Abstracts of the 2022 European Federation of Autonomic Societies (EFAS) Congress

Abstract No: EFAS-2022-01

Heart Rate Variability (HRV) as a measure of autonomic function in non-acute traumatic injury (TI): a systematic review and meta-analysis

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Background: Heart rate (HR) variability (HRV) is a non-invasive measure of autonomic function. The relationship between unselected long-term traumatic injury (TI) and HRV has not been investigated.

Objective: To examine the impact of non-acute TI (> 7 days post-injury) on standard HRV indices in adults.

Methods: Protocol was registered in the PROSPERO database (CRD42021298530). Four electronic databases (CINAHL, Medline, Scopus and Web of Science) were searched. The quality of studies, risk-of-bias (RoB), and quality of evidence (QoE) were assessed using Axis, RoBANS, and GRADE, respectively. Using the random-effects model, mean difference (MD) for root mean square of successive differences (RMSSD) and standard deviation of NN-intervals (SDNN), and standardized mean difference (SMD) for Low-frequency (LF)/High-Frequency (HF) were pooled in RevMan guided by the heterogeneity score.

Results: 2152 records were screened followed by full-text retrieval of 72 studies. Thirty one studies were assessed on the inclusion and exclusion criteria. Only 4 studies met the inclusion criteria. Three studies demonstrated a high RoB (mean RoBANS score 14.5 ± 3.31) with a low QoE. TI was associated with significantly higher resting HR. Meta-analysis of three cross-sectional studies demonstrated a statistically significant reduction in RMSSD (MD – 8.45 ms, 95% CI – 12.78, – 4.12, p < 0.0001) and SDNN (MD – 9.93 ms, 95% CI 1– 14.82, – 5.03, p < 0.0001) (low QoE) in participants with TI than the uninjured control. The pooled analysis of four studies showed a higher LF/HF ratio among injured versus uninjured (SMD 0.20, 95% CI 0.01–0.39, p < 0.04) (very low QoE).

Conclusions: Albeit low QoE, non-acute TI is associated with a reduction in HRV indicating autonomic imbalance. This might explain greater cardiovascular risk following TI.

Abstract No: EFAS-2022-02

Influence of stress symptoms on the results of COMPASS-31

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Background: Autonomic symptoms are in close relation to symptoms of stress.

Objectives: To evaluate the symptoms of anxiety on the results of Composite Autonomic Symptom Score-31 (COMPASS-31) in a large population of people referred to tilt-table testing and healthy controls (HC).

Methods: Nine hundred and sixty consecutive patients referred to tilt-table testing and 518 HC were enrolled. All participants completed Composite Autonomic Symptom Score-31 (COMPASS-31). Stress symptoms were evaluated by Depression, Anxiety and Stress-21 (DASS-21) questionnaire, and the stress part’s values were considered abnormal if > 14. Results of the tilt-table test were interpreted as normal, reflex syncope, orthostatic hypotension (OH), or postural orthostatic tachycardia syndrome (POTS).

Results: The patients’ median result of the COMPASS-31 was 25.8 (range 0–80.8), out of which 28.7% had stress symptoms. For the HC, the median COMPASS-31 result was 7.9 (0–52.9), out of which 19.5% had stress symptoms. In both groups (patients and healthy controls) COMPASS-31 was higher in participants with stress symptoms (34.3 vs 22.2, p < 0.001 and 16.5 vs 6.5, p < 0.001, respectively). On the tilt-table test, 70.7% had a normal tilt-table test, 23.2% had reflex syncope, 4.7% had OH, and 1.4% had POTS. In patients with a normal tilt-table test and reflex syncope COMPASS-31
was higher in participants with stress symptoms (35.4 vs 22.1, \( p < 0.001 \) and 29.6 vs 21.1, \( p < 0.001 \)). There was no difference in the COMAPSS-31 depending on the stress symptoms for patients with OH (37.9 vs 29.3, \( p = 0.083 \)).

**Conclusion:** People with stress symptoms score higher on COM- PASS-31 regardless of underlying autonomic pathology. These data indicate that stress symptoms should be evaluated in everyday clinical practice in the autonomic laboratory.

