Received: 12 January 2018 | Accepted: 16 March 2018

DOI: 10.1111/nmo.13354

ORIGINAL ARTICLE

WILEY Neurogastroenterology & Motility NGM

Abnormal small bowel motility in patients with hereditary transthyretin amyloidosis

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Funding information
The work was supported by grants from the Swedish Patients' Organization FAMY in Västerbotten and Norrbotten, the AMYL Foundation and the Swedish Gastroenterology Fund (Mag-tarmfonden). The authors had complete access to the data that supports the publication.

Abstract

Background: Gastrointestinal complications are common in hereditary transthyretin amyloid (ATTRm) amyloidosis. The underlying mechanisms have not been fully elucidated, and the patients' small bowel function remains largely unexplored. The aim of the present study was to compare the small bowel motility in ATTRm amyloidosis patients with that in non-amyloidosis patient controls.

Methods: ATTRm amyloidosis patients undergoing evaluation for liver transplantation were consecutively investigated with 24-hour duodenojejunal manometry (n = 19). The somatostatin analogue octreotide was used to induce fasting motility. Patients with age at onset of ≥50 years were defined as late-onset cases. For each patient, three age- and sex-matched patient controls (n = 57) were selected from the total pool of investigated patients.

Key Results: Manometry was judged as abnormal in 58% of the patients and in 26% of the patient controls (P = .01). Patients displayed significantly more daytime phase III migrating motor complexes than patient controls (median 4 vs 2, P < .01), and had a higher frequency of low-amplitude complexes (16% vs 4%; however, this difference did not reach statistical significance, P = .10). Furthermore, late-onset patients showed a delay in octreotide response (5.4 vs 3.8 minutes, P < .01), but this was not observed for early-onset patients or within the control group.

Conclusions and Inferences: Patients with ATTRm amyloidosis displayed abnormalities in their small bowel motility more frequently than non-amyloidosis patient controls, and the manometric pattern was probably best consistent with a combined neuromyopathic disorder. The delayed octreotide response in late-onset patients warrants further investigation.

KEYWORDS

familial amyloid neuropathy, functional gastrointestinal disorders, intestinal motility, manometry, octreotide acetate, transthyretin amyloidosis

Abbreviations: A45G, alanine substituted for glycine at gene position 45 of the mature protein; A97S, alanine substituted for serine at gene position 97 of the mature protein; ANS, autonomic nervous system; ATTRm, mutant (or hereditary) transthyretin amyloid; DCC, discrete clustered contractions; FAP, familial amyloid polyneuropathy; GI, gastrointestinal; HRV, heart rate variability; IBS, irritable bowel syndrome; ICC, interstitial cells of Cajal; MMC, migrating motor complex; PND, polyneuropathy disability; SeHCAT, ^{75}Se-homocholic acid taurine; TTR, transthyretin; V30M, valine substituted for methionine at gene position 30 of the mature protein.

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1 | INTRODUCTION

Amyloidosis is a localized or systemic condition caused by extracellular deposition of insoluble protein aggregates. Hereditary transthyretin amyloid (ATTRm) amyloidosis, formerly known as familial amyloid polyneuropathy, is the most common type of hereditary systemic amyloidosis, and a result of amyloidogenic transthyretin (*TTR*) gene mutations.[1] The disease is spread all over the world but clustering areas are found, for example, in Northern Sweden, Portugal, Brazil, and Japan. Most of the *TTR* gene mutations result in a decreased stability of the TTR tetramer, which facilitates separation into misfolded monomers that assemble into beta-structured fibrils and, in turn, build up the amyloid deposits.[2] During its formation and deposition, the TTR amyloid disturbs the function of the targeted tissues and a number of different complications can arise. Common disease features are peripheral and autonomic neuropathies, cardiac abnormalities, and gastrointestinal (GI) symptoms such as early satiety, constipation, diarrhea, and vomiting.[3] TTR is mainly produced by the liver, and a liver transplantation has been shown to halt disease progression in selected cases.[4] Alternative treatments are now emerging,[5] and tafamidis has already been approved for treatment of early-stage ATTRm amyloidosis.[6]

