CLINICAL REPORT

Rare variant (p.Ser43Asn) of familial transthyretin amyloidosis associated with isolated cardiac phenotype: A case series with literature review

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Abstract

Background: p.Ser43Asn is a very rare transthyretin (TTR) mutation leading to familial amyloidosis of transthyretin type, ATTR amyloidosis. It was previously observed in four patients worldwide and is associated almost invariably with an isolated cardiac phenotype.

Methods and Results: We report here on an Italian family with early-onset cardiomyopathy and aggressive disease course in the affected individuals leading untreated to cardiac death before 55 years of age. We describe the clinical phenotype and imaging findings of two affected siblings, who were treated with tafamidis at an early disease stage, and their affected mother, who died 9 years ago due to refractory heart failure. The review of the available literature highlights the fact that until recently ATTR amyloidosis may have been misdiagnosed as other types of hypertrophic cardiomyopathy.

Conclusion: A better characterization of the genotype–phenotype associations is crucial to achieve optimal outcomes and facilitate informed decisions when treating individuals with rare mutations.

KEYWORDS
ATTR, amyloidosis, cardiomyopathy, transthyretin
1 | BACKGROUND

There are currently more than 100 known pathogenic variants of the transthyretin gene (TTR, OMIM *176300) including Val50Met, the first described and most frequently observed TTR variant worldwide, which is responsible for amyloid polynucleopathy in endemic areas such as Portugal, Sweden, and Japan (Parman et al., 2016). Different TTR variants have been associated with specific phenotypes but significant heterogeneity exists among carriers of the same variant and phenotypes may differ depending on the country of origin, age, gender, fibril type, and maternal or paternal inheritance (Damy et al., 2019; Maurer et al., 2016). In Portuguese patients with the Val50Met variant symptoms begin in the third decade (early-onset), while in patients from other European countries symptoms begin in the seventh decade (late-onset) and often with a mixed neurologic and cardiac phenotype (Conceição et al., 2019; Zanos et al., 2008). The identification of large foci of this specific variant has led to a better understanding of the disease and facilitates clinical decision-making and counseling of patients and their families while rare and very rare variants pose significant treatment challenges. Consequently, the severity and type of organ involvement, the natural history and anticipated prognosis, the outcome of specific therapies including liver and heart transplantation as well as anti-amyloid medications are insufficiently characterized in such populations. In this article, we aim to share our observations from treating a family of Italian origin with hereditary ATTR amyloidosis and isolated cardiac phenotype due to the rare p.Ser43Asn variant and review available information from previously published reports. Patients provided informed consent for publication of all here mentioned data.

2 | CASE PRESENTATION

A 45-year-old woman of Italian origin was referred to our center for consultation after undergoing genetic counseling and testing heterozygous for the amyloidogenic NM_000371.4:c.128G>A transthyretin variant. This is a point mutation in exon 2, codon 43 of the TTR gene leading to a single-amino acid substitution of serine by asparagine (patient A). Her mother had died 9 years ago at the age of 55 years from cardiac ATTR amyloidosis with progressive heart failure and the sister of her mother had been diagnosed with familial amyloidosis in Italy and had previously received heart and liver transplant. At presentation, she was completely asymptomatic, reported regular sport activity, and declined symptoms pertaining to ATTR amyloidosis. Physical examination revealed a 2/6 systolic murmur at the cardiac apex. Her blood pressure was 132/83 mmHg, resting heart rate was 73 bpm. ECG showed QRS low-voltage without conduction delay or other abnormalities. Echocardiography demonstrated marked left ventricular hypertrophy (LVH) with end-diastolic interventricular septal thickness of 15 mm, normal left ventricular ejection fraction of 64% and grade II diastolic dysfunction. Mitral and aortic valve leaflets demonstrated abnormal thickening with resulting moderate regurgitation. NT-proBNP was 438 pg/ml, high sensitivity troponin I was normal with normal blood count, liver, and renal function. [99mTc]-3,3-diphosphono-1,2-propanodicarboxylic acid ([99mTc]-DPD) scintigraphy including thoracic single-photon emission computed tomography (SPECT/CT) was performed. A Perugini grade 3 cardiac uptake confirmed the diagnosis of cardiac ATTR amyloidosis given the absence of laboratory indices of monoclonal plasma cell disease. Clinical and neurophysiologic testing excluded peripheral neuropathy. The patient remained asymptomatic for 10 months after diagnosis and was put on tafamidis (61 mg daily) after its approval for ATTR cardiomyopathy in Germany in late March 2020. Previously, the patient’s health insurance had declined compassionate use of tafamidis.