**Abstract No: EFAS-2022-03**

**Influence of anxiety symptoms on the results of COMPASS-31**

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**Background:** Autonomic symptoms are in close relation to symptoms of anxiety.

**Objectives:** To evaluate the symptoms of anxiety on the results of Composite Autonomic Symptom Score-31 (COMPASS-31) in a large population of people referred to tilt-table testing and healthy controls (HC).

**Methods:** Nine hundred and sixty consecutive patients referred to tilt-table testing and 518 HC were enrolled. All participants completed Composite Autonomic Symptom Score-31 (COMPASS-31). Anxiety symptoms were evaluated by Depression, Anxiety and Stress-21 (DASS-21) questionnaire, and the anxiety part’s values were considered abnormal if \( \geq 17 \). The tilt-table test was interpreted as normal, reflex syncope, orthostatic hypotension (OH), or postural orthostatic tachycardia syndrome (POTS).

**Results:** The patients’ median result of the COMPASS-31 was 25.8 (range 0–80.8), out of which 28% had depressive symptoms. For the HC, the median COMPASS-31 result was 7.9 (0–52.9), out of which 27.2% had depressive symptoms. In both groups (patients and healthy controls) COMPASS-31 was higher in participants with depressive symptoms (34.9 vs 22.4, \( p < 0.001 \) and 13.5 vs 6.2, \( p < 0.001 \), respectively). On the tilt-table test, 70.7% had a normal tilt-table test, 23.2% had reflex syncope, 4.7% had OH, and 1.4% had POTS. In patients with a normal tilt-table test, reflex syncope, and OH, COMPASS-31 was higher in participants with depressive symptoms (35.3 vs 22.1, \( p < 0.001 \), 31.8 vs 21.9, \( p < 0.001 \), and 38.7 vs 29.5, \( p = 0.022 \), respectively).

**Conclusion:** People with depressive symptoms score higher on COMPASS-31 regardless of underlying autonomic pathology. These data indicate that depressive symptoms should be evaluated in everyday clinical practice in the autonomic laboratory.

**Abstract No: EFAS-2022-05**

**What are the predictors of COMPASS-31 questionnaire results?**

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**Background:** Several studies so far, in different illnesses, have shown that autonomic symptom burden is higher in persons with associated symptoms of depression, anxiety, and/or stress.

**Objectives:** To evaluate the influence of demographic characteristics, results of the tilt-table test, and symptoms of depression, anxiety, and stress on the results of Composite Autonomic Symptom Score-31 (COMPASS-31) in a large population of people referred to tilt-table testing and healthy controls (HC).

**Methods:** Nine hundred and sixty consecutive patients referred to tilt-table testing and 518 HC were enrolled. All participants completed Composite Autonomic Symptom Score-31 (COMPASS-31). We performed a linear regression analysis (with the following independent variables: age, sex, marital status, education, employment, number of children, healthy control or participant referred to tilt-table test (normal tilt-table test, reflex syncope, orthostatic hypotension (OH), postural orthostatic tachycardia syndrome (POTS)), depression, anxiety and stress symptoms measured with Depression, Anxiety and Stress-21 (DASS-21) questionnaire (the cut-off value for each symptom being defined as \( > 9, > 7, \) and \( > 14 \), respectively to
detect which variables were associated with the results of COMPASS-31. Statistically significant predictors from the univariable analysis were included in the multivariable regression analysis.

**Results:** In the univariable linear regression analysis HC, having a university degree and being employed were negative, while age, female sex, being widowed, having 8 or 12 years of education, being retired, depression, anxiety, and stress symptoms were positive predictors of COMPASS-31. In a multivariable linear regression analysis HC (B = −12.878, 95% CI −14.214 to 11.541) was negative, while female sex (B = 3.424, 95% CI 2.067–4.780), depression (B = 3.884, 95% CI 2.168–5.601), anxiety (B = 7.652, 95% CI 6.172–9.133) and stress (B = 4.434, 95% CI 2.593–6.276) symptoms were positive predictors of COMPASS-31.

