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# PROGRESSION OF PERIPHERAL AND AUTONOMIC NERVE DYSFUNCTION IN HEREDITARY TRANSTHYRETIN AMYLOIDOSIS

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## INTRODUCTION

Hereditary transthyretin amyloidosis (hATTR) is a systemic disease predominantly affecting peripheral nerves and heart. Autonomic dysfunction is an undervalued feature of hATTR caused by small nerve fiber involvement. Autonomic involvement is often subtle and undetected if not specifically investigated.

## OBJECTIVE

We conducted an observational, retrospective, longitudinal study in order to assess cardiovascular autonomic function in patients carrying ATTR pathogenic mutations starting at presymptomatic stage.

## MATERIALS AND METHODS

Patients underwent to cardiovascular reflex test (CRTs) including head-up tilt test (HUTT), Valsalva manoeuvre (VM), deep breathing (DB), cold face (CF) and hand-grip test (HG). CRTs were conducted in Policlinico Tor Vergata Autonomic Unit under continuous blood pressure (BP) and heart rate (HR) monitoring. On the same day patients performed nerve conduction studies (NCS) to assess large fiber involvement. A 60 months (5 years) median follow up time was considered.

## RESULTS

10 patients from 4 different families were enrolled in the study (6 female and 4 male). All patients were asymptomatic carrier of Val30Met TTR mutation. Median age was 50 years at first evaluation. At first assessment (**T0**) none of the patients had polyneuropathy at NCS; carpal tunnel syndrome was detected in 4 out of 10 subjects. CRTs revealed lower respiratory sinus arrythmia at deep breathing test (Δ I-E) in 2 out of 10 patients. Other CRTs were within the normal ranges. At 5 years (**T5**) follow up, 2 out of 10 patients developed an axonal length-dependent motor-sensory polyneuropathy. Deep breathing (Δ I-E), was out of normal ranges in 4 subjects with significantly lower values in T5 compared to T0 evaluation (p = 0.05) *(Figure 1)*. Five and three patients had pathological responses to cold face and hand grip test, respectively. During HUTT, HR changes at the third minute significantly decreased between T0 and T5 (p = 0.006) *(Figure 2)*. During VM, a decrease of Valsalva ratio was observed in T5 assessment (p = 0.07) *(Figure 3)*. Cold face test revealed significant lower responses in both diastolic blood pressure (DBP) and HR at T5 (p = 0.03 and 0.06, respectively). SBP and HR were also significantly decreased during hand grip test at T5 (p = 0.01, 0.008).

| | Sex/ Age | PNP | | HUTT | | DB | | VM | | HG | | CF | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | T0 | T5 | T0 | T5 | T0 | T5 | T0 | T5 | T0 | T5 | T0 | T5 |
| **1** | F/51 | No | No | N | N | N | N | N | N | N | N | N | N |
| **2** | F/52 | No | No | N | N | N | N | N | N | N | A | N | N |
| **3** | M/41 | No | No | N | N | N | N | N | A | N | A | N | A |
| **4** | M/44 | No | Yes | N | N | N | A | N | N | N | N | N | N |
| **5** | F/51 | No | No | N | N | A | A | N | N | N | N | N | N |
| **6** | F/46 | No | No | N | N | N | N | N | N | N | N | N | N |
| **7** | F/49 | No | No | N | N | N | N | N | N | N | N | N | A |
| **8** | M/40 | No | No | N | N | A | A | N | N | N | N | N | A |
| **9** | M/70 | No | No | N | N | N | A | N | N | N | N | N | A |
| **10** | F/76 | No | Yes | N | N | N | N | N | A | N | A | N | A |

*N = normal; A = abnormal*

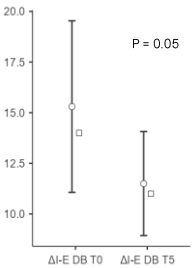

Figure 1

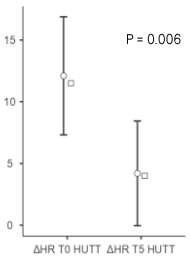

Figure 2

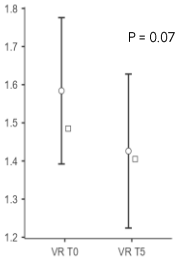

Figure 3

## CONCLUSIONS

Longitudinal assessment of CRTs in hATTR patients revealed an involvement of autonomic system also in asymptomatic subjects without polyneuropathy. Involvement of cardiovagal response could be considered as an early marker of autonomic dysfunction (1). Sympathetic adrenergic dysfunction was also observed at follow up evaluation. A complete battery of standardized CRTs could be useful to detect initial peripheral nervous system involvement in hATTR.

(1) Guaraldi P, Rocchi C, Cani I, et al. Cardiovascular reflex tests detect autonomic dysfunction in symptomatic and pre-symptomatic subjects with hereditary transthyretin amyloidosis. *Clin Auton Res.* 2023;33(1):15-22. doi:10.1007/s10286-022-00921-x