The GI complications of ATTRm amyloidosis were formerly considered a consequence of the patients' autonomic and enteric neuropathies; however, more recent studies imply that a destruction of autonomic and enteric nerves is not the sole determinant of their GI disturbances.[7-9] Data from our center suggest that a loss of interstitial cells of Cajal (ICC) is of importance,[10] as are changes in the endocrine system of the gut.[11-13] These changes negatively affect GI motility, and accordingly previous studies have demonstrated a delayed gastric emptying[7,14,15] and slow transit constipation in patients with ATTRm amyloidosis.[16] Attempts to assess enteric motility using barium follow-throughs have been contradictory,[14,17] and so far no data on intestinal manometry have been presented; however, indirect measures of small bowel function such as fecal fat determination,[18,19] hydrogen breath tests,[19] and ^{75}Se-homocholic acid taurine (SeHCAT) tests[19,20] have indicated an impaired small intestinal motility. Prolonged small bowel manometry allows us to define both qualitative and quantitative abnormalities of motility, and it is generally considered the best available tool for the investigation of enteric dysmotility.[21,22] Thus, the primary aim of the current study was to determine the manometric properties of the small bowel in patients with ATTRm amyloidosis compared to non-amyloidosis patient controls. A secondary aim was to characterize motility patterns in relation to clinical symptoms of ATTRm amyloidosis patients, to better understand the mechanisms behind their usually troublesome GI disturbances.

Key points

- The reasons for gastrointestinal disturbances in patients with hereditary transthyretin amyloidosis remain unclear; this study explores the small bowel function of these patients.
- Small bowel manometries showed abnormal findings more frequently in patients than in non-amyloidosis controls. Amyloidosis patients also showed a delayed response to octreotide (used to induce fasting motility).
- To find better treatments, it is important to recognize the underlying mechanisms of the gastrointestinal symptoms in transthyretin amyloidosis, and this study adds another piece to the puzzle.

2 | MATERIALS AND METHODS

2.1 | ATTRm amyloidosis patients and patient controls

Patients with ATTRm amyloidosis undergoing evaluation for liver transplantation at Karolinska University Hospital, Huddinge, Sweden were consecutively selected for small bowel manometry from July 2009 to September 2014. For each ATTRm amyloidosis patient, three sex- and age-matched (to the nearest extent) patient controls that were investigated at the same center were selected. Healthy volunteers, as well as patients with inflammatory bowel disease, neurofibromatosis, and/or chronic intestinal pseudo-obstruction were omitted as controls. Patients with ATTRm amyloidosis and an age at disease (symptom) onset of ≥50 years were defined as late-onset cases in accordance with current clinical praxis.

2.2 | Small bowel manometry

Ambulatory 24-hour small bowel manometries were performed at the Gastrolab, Karolinska University Hospital, Huddinge, Sweden. Subjects were instructed to discontinue all medication that could possibly affect bowel motility at least 48 hours prior to manometry. After an overnight fast, a 6-channel catheter (Konigsberg, Pasadena, CA, USA) was inserted trans-nasally into the stomach of the subjects, and its progression was monitored using fluoroscopy. Pressure sensors were located at 0, 15, 30, 45, 47, and 49 cm from the tip of the catheter. When the tip of the catheter was observed to pass through the pylorus, a latex balloon attached to the tip was inflated with 5-10 mL of air to aid propulsion. The catheter was then advanced until the tip reached beyond the ligament of Treitz, after which the balloon was deflated and the catheter position secured to the cheek. After the start of the motility registration, subjects were allowed free activity but were instructed to keep a diary of their activities during the study period that included the time that they retired to bed and the time of getting up in the morning. Three standardized test meals were served—at noon (lunch, 500 kcal), at 19:00 hours (dinner, 680 kcal), and at 07:00 hours (breakfast, 400 kcal). Fluid intake was unrestricted. Octreotide (50 μg subcutaneously) was used for inducing fasting motility 2 hours after the last test meal (breakfast). Pressure data were recorded using Medtronic Synectics Flash μ-Digitrapper (Medtronic Synectics, Stockholm, Sweden) and was downloaded to a PC for analysis with Multigram

