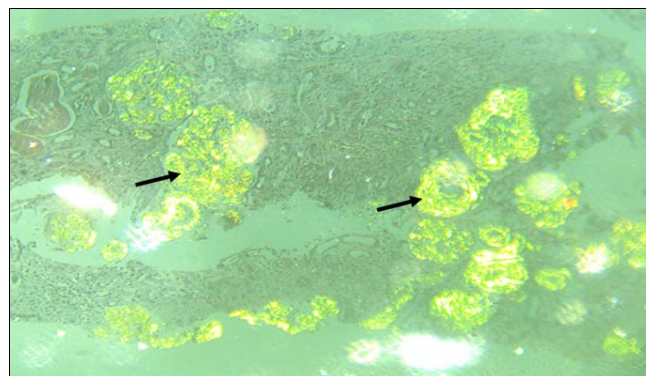
Inflammation was present with C-reactive protein (CRP) at 120 mg/L and anemia (hemoglobin 9 g/dL). Immunological workup was unremarkable for autoimmune diseases (normal complement C3, C4, negative anti-nuclear antibodies, anti-DNA and anti-neutrophil cytoplasm antibodies), while serum protein electrophoresis and immunofixation excluded gammopathies. Kidney biopsy disclosed AA amyloidosis (Fig 2, A, B, C). Genetic study, performed after informed consent, showed no mutation in the *MEFV* gene and disclosed the heterozygous p.Thr79Met (formerly T50M) mutation in the *TNFRSF1A* gene.



A: Trichrome Masson stain (×40): Amorphous eosinophilic deposits are visible in the glomerular mesangium and along the glomerular basement membrane, as well as in the arterial vessel wall



B: Congo red stain under transmitted non-polarized light (×20): The deposits appear brick red, confirming amyloid affinity



C: Congo red stain under polarized light (×20): Apple-green birefringence is observed in both glomerular and vascular deposits, diagnostic of AA amyloidosis. Gl = glomerulus; V = vessel

Fig 2: Renal biopsy of Patient II/7 (Fig 1). (A) Congo red; (B) Congo red under polarized light. Congo red stain disclosed amyloid deposits in the glomeruli, mainly in the mesangium and in an interlobular artery

From August 2013, the patient was on chronic hemodialysis. She experienced many complications, including hypotension and recurrent thrombosis of the vascular access. Attacks became less frequent, with one episode every six months, but remained very painful, especially when fasciitis occurred on the side of the fistula, associated with hyperleukocytosis, thrombocytosis, and CRP at 130 mg/L. Attacks remained responsive to intravenous corticosteroid therapy. Amyloidosis was still evolutive, as the patient developed a probable amyloid goitre. Ultimately, the proband died from complications related to end-stage renal disease.

Her father (Patient I/2, Fig 1) was a 70-year-old man who had been on hemodialysis since the age of 40 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 lasted 15 days and included fever, fasciitis, arthralgias, abdominal pain, unilateral scrotitis, and periorbital edema. Edematous syndrome appeared at the age of 38 years, and hemodialysis was started at the age of 40. Since he had been on hemodialysis, the patient remained free of clinical inflammatory attacks; a fistula performed at the left radial artery 30 years ago remained functional. He developed a euthyroid goiter, and his CRP remained normal. Salivary gland biopsy returned in favour of AA amyloidosis. Genetic study showed no mutation in the *MEFV* gene and disclosed the same heterozygous p.Thr79Met mutation in *TNFRSF1A*. He later died from cardiovascular complications.

A sister (Patient II/8, Fig 1), aged 34 years, presented with the same symptoms as her elder sister since age 6, with a periodic biannual attack of 2 weeks: fever, fasciitis, arthralgias, and skin lesions. She underwent appendectomy at the age of 20, but without renal involvement. Colchicine was started gradually up to 3 mg/day for one year without any clinico-biological improvement. Genetic study disclosed the same heterozygous p.Thr79Met mutation in *TNFRSF1A*. Since 2015, the patient has been on long-term corticosteroid therapy (prednisone 10 mg/day) and remains free of clinical symptoms of TRAPS. Her CRP remains slightly elevated between 7 and 10 mg/L. However, long-term follow-up revealed the development of AA amyloidosis, confirmed by salivary gland biopsy. Her current creatinine clearance is 60 mL/min, indicating preserved but reduced renal function. She remains under regular nephrological surveillance but continues corticosteroid therapy as her sole treatment.

