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Case Report

Hereditary transthyretin amyloidosis with hydrocephalus at 27 years old: A case report

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ABSTRACT

Hereditary transthyretin amyloidosis is autosomal dominant and results from mutations in the transthyretin gene. The Val30Met variant is the most common genetic mutation, although mutations vary within populations. More than 150 mutations in transthyretin have been reported; however, the Leu111Glu (p. Leu131Glu) mutation has been reported to date. We report the case of a 32-year-old Japanese male with a history of cerebral hemorrhage and hydrocephalus at age 27 years. The patient was referred to our department after his sibling had been diagnosed with hereditary transthyretin amyloidosis. Twelve-lead electrocardiography exhibited poor R progression, and transthoracic echocardiography showed normal findings. ^{99m}Tc-labelled pyrophosphate scintigraphy showed high accumulation in the heart. Histological tests using a right ventricular endomyocardial biopsy showed amyloid deposits and immunostaining only for transthyretin. Genetic analysis confirmed a novel missense variant, Leu111Glu, on the transthyretin gene. We diagnosed the patient with hereditary transthyretin amyloidosis, and the patient received genetic counseling. Patients with hereditary transthyretin amyloidosis carrying the Leu111Gln variant may present as a patient with a hydrocephalus-dominant phenotype. To the best of our knowledge, this is the first case report of the transthyretin Leu111Glu variant.

Learning objective: Hereditary transthyretin amyloidosis with the Leu111Gln variant has not been previously reported in Japan. While cardiac involvement progresses without overt abnormal findings on electrocardiogram and echocardiogram, ^{99m}Tc-labelled pyrophosphate scintigraphy can be a useful tool for the early diagnosis of hereditary transthyretin amyloidosis. This mutation may result in a predominantly hydrocephalus phenotype, and organ damage is expected to progress rapidly. Therefore, early diagnosis and appropriate treatment are necessary.

Introduction

Hereditary transthyretin (ATTRv) amyloidosis is an autosomal dominant disorder resulting from a hereditary deficiency, which causes extracellular accumulation of amyloid fibrils [1]. The extracellular deposits lead to dysfunction of specific organs, including the nervous system and heart [2]. ATTRv amyloidosis cases associated with the Val30Met mutation have generally been studied as a cause of progressive neurological disability, whereas the leptomeningeal predominant phenotype, which is rare, has scarcely been studied [3]. More than 150 genotypes of transthyretin (*TTR*) have been reported, but the Leu111Gln (p. Leu131Glu) variant has not been documented to date. This report highlights the importance of early ATTRv amyloidosis detection. Herein, we present the case of a patient with ATTRv and hydrocephalus due to the novel missense Leu111Gln (p. Leu131Glu) variant.

Case report

The patient was a 32-year-old Japanese male. He developed urinary disturbances in his 20s, had a history of cerebral hemorrhage and hydrocephalus at the age of 27 years, and was admitted to our neurosurgery department for a ventriculoperitoneal shunt to treat recurrent hydrocephalus at the age of 28 years. His father was diagnosed with hydrocephalus in his 50s and died of a persistent vegetative disorder in his 60s. The patient's sibling was diagnosed with ATTRv amyloidosis owing to vitreous opacity and died from hydrocephalus in his 30s. Therefore, the patient, who was diagnosed with systemic amyloidosis, was referred to our cardiology department.

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On admission, the patient's blood pressure was 132/74 mmHg, and pulse rate was regular at 67 beats per minute. On physical examination, heart sounds were regular and pulmonary auscultation revealed no pulmonary rales. Jugular venous distention and leg edema were not present, and peripheral neuropathies, such as carpal tunnel syndrome, were absent. Twelve-lead electrocardiogram (ECG) presented a poor R-progression pattern in the precaudal leads, indicating a change in results compared with that observed when he was 27 years old (Fig. 1A).