TABLE 1 Patient characteristics

Variable	Amyloidosis patients, n = 19	Patient controls, n = 57	*P* value
Proportion of males	15 (79%)	45 (79%)	NS
Age at manometry (years)	53 (31-66)	46 (24-66)	NS
Age at disease onset (years)	50 (28-64)	N/A	N/A
Early-onset cases (n = 9)	38 (28-49)		
Late-onset cases (n = 10)	53 (50-64)		
Proportion with late-onset (≥50 years)	10 (53%)	N/A	N/A
Disease duration at manometry (years)	2.3 (0.5-9.7)	N/A	N/A

Data shown are medians (full range) and valid percentages. $P < .05$ was regarded statistically significant. N/A = not available; NS = not significant.

version 6.30 (Medtronic Synectics). Two examiners (GL and HT, co-authors) performed the data evaluation.

2.3 | Criteria for abnormal small bowel motility

The manometric signs of abnormal small bowel motility were previously described in detail.[22-24] Briefly, aberrant propagation (<1.0 cm min^{-1} or >25 cm min^{-1}) or configuration (baseline elevation >30 mm Hg for over 3 minutes) of at least 2 of the phase III of the migrating motor complex (MMC), 2 or more bursts of non-propagated phasic pressure activity (duration >2 minutes, amplitude >20 mm Hg and frequency >9 min^{-1}), sustained uncoordinated phasic pressure activity in an isolated segment of the intestine for more than 30 minutes, absence of a fed motility pattern after a meal, severe hypomotility with mainly low-amplitude contractions (<20 mm Hg), and a complete absence of MMC during 24 hours or >12 hours after a meal were all considered abnormal.

2.4 | Clinical evaluation of ATTRm amyloidosis patients

Patients' medical records were scrutinized for data from pre-transplant clinical evaluations that all had been performed at Umeå University Hospital, Sweden. Presence of GI symptoms and severity of peripheral neuropathy had been recorded per protocol by three different investigators (JW, IA, and OBS) during routine clinical examination at the Department of Medicine. The different GI symptoms that had been evaluated were nausea, vomiting, abdominal pain, constipation, diarrhea, and alternating diarrhea/constipation. Patients' peripheral neuropathy was assessed using the polyneuropathy disability (PND) score[25] that consists of five levels—I (sensory disturbances but preserved walking capacity), II (impaired walking capacity but ability to walk without stick or crutches), IIIa (walking with the help of one stick or crutch), IIIb (walking with the help of two sticks or crutches, or a walker), and IV (confined to a wheelchair or bedridden).

Most patients also underwent upper GI endoscopy and gastric emptying scintigraphy that were performed at the Endoscopy Unit and the Department of Radiology, respectively. Autonomic nervous system (ANS) function was evaluated with analyses of heart rate variability (HRV) in which power spectrum analysis was performed on heart rate data from 2-minute sequences in the supine and upright positions. The respiration-related high-frequency component in a supine position represents an estimate of parasympathetic control, whereas the low-frequency component after a postural change from a supine to an upright position is a useful maker of sympathetic activity.[26,27] The HRV recordings were carried out at the Department of Clinical Physiology.

2.5 | Clinical diagnosis in patient controls

The clinical diagnoses of the patient controls were settled at the Gastrolab, Karolinska University Hospital, Huddinge, and were based on clinical symptoms together with manometry results. The 10th version of the International Classification of Diseases (ICD-10) was used for diagnostic classification to the best possible extent.

2.6 | Statistical analyses

Data are expressed as medians and full range since a normal distribution could not be guaranteed. Non-parametric tests were used for all analyses. Nominal data were analyzed using the χ^2 test and Fisher's exact test, whereas the Mann-Whitney *U* test was used for numerical data. *P* values below .05 were considered statistically significant.