A brother (Patient II/11, Fig 1), aged 30 years, had similar symptoms in childhood, with a periodic biannual attack of 2 weeks: arthralgias of the large joints, scrotoitis, and migrating skin lesions of the limbs. Colchicine was inefficient in preventing attack recurrences. He had no overt clinical renal disease, and salivary gland biopsy initially showed no amyloid deposits. No mutation was found in *MEFV*, and genetic study disclosed the heterozygous p.Thr79Met mutation in *TNFRSF1A*. Since 2015, he has been treated with prednisone 10 mg/day and has no clinical symptoms. His CRP is measured at a maximum of 7 mg/L. Recent evaluation, however, disclosed AA amyloidosis on salivary gland biopsy, with a current creatinine clearance of 78 mL/min. He has no overt renal failure but shows persistent low-grade inflammation. He continues on corticosteroid monotherapy.

Another brother (II/2, Fig 1) is an asymptomatic man aged 40 years, in good general condition, with no specific history of inflammatory attacks and no signs of renal disease. His daughter (Patient III/1, Fig 1) is a 15-year-old girl with a history, since age 5, of quarterly inflammatory attacks of fever, arthralgias, and skin lesions. She had several hospitalizations in paediatric wards; a 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, CRP at 20 mg/L, and no renal disease. Salivary gland biopsy showed no amyloid deposits. She was first treated with colchicine at 2 mg/day without clinical or biological benefit; after genetic results, she was switched to prednisone at 10 mg/day. She has since been clinically asymptomatic, with a CRP at 10 mg/L. Repeated salivary gland biopsies and renal function tests (creatinine clearance >90 mL/min) have shown no evidence of AA amyloidosis to date. Both this patient and her father harbour the p.Thr79Met mutation of the *TNFRSF1A* gene.

The twin brother of II/11 (II/12) is also heterozygous for the p.Thr79Met mutation and remains healthy to date, illustrating incomplete penetrance.

2.2 Therapeutic Challenges and Patient Preferences

Since 2020, anakinra (an IL-1 receptor antagonist) has become available in Algeria for the treatment of TRAPS. This therapy has been proposed to all living affected patients (II/8, II/11, and III/1) as a more targeted and potentially more effective option to control inflammation and prevent

amyloid progression. However, all three patients have declined this treatment for practical and socioeconomic reasons. They reside in remote provinces in southern Algeria, several hundred kilometres from Algiers, where the medication is dispensed. Monthly travel to the capital to collect the syringes would impose a significant financial burden (transportation costs) and logistical hardship (time away from work and family). Furthermore, the patients lack adequate refrigeration facilities at home for storing multiple syringes, and they are not comfortable with self-injection. Consequently, they have elected to continue long-term oral corticosteroid therapy (prednisone 10 mg/day), which they can obtain from local health facilities, despite being aware of the potential limitations of this approach in fully halting amyloid deposition. This therapeutic decision reflects the real-world challenges of managing rare autoinflammatory diseases in resource-limited and geographically dispersed populations.

3. Discussion

We report a TRAPS family native to the south of Algeria. Clinical presentation is quite typical of the TRAPS phenotype, with quarterly or even semi-annual inflammatory attacks lasting 15 to 21 days. Symptoms observed during attacks are: migratory fasciitis, arthralgias of large joints, abdominal pain simulating a surgical emergency, unilateral scrotoitis, with a frank acute phase response, all spontaneously resolving in 15 to 28 days [4, 5]. The p.Thr79Met 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 three generations harbour the mutation. However, two individuals harbour this mutation and remain currently free of clinical symptoms (II/2 and II/12), thus conveying the incomplete penetrance of the mutation in this family.

Clinical expression is relatively similar in all patients except for amyloidosis, which occurred in four members (I/2, II/7, II/8, and II/11). 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.Thr79Met [5, 6]. These two characteristics—incomplete penetrance and variable expression of the disease, including the presence of amyloidosis have been widely described in TRAPS [6, 7].

The p.Thr79Met mutation of the *TNFRSF1A* gene is one of the most frequent mutations associated with TRAPS. It has been described in a number of families, mainly of European ancestry [1]. To our knowledge, it has not been previously described in patients of Algerian origin. Several cases of TRAPS have already been reported among Arab populations from the Middle East (Iraq, Kuwait) and the Maghreb (Mauritania), as well as in Africans, 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 setting 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, allowing a more appropriate treatment with corticosteroids, to which the patients were sensitive.

The long-term follow-up of this family provides important insights into the natural history of TRAPS under corticosteroid therapy. While prednisone at 10 mg/day effectively controlled clinical attacks in all treated patients (II/8, II/11, and III/1), it did not fully prevent the progression of AA amyloidosis in the two older siblings (II/8 and II/11), who developed amyloid deposition despite years of clinical remission. This finding suggests that corticosteroids, although beneficial for symptom control, may not be sufficient to halt the subclinical inflammatory process driving serum amyloid A (SAA) deposition. In contrast, the younger patient (III/1), who started corticosteroids earlier in childhood, has not developed amyloidosis to date, raising the possibility that early intervention may slow or prevent amyloidogenesis. However, longer follow-up is required to confirm this hypothesis.