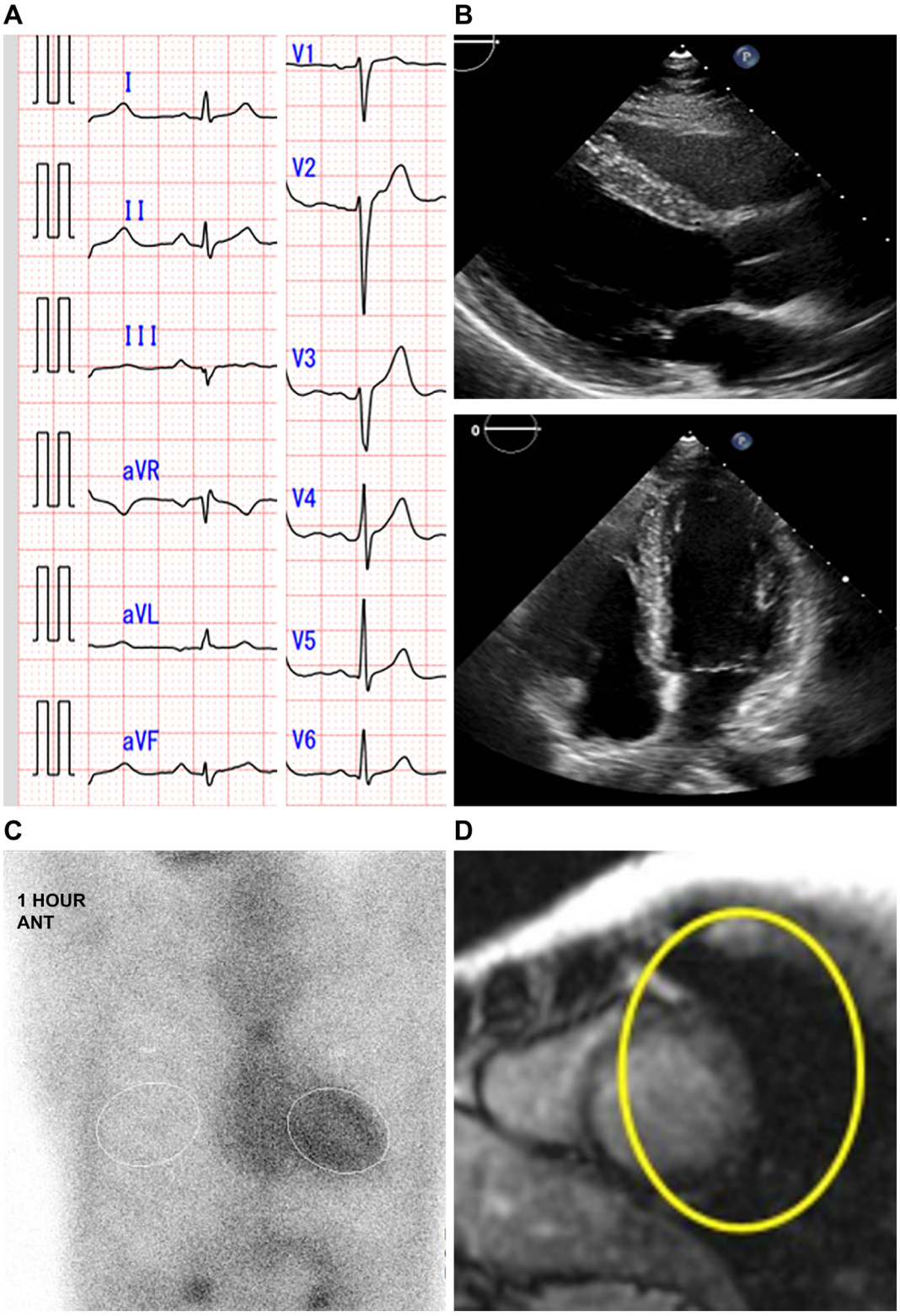

Fig. 1. Electrocardiography at the time of diagnosis (A) showed sinus rhythm and poor R progression pattern. Transthoracic echocardiography (TTE) at the time of diagnosis (B). Top: end diastole in the long-axis view. Bottom: end diastole in the four-chamber view. TTE shows left ventricular wall thickness within the normal range and preserved ejection fraction. ^{99m}Tc-labelled pyrophosphate scintigraphy at the time of diagnosis (C) shows abnormal accumulation in the heart, Perugini grade 3. Cardiac magnetic resonance imaging at the time of diagnosis (D). The end diastole in the short-axis view show left ventricular late gadolinium enhancement in the anterolateral wall (yellow circle).