2.7 | Ethics

The study was part of a larger project that had been approved by the Regional Ethics Board in Umeå, Sweden (reference number 06-084M), and patients were included after giving informed consent.

3 | RESULTS

In all, 19 ATTRm amyloidosis patients and 57 patient controls were included. Their detailed characteristics are displayed in Table 1. In

all, 17 (89%) of the patients carried the *TTR* V30M mutation; the other two variants were the *TTR* A45G and A97S mutations. A final diagnosis was available for 51 (89%) of the controls and, of those, 26 were finally diagnosed with an irritable bowel syndrome of some kind, 9 with unspecified abdominal pain, 5 with enteric dysmotility (other specified functional intestinal disorders), 3 with functional diarrhea, 3 with nausea and vomiting, 3 with functional dyspepsia, and 2 with functional constipation (other specified functional intestinal disorders).

3.1 | Manometry findings

All patients and 51 (89%) of the controls had complete small bowel manometry tracings. The reasons for incomplete manometry data were an unexplained interruption of the recordings in 2 cases (for 35 minutes and 2 hours, respectively), a voluntary discontinuation of the manometry after 5 hours and 25 minutes in one case, missing data (on time to octreotide response) in 2 cases, and failure to ingest 2 out of 3 test meals in one case.

For those who had completed the manometry, results were judged to be abnormal in 11 (58%) of the ATTRm amyloidosis patients and in 15 (27%) of the patient controls ($P = .01$). A more detailed presentation of the manometry findings is displayed in Table 2. In summary, ATTRm amyloidosis patients displayed a higher frequency of daytime bursts and phase III complexes than patient controls (both in the interdigestive period and after octreotide injection), and also a longer time delay before an octreotide-induced phase III activity front was detected. No significant differences in any motility parameters were found between the groups during the digestive period.

Subgroup analyses among the amyloidosis patients revealed no significant differences in manometry results related to sex, *TTR* mutation, or duration of disease (cutoff 3 years). However, a significant difference was found in relation to age at disease onset; late-onset cases displayed a longer time delay in response to octreotide injection, but no such age-related difference was found in the control group (Figure 1).

3.2 | Evaluation of GI symptoms and neuropathy in ATTRm amyloidosis patients

The routine clinical evaluations were performed in median 3 (full range: 0-6) months prior to manometry. In all, 11 (58%) of the ATTRm amyloidosis patients had reported GI symptoms, most commonly constipation. The prevalence of the individual symptoms is shown in Table 3. In all, 16 (84%) of the patients had undergone upper GI endoscopy and/or gastric emptying scintigraphy and, of those, 3 (19%) showed signs of gastric retention on any of the 2 examinations. No significant difference in manometry results was found in relation to the presence of GI symptoms or to gastric retention. Furthermore, subgroup analyses disclosed no difference related to the presence of constipation. Detailed symptom data were unavailable for the patient controls, as were GI tissue samples from both patients and patient controls.

TABLE 2 Small bowel manometry findings in patients with hereditary transthyretin amyloidosis and non-amyloidosis patient controls

Variable	Amyloidosis patients, n = 19	Patient controls, n = 57	*P* value
Presence of MMC	19 (100%)	56 (100%)	NS
Aberrant phase III MMC	4 (21%)	12 (21%)	NS
Number of daytime phase III MMC	4 (1-11)	2 (0-7)	<.01
Number of nighttime phase III MMC	3 (1-8)	3 (0-8)	NS
Mainly low amplitude complexes	3 (16%)	2 (4%)	.10
Bursts of non-propagated activity	4 (21%)	5 (9%)	NS
Number of daytime bursts	0 (0-5)	0 (0-3)	.04
Number of nighttime bursts	0 (0-1)	0 (0-3)	NS
Abnormal digestive pattern	2 (12%)	3 (6%)	NS
Digestive period duration, lunch (hours)	4.3 (0.9-6.0)	4.0 (0.6-6.0)	NS
Digestive period duration, dinner (hours)	4.7 (1.0-9.0)	5.4 (0.7-11.1)	NS
Time to octreotide response (min)	5.0 (2.8-9.0)	3.8 (0-7.3)	.02
Number of phase III MMC post-octreotide	3 (1-5)	1 (1-6)	<.01

Data shown are medians (full range) and valid percentages. $P < .05$ was regarded statistically significant. MMC = migrating motor complex; NS = not significant.