Cascade testing of the two male siblings of this patient was performed thereafter, with only one of them (patient B), a 44-year-old man, testing heterozygous for the same TTR variant. He denied having any symptoms and his past medical history was unremarkable. There were no clinical indices of autonomic or peripheral neurologic dysfunction or extra-cardiac disease manifestations. Physical examination did not reveal any abnormalities. Blood pressure was 127/79 mmHg and heart rate was 81 bpm. NT-proBNP was 677 pg/ml and high sensitivity troponin I was normal. Echocardiography showed LVH with septal thickness of 15 mm, normal ejection fraction of 54%, and grade II diastolic dysfunction with only trace mitral valve regurgitation. ECG demonstrated low QRS voltage without further abnormalities. [99mTc]-DPD scintigraphy including thoracic SPECT/CT was strongly positive for cardiac amyloidosis (Perugini grade 3), while extracardiac tracer uptake in bowel, kidney, and liver suggested subclinical extracardiac amyloid infiltration. The patient declined any gastrointestinal symptoms and serum indices of renal function were normal. Peripheral neurography was unremarkable. Tafamidis was initiated due to the extensive subclinical disease despite the absence of cardiac symptoms. Both our patients have no offspring while other maternal relatives have lived or live in Italy.

The deceased mother of patients A and B (patient C), was treated at our clinic between 12/2007 and 01/2008, before her death in 2010, due to progressive heart failure. According to her medical records, she was diagnosed with cardiac ATTR amyloidosis at our clinic in 01/2008 at the age of 53 years, approximately 1 year after first complaining of dyspnea on exertion. The patient presented initially with decompensated heart failure and advanced New York heart Association Class IV dyspnea. ECG recording was not available but it was reported normal. Echocardiography demonstrated LVH, grade
III diastolic dysfunction with restrictive filling and moderate mitral valve insufficiency. BNP was 258 pg/ml and a non-sensitive troponin I assay showed a mildly elevated value of 0.2 ng/ml (ULN 0.1 ng/ml). No significant renal or liver dysfunction was noted. Coronary artery disease was excluded by coronary angiography. Cardiac MRI demonstrated typical findings of extensive infiltrative cardiomyopathy. Genetic testing revealed heterozygosity for the p.Ser43Asn TTR variant, while rectal biopsies were negative for amyloid. At the time of diagnosis, only one report of amyloidosis linked to this variant was published in the literature by Connors et al. (1999). Beyond the typical clinical and imaging findings, her family history was highly suggestive of hereditary amyloidosis with aggressive cardiac phenotype (the mother of patient C had died due to sudden cardiac death at 47 years, her sister had been diagnosed with cardiac ATTR amyloidosis, had already received liver transplant and was awaiting heart transplant, her brother had died due to unknown cardiac causes). Patient C had received an ICD for primary prevention of sudden cardiac death but died due to refractory heart failure 2 years after diagnosis at the age of 55, approximately 3 years after symptom onset.

The family's pedigree including available information is shown in Figure 1. Figure 2 presents imaging findings of two affected family members (patient A, and B), who are currently being treated at our center.