Transthoracic echocardiography showed a preserved ejection fraction of 60 % without concentric left ventricular hypertrophy (Fig. 1B). Laboratory examination revealed a serum B-type natriuretic peptide of 19.2 pg/mL and a troponin T level of 0.009 ng/mL. Based on the family history of ATTR amyloidosis, we performed ^{99m}Tc-labelled pyrophosphate scintigraphy, which revealed abnormally high accumulation in the heart (Fig. 1C). Cardiac magnetic resonance imaging revealed transmural late gadolinium enhancement in the left ventricular anterolateral wall (Fig. 1D). Coronary angiography revealed normal coronary artery stenosis. While an abdominal fat pad biopsy did not reveal amyloid deposits, a right heart endomyocardial biopsy revealed amyloid deposition with immunohistochemical staining only for *TTR* (Fig. 2).

Genetic analysis revealed a novel missense variant p. Leu131Gln in *TTR* (Fig. 3). This mutation has been suggested to be amyloidogenic; however, the variant has not been reported in variant databases to date. We investigated myocardial specimens by laser microdissection using liquid chromatography-tandem mass spectrometry. The spectral count ratio between the peptide containing the Leu131Gln mutation and the wild-type peptide was 76:24. The patient was diagnosed with ATTRv amyloidosis, administered patisiran once every 3 weeks without any adverse events, and referred to our genetic counseling department to make informed decisions.

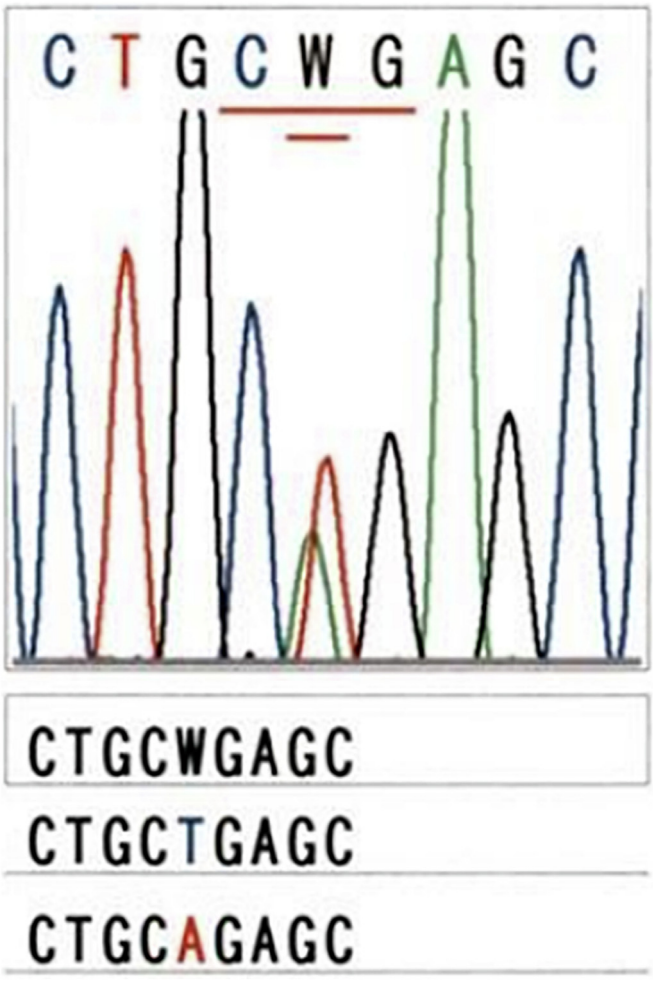

Fig. 3. A DNA sequence of transthyretin indicating a mutation in exon 4, resulting in the p. Leu131Gln variant of the transthyretin protein.