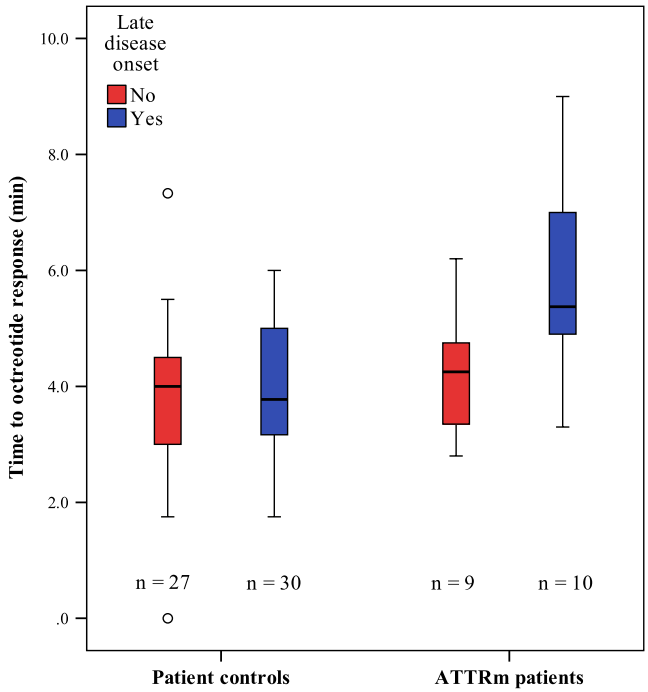

FIGURE 1 Time to octreotide response in amyloidosis patients and patient controls. During ambulatory 24-h small bowel manometry, the somatostatin analogue octreotide was used for inducing fasting motility after the last test meal. Overall, hereditary transthyretin amyloidosis (ATTRm) patients displayed a slower response to octreotide injection than patient controls (median 5.0 vs 3.8 min, $P = .02$), and subgroup analyses showed that this was explained by the difference found in the late-onset (≥50 y) patient group (5.4 vs 3.8 min, $P < .01$). No significant delay in octreotide response was observed for early-onset amyloidosis patients compared to patient controls (4.3 vs 4.0 min, $P = .58$), or for the age-matched cases within the control group (4.0 vs 3.8 min, $P = .63$)

Polyneuropathy disability scores were available for all amyloidosis patients, and 16 (84%) had a PND score of I, whereas 2 patients had a PND score of II and one patient had a score of IIIb. No significant differences in manometric findings were found between patients with a PND score of I and those with higher scores. Moreover, the patient with the most advanced PND score (IIIb), who also suffered from constipation and autonomic neuropathy, displayed a normal small bowel manometry with no signs of neuropathy, myopathy, or mechanical obstruction.

All the amyloidosis patients except one had completed the HRV recordings, and 9 (50%) of them showed signs of ANS dysfunction—4 (44%) had signs of a pure parasympathetic dysfunction, whereas 5 (56%) showed signs of both sympathetic and parasympathetic dysfunctions. Patients with evidence of an autonomic neuropathy more frequently displayed abnormal manometries than those with normal HRV (70% vs 30%); however, the difference did not reach statistical significance ($P = .15$). No differences related to ANS function were found for any of the other manometric variables.

Subgroup analyses showed that early-onset patients more frequently reported GI symptoms than late-onset cases (67% vs 50%); however, the difference was not statistically significant ($P = .65$). Fifty percent of the patients with early disease onset, but none of those with late-onset, showed signs of gastric retention ($P = .04$). No differences related to age at onset were found for ANS function or PND scores.