**Conclusion:** These results indicate that symptoms of depression, anxiety, and stress are independent positive predictors of COMPASS-31.

**Abstract No: EFAS-2022-06**

Daytime autonomic evaluation in patients affected by chronic insomnia: a case–control study

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**Background:** Chronic insomnia (CI) is considered a risk factor for cardiovascular disease which may result from increased sympathetic modulation.

**Objective:** To explore cardiovascular autonomic function in patients with CI during wakefulness.

**Methods:** CI patients and healthy controls underwent to cardiovascular reflexes consisting of a head-up tilt test (HUTT), Valsalva maneuver, deep breathing, hand grip, and cold face test. Heart rate variability (HRV) was analyzed in rest conditions and during HUTT.

**Results:** Seventeen CI patients and sixteen controls were evaluated. CI patients showed an increased delta systolic blood pressure (ΔSBP) (p = 0.003), and decreased delta heart rate (ΔHR) (p < 0.001) at 10 min of HUTT, and a lower Valsalva ratio (VR) (p = 0.021) than controls. Spectral analysis of HRV during HUTT showed a lower LFnu (p = 0.013), a higher HFnu (p = 0.013), and a lower LF/HFnu (p = 0.013) in CI.

**Conclusions:** Patients with CI showed an increased ΔSBP and a reduced ΔHR at HUTT. Moreover, CI patients showed a significantly reduced VR at Valsalva maneuver, mostly dependent on cardiovascular integrity and, thus, on parasympathetic activity. HRV components in resting condition were comparable to HC; however, a decrease in the magnitude of LFnu and in LF/HFnu and an increase in HFnu was observed at HUTT, indicating that the increase in cardiac sympathetic modulation and the reduction in cardiac vagal control physiologically induced by HUTT are unbalanced in CI with respect to healthy subjects. Our study suggests that CI patients have an impaired capability to correctly respond to stressor stimuli. This reduced autonomic efficiency may contribute to their increased susceptibility to cardiovascular disease.

**Abstract No: EFAS-2022-07**

Assessment of bladder function using COMPASS-31 and uroflowmetry among patients with relapsing–remitting multiple sclerosis

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**Background:** Bladder symptoms are common in patients with relapsing–remitting multiple sclerosis (RRMS) and require early detection. As uroflowmetry and bladder-sonography require specified equipment and expertise, the Composite-Autonomic-Symptom-Score-31 (COMPASS-31), a self-questionnaire, may facilitate detecting bladder symptoms.

**Objective:** We aimed to evaluate whether abnormal COMPASS-31 bladder-scores predict abnormal residual urine-volume or uroflowmetry values in RRMS-patients.

**Methods:** In 70 RRMS-patients and 30 healthy participants, we assessed voided urine-volume, maximal and average flow-rates, flow-time, time to maximum flow by uroflowmetry (Solar-Uroflow™, MMS, Germany), pre-voiding urine-volume and post-voiding residual urine-volume by bladder ultrasonography (Scanmaster™, MMS, Germany). Our RRMS-patients completed the German version of COMPASS-31 and were classified into the subgroups with or without abnormal COMPASS-31 bladder-scores. Parameters between the two groups of patients and controls were compared by the Kruskal–Wallis-test. Mann–Whitney-U-tests were used for post-hoc comparisons between two groups. The Spearman-test assessed correlations between COMPASS31 scores and voiding parameters. Significance was assumed for p < 0.05.

**Results:** According to COMPASS-31, 43 RRMS-patients had, and 27 RRMS-patients did not have any bladder symptoms. Average and maximal flow-rates were significantly lower in RRMS-patients with bladder symptoms than in RRMS-patients without bladder symptoms or healthy participants, both parameters negatively correlated with the COMPASS-31 bladder-scores. Post-voiding residual urine-volume was higher in both patient groups than in healthy participants.