Discussion

Here, we present the case of a patient with ATTRv and hydrocephalus in his 20s and cardiac amyloidosis in his 30s.

ATTRv amyloidosis can cause organ damage owing to the accumulation of *TTR* protein in various organs, including the heart, nerves, brain, pia mater, and retina. Val30Met is the most common mutation associated with familial polyneuropathy. However, other mutations associated with different phenotypes have been identified, including the brain, pia mater, and retina [3]. Amyloid deposits in the leptomeningeal cerebrovascular system are thought to cause these central nervous system symptoms, but the exact mechanism remains unclear [2]. The Leu111Gln variant is a novel mutation that has not been previously reported in Japan. Although central nervous system biopsies may not always be feasible or necessary, this genotype suggests an association with hydrocephalus. Magnetic resonance imaging is useful for the differential diagnosis of leptomeningeal amyloidosis, but it could not be performed in this case because of the tolerance level of the ventriculoperitoneal shunt [4]. Imaging studies such as ^{99m}Tc-labelled pyrophosphate scintigraphy can aid in the diagnosis of ATTRv amyloidosis, which exhibits various phenotypes.

In ATTR cardiomyopathy, abnormal protein deposits accumulate in the heart, leading to progressive heart failure and arrhythmias [5]. Several treatments are available for ATTR cardiac amyloidosis. Liver transplantation has been reported to improve survival in some variants such as the Val30Met mutation. However, its efficacy for leptomeningeal amyloidosis has not been fully established [6]. ATTRv cardiac amyloidosis treatment aims to prevent the formation of amyloid deposits from misfolded *TTR* proteins in two pharmacological approaches. One approach is to use tafamidis, which prevents *TTR* from misfolding and transforming into amyloid fibrils, and the other is to use patisiran, which primarily reduces the amount of *TTR* produced by the liver. Early intervention in ATTR cardiomyopathy with tafamidis has been shown to improve all-cause mortality, as demonstrated by the ATTR-ACT trial [7]. Therefore, it is essential to consider cardiac amyloidosis among the differential diagnoses, even if the initial symptoms do not appear to be related to the heart. Patisiran is an RNA

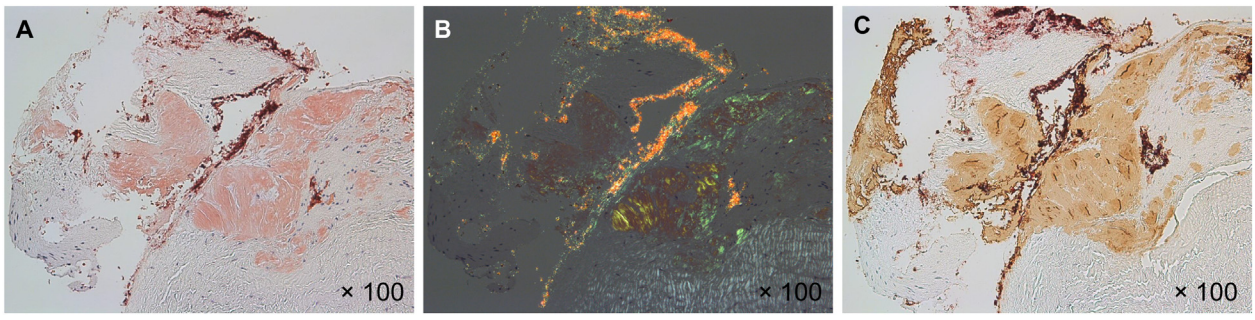

Fig. 2. Biopsy of the right ventricular myocardium. (A) Congo red stain shows amyloid deposits with an orange color. (B) Apple-green birefringence under polarized light. (C) Immunohistochemical staining is positive only for transthyretin antibody (×100 magnification).