The proband (II/7) and her father (I/2) both died from complications of end-stage renal disease, underscoring the severity of renal involvement in TRAPS-associated amyloidosis. The fact that II/8 and II/11 have preserved renal function (creatinine clearance 60 and 78 mL/min, respectively) despite proven amyloid deposition highlights the importance of regular screening for proteinuria and renal function decline, as well as the need for salivary gland or renal biopsy in asymptomatic carriers with persistent inflammation.

A particularly noteworthy aspect of this family's management is the therapeutic decision-making process. Although anakinra has been available in Algeria since 2020, the living patients have declined this treatment. The reasons are multifactorial: geographical distance from the dispensing centre (Algiers), financial constraints related to monthly travel, lack of appropriate home storage for refrigerated medication, and discomfort with self-administration of injectable therapy. This situation illustrates a significant gap between therapeutic recommendations and real-world feasibility in resource-limited settings. Patients have thus opted for the more accessible and familiar option of oral corticosteroid therapy, which they can obtain locally, despite its potential inferiority in preventing long-term amyloid complications.

This case series highlights the need for decentralized distribution of biologic therapies for rare diseases, perhaps through regional hospital pharmacies or trained local healthcare providers. Telemedicine and remote monitoring could also facilitate follow-up and reduce the need for frequent travel. Until such measures are implemented, a significant proportion of patients in remote areas will continue to rely on suboptimal therapeutic options, with potential consequences for their long-term renal and overall prognosis.

4. Conclusion

This updated family follow-up demonstrates that in TRAPS, corticosteroid therapy, while effective for symptom control, may not be sufficient to halt the progression of AA amyloidosis in all patients. Regular monitoring of renal

function and amyloid burden is essential. Early diagnosis and closer surveillance are critical, especially in populations where FMF is common and may mask the diagnosis of TRAPS. However, even when more targeted therapies such as anakinra become available, their accessibility is limited by geographical, financial, and logistical barriers. The patients in this family have chosen to continue corticosteroid therapy despite the availability of anakinra, underscoring the importance of patient-centered decision-making and the need for healthcare systems to develop decentralized strategies for the delivery of biologic treatments to underserved and remote populations. Addressing these barriers is essential to improve long-term outcomes in TRAPS and other rare autoinflammatory diseases.

5. Conflict of Interest

The authors have no conflict of interest to declare.

6. Consent Obtained

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

7. Ethical Approval for This Study

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

8. Abbreviations

CRP: C-Reactive Protein; FMF: Familial Mediterranean Fever; IL: Interleukin; MEFV: Mediterranean Fever gene; SAA: Serum Amyloid A Protein; TNFRSF1A: Tumor Necrosis Factor Receptor Superfamily 1A; TRAPS: TNF Receptor Associated Periodic Syndrome.

9. References

- McDermott MF, *et al.* Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes, (in eng), *Cell*, Apr 2, 1999; 97(1):133-144. Doi: 10.1016/s0092-8674(00)80721-7
- Williamson LM, Hull D, Mehta R, Reeves WG, Robinson BH, Toghil PJ. Familial Hibernian fever, (in eng), *Q J Med*. 1982; 51(204):469-480.
- Lainka E, *et al.* Incidence of TNFRSF1A mutations in German children: Epidemiological, clinical and genetic characteristics, (in eng), *Rheumatology (Oxford)*, Aug 2009; 48(8):987-991. Doi: 10.1093/rheumatology/kep140
- Hull KM, *et al.* The TNF receptor-associated periodic syndrome (TRAPS): Emerging concepts of an autoinflammatory disorder, (in eng), *Medicine (Baltimore)*, Sep 2002; 81(5):349-368. Doi: 10.1097/00005792-200209000-00002
- Aksentijevich I, *et al.* The tumor-necrosis-factor receptor-associated periodic syndrome: New mutations in TNFRSF1A, ancestral origins, genotype-phenotype studies, and evidence for further genetic heterogeneity of periodic fevers, (in eng), *Am J Hum Genet*, Aug 2001; 69(2):301-314. Doi: 10.1086/321976
- Dodé C, *et al.* The enlarging clinical, genetic, and population spectrum of tumor necrosis factor receptor-associated periodic syndrome, (in eng), *Arthritis*

- Rheum, Aug 2002; 46(8):2181-2188. Doi: 10.1002/art.10429
7. Aganna E, *et al.* Heterogeneity among patients with tumor necrosis factor receptor-associated periodic syndrome phenotypes, (in eng), Arthritis Rheum, Sep 2003; 48(9):2632-2644. Doi: 10.1002/art.11215
 8. Lachmann HJ, *et al.* The phenotype of TNF receptor-associated autoinflammatory syndrome (TRAPS) at presentation: A series of 158 cases from the Eurofever/EUOTRAPS international registry, (in eng), Ann Rheum Dis, Dec 2014; 73(12):2160-2167. Doi: 10.1136/annrheumdis-2013-204184