4 | DISCUSSION

The present study is the first analysis of small bowel motility in patients with ATTRm amyloidosis, a disorder in which GI disturbances frequently occur alongside peripheral and autonomic neuropathies. Prior studies using indirect measurements have indicated an impaired small bowel function in these patients[18-20] and, hence, intestinal motility was now assessed using standard ambulatory 24-hour small bowel manometry, including octreotide injection to induce fasting motility. Data validity was supported by high completion rates.

A majority of the patients (58%), but only one-fourth of the controls, was judged to have abnormal manometry results, which (as expected) implies that small intestinal dysmotility is a common feature of ATTRm amyloidosis. The overall judgment was based on previously described criteria for abnormal manometry,[23,24] and the assessments were limited to two examiners. Discrete clustered contractions (DCC) were considered unspecific,[28,29] and were not further analyzed.

The most frequently observed manometric abnormalities were bursts of non-propagated activity and abnormal MMC phase III complexes. The frequencies of these anomalies did not differ significantly between amyloidosis patients and patient controls, but this might have been influenced by the relatively small sample sizes and the fact that the control group did not consist of healthy volunteers. Presence of bursts and abnormally configured or propagated phase III complexes are indicative of a neuropathic disease,[29-31] and the higher number of daytime bursts in amyloidosis patients, as well as the higher number of phase III complexes during daytime and after octreotide injection, points toward a neuropathic cause with loss of inhibitory motor neurons.[30] However, the amyloidosis patients also displayed a numerically higher frequency of low amplitude complexes than the patient controls, which would rather suggest an enteric myopathy as the underlying mechanism.[32] Altogether, these findings primarily support a neuropathic origin of the GI disturbances in ATTRm amyloidosis (although a myopathic component cannot be ruled out), and this can probably be related to the ANS dysfunction,[7,33] local amyloid deposits,[9,34] and possibly also to a loss of gut ICC[10] that have been demonstrated in these patients.

Apart from the above abnormalities, ATTRm amyloidosis patients showed a delayed response to octreotide injection compared to patient controls. This was perhaps the most prominent deviation in the study, and a finding different from most other patient groups examined at our center. An impaired conversion to fasting motility might cause a decreased ability to clear the small intestine of remaining residuals and predispose bacterial

TABLE 3 Gastrointestinal symptoms and manometry results in patients with hereditary transthyretin amyloidosis

Patient	Nausea	Vomiting	Pain	Constipation	Diarrhea	Alt. diarrhea/ constipation	Gastroparesis[a]	Main manometric feature
01	–	–	–	–	–	–	N/A	Delayed octreotide response
02	+	–	–	–	–	+	–	Short digestive periods
03	+	–	–	+	–	–	+	Normal findings
04	–	–	+	–	–	+	+	Normal findings
05	+	+	+	–	+	–	N/A	Low amplitude
06	–	–	–	–	–	–	–	Delayed octreotide response
07	–	–	–	+	–	–	–	Discrete clustered contractions
08	–	–	–	–	+	–	+	Short digestive periods
09	–	–	––	–	–	–	–	Normal findings
10	–	–	–	–	–	–	N/A	Delayed octreotide response
11	–	–	–	–	–	–	–	Delayed octreotide response
12	–	–	–	–	–	––	–	Normal findings
13	–	–	–	+	–	–	–	Delayed octreotide response
14	–	–	–	+	–	–	–	Discrete clustered contraction
15	–	–	–	–	–	–	–	Delayed octreotide response
16	–	–	–	+	–	–	–	Normal findings
17	–	–	–	+	–	–	–	Discrete clustered contractions
18	–	–	–	–	–	–	–	Delayed octreotide response
19	–	–	–	+	–	–	–	Short digestive periods
N	3	1	2	7	2	2	3	N/A
Prevalence	16%	5%	11%	37%	11%	11%	19%	N/A

[a]At upper gastrointestinal endoscopy and/or gastric emptying scintigraphy. Alt. = alternating; + = reported present at clinical evaluation; – = reported absent at clinical evaluation; N/A = not available.