therapy that aims to reduce the hepatic production of both mutant and wild-type *TTR* proteins. The APPOLO trial demonstrated improvements in neurological symptoms and potential cardiac benefits in ATTRv amyloidosis with polyneuropathy after patisiran administration [8]. These findings indicate that the early initiation of drug therapy may be beneficial for preventing cardiac events before amyloid fibril storage causes irreversible organ dysfunction. However, it is necessary to accumulate cases and conduct further research to determine how the treatment results should be interpreted in the gene mutation groups that were not included in clinical trials. Furthermore, regulation of *TTR* proteins produced by the brain and eyes is problematic because existing drugs cannot cross the blood-brain barrier. Patisiran is administered to prevent the accumulation of wild-type *TTR* protein and improve autonomic neuropathy; however, it is necessary to consider whether more effective pharmacological treatments can be identified. ATTRv amyloidosis is caused by various mutations, and clinical trials may not provide sufficient conclusions regarding treatment efficacy and safety in novel or rare mutation groups. Future studies are required to identify further novel or rare mutations to guide the development of effective and safe treatment strategies for such patients.

In cases of a novel mutation, it could be difficult to predict clinical courses such as penetrance [9]. Given the autosomal nature and diverse phenotypes of ATTRv amyloidosis, it is crucial to establish clinical integration of various fields with genetic counseling [10]. Genetic counseling is composed of medical services provided by staff trained in medical genetics and can help patients and their families make informed decisions regarding treatment management through informational support.

In conclusion, this case report emphasizes the importance of considering ATTR amyloidosis as a differential diagnosis, particularly in cases of early onset hydrocephalus with a relevant family history. Early diagnosis and intervention are crucial for disease management.

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Consent statement

The authors confirm that written consent for the submission and publication of this case report, including images and associated text, has been obtained from the patient in line with the COPE guidance.

Declaration of competing interest

None declared.

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References

[1] Naiki H, Yamaguchi A, Sekijima Y, Ueda M, Ohashi K, Hatakeyama K, et al. Steep increase in the number of transthyretin-positive cardiac biopsy cases in Japan: evidence obtained by the nation-wide pathology consultation for the typing diagnosis of amyloidosis. Amyloid 2023;30:321–6.
[2] Ando Y, Coelho T, Berk JL, Cruz MW, Ericzon BG, Ikeda S, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis 2013;8:31.
[3] Sekijima Y, Ueda M, Koike H, Misawa S, Ishii T, Ando Y. Diagnosis and management of transthyretin familial amyloid polyneuropathy in Japan: red-flag symptom clusters and treatment algorithm. Orphanet J Rare Dis 2018;13:6.
[4] Qin Q, Wei C, Piao Y, Lian F, Wu H, Zhou A, et al. Current review of leptomeningeal amyloidosis associated with transthyretin mutations. Neurologist 2021;36:189–95.
[5] Maurer MS, Hanna M, Grogan M, Dispenzieri A, Witteles R, Drachman B, et al. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (transthyretin amyloid outcome survey). J Am Coll Cardiol 2016;68:161–72.
[6] Ando Y, Terazaki H, Nakamura M, Ando E, Haraoka K, Yamashita T, et al. A different amyloid formation mechanism: de novo oculoleptomeningeal amyloid deposits after liver transplantation. Transplantation 2004;77:345–9.
[7] Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med 2018;379:1007–16.
[8] Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med 2018;379:11–21.
[9] Adams D, Algalarrondo V, Polydefkis M, Sarswat N, Slama MS, Nativi-Nicolau J. Expert opinion on monitoring symptomatic hereditary transthyretin-mediated amyloidosis and assessment of disease progression. Orphanet J Rare Dis 2021;16:411.
[10] Barker N, Judge DP. Counseling family members and monitoring for evidence of disease in asymptomatic carriers of amyloid transthyretin cardiac amyloidosis. Am J Cardiol 2022;185(Suppl. 1):S43–50.