### DISCUSSION

The p.Ser43Asn TTR variant was first described by Connors et al in 1999 in a 44-year-old male of Portuguese origin. At this time only 29 amyloidogenic TTR variants were known. The patient had been diagnosed with AV conduction disease requiring pacemaker implantation. Due to rapid deterioration of his condition after initial diagnosis he underwent left ventricular assist-device implantation and ultimately received heart transplantation (Connors et al., 1999). Subsequently, Mueller et al reported the case of a 46-year-old female patient of German–Italian origin carrying the same variant (Mueller et al., 2010). The first manifestation of the disease was restrictive cardiomyopathy with severe heart failure without evidence of polyneuropathy or involvement of other organs. The patient died due to complications of sepsis while awaiting heart transplantation. According to the medical history, no other family members were diagnosed with amyloidosis or cardiac disease including the close relatives of patient's mother but no information existed regarding the Italian father of the patient and his ancestors. Daoko et al found the same variant in a 41-year-old male patient originating from Peru presenting with angina and dyspnea (Daoko et al., 2010). The patient had a family history of sudden cardiac death (mother and two brothers in Peru) due to presumed hypertrophic cardiomyopathy (HCM). Amyloidosis in this patient was limited to the heart, without involvement of any other organ. The patient underwent an implantable defibrillator placement and was referred for liver and heart transplantation. Castaño et al. (2012) described the same variant in a 41-year-old male from Ecuador with Italian and Spanish origin, who exhibited a mixed cardiac and neuropathic phenotype. This was the first report of the variant being associated with neurological symptoms. A seven-generation pedigree was constructed revealing that 29 family members of the index patient had suffered cardiac death, 24 of them before the age of 55. The patient subsequently underwent successful heart and liver transplant. His liver was used for domino liver transplantation in a 77-year-old patient with end-stage liver disease suffering from cirrhosis secondary to nonalcoholic steatohepatitis. The recipient developed cardiac amyloidosis 1 year after liver transplantation, suggesting a very uncommon, rapidly progressive disease compared to previously reported cases (Table 1) (Dixit et al., 2016).

Apart from the previous reports and the patients presented here this specific variant was observed only in one out of 1286 participants of the THAOS registry from continental Western Europe and in none from Latin America (Cruz et al., 2017; Damy et al., 2019). The geographic region and clinical characteristics of this single subject are not known. Furthermore, it was reported in two patients from two different families in an Italian multicenter study including 186 patients with familial ATTR amyloidosis (Rapezzi et al., 2013). Considering all available information and that from our own experience, we suggest that this very rare variant may be of significance in individuals of Italian descend, while its prevalence in other parts of the world may be still unrecognized.
In the vast majority of patients, an isolated cardiac phenotype was observed with patients having already typical findings of cardiac amyloid infiltration (LVH, diastolic dysfunction) at their early 40’s. Based on these findings and despite the limited population studied, genetic counseling of first-degree relatives of affected individuals and close follow-up of variant carriers should be considered on time, for example, at their early thirties to prevent delayed recognition of the disease. In three of four studies (including ours) with available family history cardiac death was observed among

**FIGURE 2** Imaging findings by echocardiography and [99mTc]-DPD planar scintigraphy/thoracic SPECT/CT in two patients treated for hereditary ATTR cardiomyopathy at our center. Patient A is a 45-year-old female and patient B is a 44-year-old male. From left to right: echocardiographic four-chamber view, [99mTc]-DPD planar scintigraphy and thoracic SPECT/CT. [99mTc]-DPD, [99mTc]-3,3-diphosphono-1,2-propanodicarboxylic acid; ATTR, transthyretin amyloidosis; SPECT/CT, single-photon emission computed tomography

**TABLE 1** Clinical characteristics of patients diagnosed with cardiac ATTR amyloidosis and heterozygosity for the p.Ser43Asn mutation