overgrowth,[29] which is a common complication of ATTRm amyloidosis.[19,35,36] Interestingly, subgroup analyses showed that the delay in octreotide response was only found in patients with a late (≥50 years) disease onset. This was unexpected since octreotide-induced small bowel MMC activity has been suggested as a marker of neural intactness,[37] and since late-onset ATTRm amyloidosis patients generally suffer less from autonomic neuropathy and GI symptoms than early-onset cases,[38-40] and also have less amyloid deposits in the gut, the pancreas and in small unmyelinated nerve fibers.[41] No significant differences in the frequency of GI symptoms, ANS function or PND scores were found between early- and late-onset cases in our material although gastric retention was only demonstrated in early-onset cases.

A difference in amyloid fibril composition may contribute to this delayed conversion to fasting motility in late-onset patients as well as to some of the other phenotypic variations that have been observed in the disease[42,43], but the mechanisms are not obvious. Age itself does not appear to be important for the octreotide response since no corresponding difference was found in the age-matched controls. The higher frequency of DCC in late-onset cases (data not shown), on the other hand, is probably age-related[44,45] but not clearly related to the delay in octreotide response. The gut neuroendocrine system,[29,46,47] ICC,[48,49] nitric oxide,[50] as well as pancreatic polypeptide and secretory enzymes,[51-53] all seem important for the control of the MMC and fasting motility of the small bowel and alterations in these systems may contribute to our results. Although there is evidence of a depletion of GI endocrine cells and ICC,[10-13,54] reduced nitric oxide synthesis[55], and pancreatic amyloid deposits[56-58] in patients with ATTRm amyloidosis, there is no evidence of a more severe loss of nitric oxide, enteric neurons, endocrine cells, or ICC in late-onset cases so far.

Aside from the differences related to age at disease onset, no major manometric differences were found for the other variables analyzed among ATTRm amyloidosis patients. This might be related to the small sample sizes, but also to the complex control of GI motility. Interestingly, the most disabled patient, suffering from a rather severe peripheral polyneuropathy, autonomic neuropathy with orthostatic hypotension and constipation, displayed a normal small bowel manometry. Thus, as with gastroparesis,[7,59] it appears difficult to predict GI motility from the patients' clinical symptoms alone, and multiple factors probably contribute to the impaired intestinal motility in ATTRm amyloidosis.

In conclusion, patients with ATTRm amyloidosis, even at early stages, displayed abnormalities in their small bowel motility more frequently than non-amyloidosis patient controls. The manometric pattern was not distinct, but probably best consistent with a combined neuromyopathic disorder, which could reflect the autonomic neuropathy and changes in the gut neuroendocrine system seen in these patients. Late-onset patients showed a delay in octreotide response although they usually have less GI symptoms than early-onset cases, which is a finding that warrants further histopathological investigation of potential differences in the enteric nervous system and gut endocrine cells between patients with early and late disease onset.

ACKNOWLEDGMENTS

Special thanks to Professor Ole B Suhr, Department of Public Health and Clinical Medicine, Umeå University, who helped with the clinical examinations and contributed with his extensive knowledge in the field of ATTRm amyloidosis and gastroenterology, and to Dr. Rolf Hörnsten at the Department of Clinical Physiology, Umeå University Hospital who analyzed the HRV recordings.

DISCLOSURES

The authors have no conflicts of interest to declare for the current study.

AUTHOR CONTRIBUTION

JW contributed to the design of the study, performed clinical examinations and statistical analyses, and wrote the paper. GL and HT analyzed the small bowel manometries and contributed to the planning and the design of the study. IA performed clinical examinations and contributed to the design of the study. PK participated in the planning and design of the study. All authors read and approved the final manuscript.

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How to cite this article: Wixner J, Törnblom H, Karling P, Anan I, Lindberg G. Abnormal small bowel motility in patients with hereditary transthyretin amyloidosis. *Neurogastroenterol Motil*. 2018;30:e13354. https://doi.org/10.1111/nmo.13354