|   | Author (year) | Age | Gender | Origin          | Inheritance       | Phenotype                      | Family history of early cardiac death |
|---|---------------|-----|--------|-----------------|-------------------|-------------------------------|--------------------------------------|
| 1 | Connors et al. (1999) | 44  | Male   | Portuguese      | Unknown           | Cardiomyopathy                | No                                   |
| 2 | Mueller et al., (2010) | 46  | Female | German–Italian  | Likely paternal    | Cardiomyopathy                | No (incomplete history)              |
| 3 | Daoko et al. (2010) | 41  | Male   | Peruvian        | Likely maternal   | Cardiomyopathy                | Yes                                  |
| 4 | Castaño et al. (2012) | 41  | Male   | Ecuadorian (Italian/spanish) | Maternal          | Cardiomyopathy, polyneuropathy | Yes                                  |
| 5-A | Papathanasiou (2020) | 45  | Female | Italian         | Maternal          | Cardiomyopathy                | Yes                                  |
| 5-B |               | 44  | Male   | Italian         | Maternal          | Cardiomyopathy                |                                       |
| 5-C |               | 53  | Female | Italian         | Maternal          | Cardiomyopathy                |                                       |

**a** GenBank reference sequence NM_000371.4.
deceased relatives and early cardiac death ≤55 years was reported in two families. As the mode of these deaths was not sufficiently reported, conclusions regarding the role of antiarrhythmic therapies such as implantable defibrillators cannot be made. Overall, this specific variant was until now associated with an aggressive clinical course, leading to advanced heart failure that necessitated listing for heart transplant in all four patients reported so far. Both of our patients were and remain asymptomatic approximately 1 year after diagnosis despite extensive cardiac amyloid infiltration, and are therefore the first two patients in the literature, who were diagnosed early in the disease course. Regarding the deceased mother, she may have benefited from heart transplantation but was treated conservatively due to history of breast malignancy. It is possible that in families with clusters of early cardiac death attributed to HCM, hereditary amyloidosis has long been overseen, as reported in the case from Daoko et al. In a prospective whole-exome sequencing study from United Kingdom only six out of 770 patients with HCM had TTR gene variants, partially in double heterozygosity with pathogenic sarcomere variants. Nevertheless, only one patient was diagnosed with ATTR amyloidosis by [99mTc]-DPD scintigraphy (Lopes et al., 2019). Furthermore, the study included carefully assessed patients with HCM treated in a referral U.K. center. It is still possible that in lower income countries, where genetic testing and advanced cardiac imaging, for example, magnetic resonance imaging are not widely available, phenocopies such as cardiac amyloidosis are still misdiagnosed as HCM.

All previously reported patients and their families were diagnosed and treated in an era when the only available disease-modifying therapy for isolated ATTR cardiomyopathy was combined liver and heart transplantation. Transthyretin stabilizers are nowadays approved in many countries for ATTR cardiomyopathy and represent a promising option if initiated early (Maurer et al., 2018), while agents acting via RNA interference are investigated in ongoing studies (NCT 04153149, NCT 03728634). As the long-term benefit of such agents remains to be proved, genotype–phenotype characterization is crucial when treating patients with rare variants and may aid in clinical decision-making and family counseling.

CONFLICT OF INTEREST
PL received consultant fees from Pfizer. MP received consultant fees from Alnylam Pharmaceuticals.

AUTHOR CONTRIBUTIONS
MP conceived and designed the study, conducted literature search, received patient’s consent, and drafted the manuscript. AC conducted literature search and wrote part of the manuscript, DK, TWS, and CR conducted literature search, collection and interpretation of data, and revised the manuscript. AMJ drafted the manuscript and participated in data interpretation. TH and TR revised the manuscript for important intellectual content, PL designed and supervised the study and wrote the manuscript.

DATA AVAILABILITY STATEMENT
All data presented here are available upon request.

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REFERENCES
Castano, A., Bokhari, S., Brannagan, T. H., Wynn, J., & Maurer, M. S. (2012). Technetium pyrophosphate myocardial uptake and peripheral neuropathy in a rare variant of familial transthyretin (TTR) amyloidosis (Ser23Asn): A case report and literature review. *Amyloid, 19*(1), 41–46. https://doi.org/10.3109/13506129.2011.638682
Conceição, L., Coelho, T., Rapezzi, C., Parman, Y., Obici, L., Galán, L., & Rousseau, A. (2019). Assessment of patients with hereditary transthyretin amyloidosis—Understanding the impact of management and disease progression. *Amyloid, 26*(3), 103–111. https://doi.org/10.1080/13506129.2019.1627312
Connors, L. H., Théberge, R., Skare, J., Costello, C. E., Falk, R. H., & Skinner, M. (1999). A new transthyretin variant (Ser23Asn) associated with familial amyloidosis in a Portuguese patient. *Amyloid, 6*(2), 114–118. https://doi.org/10.3109/1350612990007311
Cruz, M. W., Barroso, F., González-Duarte, A., Mundayat, R., & Ong, M. L. (2017). The demographic, genetic, and clinical characteristics of Latin American subjects enrolled in the Transthyretin Amyloidosis Outcomes Survey. *Amyloid, 24*(May), 107–108. https://doi.org/10.1080/13506129.2017.1292239
Damy, T., Kristen, A. V., Suhr, O. B., Maurer, M. S., Planté-Bordeneuve, V., Yu, C.-R., Ong, M.-L., Coelho, T., & Raperzezi, C. (2019). Transthyretin cardiac amyloidosis in continental Western Europe: an insight through the Transthyretin Amyloidosis Outcomes Survey (THAOS). *European Heart Journal*. https://doi.org/10.1093/eurheartj/ehz173
Daoko, J., Elinahar, Y., El Kersh, K., Mohammad, N., & Shamoon, F. (2010). Cardiac MRI detection of a rare case of familial cardiac amyloidosis (Ser23Asn): Case report with literature review. *Reports in Medical Imaging, 3*, 123–127. https://doi.org/10.2147/RMI.S14552
Dixit, N., Castano, A., Farr, M. J., Traub, R., Lentzsch, S., Brown, R. S., Maurer, M. S., & Brannagan, T. H. (2016). Rapidly progressive transthyretin-mediated amyloidosis in a domin liver transplant recipient of a Ser23Asn donor. *Journal of Clinical Neuromuscular Disease, 17*(3), 142–145. https://doi.org/10.1097/CND.0000000000000110
Lopes, L. R., Futema, M., Akhtar, M. M., Lorenzini, M., Pittman, A., Syrris, P., & Elliott, P. M. (2019). Prevalence of TTR variants detected by whole-exome sequencing in hypertrophic cardiomyopathy. *Amyloid, 26*(4), 243–247. https://doi.org/10.1080/13506129.2019.1665996
Maurer, M. S., Hanna, M., Grogan, M., Dispenzieri, A., Witteles, R., Drachman, B., Judge, D. P., Lenihan, D. J., Gottlieb, S. S., Shah, S. I., Steidley, D. E., Ventura, H., Murali, S., Silver, M. A., Jacoby, D., Fedson, S., Hummel, S. L., Kristen, A. V., Damy, T., … Raperzezi, C. (2016). Genotype and phenotype of transthyretin...
cardiac amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). Journal of the American College of Cardiology, 68(2), https://doi.org/10.1016/J.JACC.2016.03.596

Maurer, M. S., Schwartz, J. H., Gundapaneni, B., Elliott, P. M., Merlini, G., Waddington-Cruz, M., Kristen, A. V., Grogan, M., Witteles, R., Damy, T., Drachman, B. M., Shah, S. J., Hanna, M., Judge, D. P., Barsdorf, A. I., Huber, P., Patterson, T. A., Riley, S., Schumacher, J., ... Rapezzi, C. (2018). Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. New England Journal of Medicine, 379(11), 1007–1016. https://doi.org/10.1056/NEJMoa1805689

Mueller, I. I., Gawaz, M., Linke, R. P., Zuern, C., Steiner D., Altland, K., Von Beckerath, N., & Weig, H.-J. (2010). Restrictive cardiomyopathy in inherited ATTR amyloidosis (TTR-Ser23Asn) in a patient of German-Italian extraction. BMJ Case Rep, 2010. https://doi.org/10.1136/BCR.06.2009.2032

Parman, Y., Adams, D., Obici, L., Galán, L., Guergueltcheva, V., Suhr, O. B., & Coelho, T. (2016). Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP. Current Opinion in Neurology, S3–S13. https://doi.org/10.1097/WCO.0000000000000288

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