**Conclusion:** In our RRMS-patients, increased COMPASS-31 bladder-scores correlated with decreased uroflow-rates. Post-voiding residual urine-volume was increased even in RRMS-patients without bladder symptoms. Therefore, the COMPASS-31 is valuable for screening bladder dysfunction but should be complemented by uroflowmetry and sonographic assessments.

**Abstract No: EFAS-2022-08**

Erectile dysfunction in men with multiple sclerosis

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**Background:** Erectile dysfunction (ED) is a common and frequent complication of multiple sclerosis (MS). It affects up to 80% of men with MS and is associated with a reduced quality of life. ED is often multifactorial and is influenced by various factors, including neurological, psychological, and vascular factors.

**Objective:** The primary objective of this study was to determine the prevalence of ED in men with relapsing–remitting multiple sclerosis (RRMS) and to explore the relationship between ED and various factors, including disease duration, disability, and quality of life.

**Methods:** We conducted a cross-sectional study of 100 men with RRMS, aged 20–70 years, and 100 healthy controls, matched for age and ethnicity. All participants were evaluated using the International Index of Erectile Function (IIEF) questionnaire, which assesses sexual function and its impact on daily life.

**Results:** The overall prevalence of ED was 52% in men with RRMS, compared to 20% in healthy controls (p < 0.001). The prevalence of ED was higher among men with longer disease duration and more severe disability. ED was associated with lower quality of life and lower sexual activity.

**Conclusion:** Our findings highlight the high prevalence of ED in men with RRMS and underscore the importance of addressing this issue in clinical practice. Further research is needed to understand the underlying mechanisms and to develop effective interventions.
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**Background:** Sexual difficulties are common in men with multiple sclerosis (mWMS), and different domains of sexual function—desire, arousal, orgasm, and ejaculation—can be affected.

**Objectives:** To evaluate the prevalence and predictors of erectile dysfunction in mWMS.

**Methods:** 179 consecutive mWMS (age 37.25 ± 9.48 years, disease duration 7.64 ± 5.54 years) during their regular follow-up visit at the Department of Neurology, University Hospital Center Zagreb, and 32 (33.72 ± 8.53 years) healthy controls (HC) were enrolled. mWMS completed the sexual health inventory for men (IIEF-5), Modified Fatigue Impact Scale (MFIS) (cognitive, physical, and psychosocial subdomain), Beck depression inventory (BDI-2), and the 5-level EQ-5D questionnaire (your health today question, range from 0–100). HC completed the IIEF-5. We performed a linear regression analysis (with the following independent variables: age, disease duration, the initial presentation of MS, Expanded Disability Status Scale (EDSS), evident MRI lesions in the brainstem or spinal cord, and results of the BDI-2, subscales of the MFIS and your health today question of the EQ-5D). Statistically significant predictors from the univariable analysis were included in the multivariable regression analysis.

**Results:** From the available cohort, 10 (5.6%) mWMS and 1 (3.1%) HC did not have sexual intercourse. mWMS scored less on IIEF-5 compared to HC (23, range 6–25 vs 24, range 14–25, p = 0.017). Erectile dysfunction (defined as IIEF-5 score ≤ 21) was present in 37.9% of mWMS and 25.8% of HC, p = 0.014. The multifunctional initial presentation of MS, MRI lesions in the brainstem, EDSS, physical, cognitive, and psychosocial domains of MFIS were negative and your health today question of the EQ-5D was a positive predictor of the IIEF-5 score. In a multivariable linear regression analysis age (B = −0.155, 95% CI −0.275 to −0.035), the multifunctional initial presentation of MS (B = −7.857, 95% CI −15.625 to −0.089) and cognitive part of MFIS (B = −0.212, 95% CI −0.410 to −0.014) were negative predictors of the IIEF-5 score.

**Conclusion:** Erectile dysfunction is very frequent in mWMS. Increased age and presentation with multifunctional symptoms at disease onset and cognitive fatigue are negative predictors of the IIEF-5 score.

**Abstract No: EFAS-2022-09**

Cardiovascular reflex tests detect autonomic dysfunction in symptomatic and pre-symptomatic subjects with hereditary transthyretin amyloidosis

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**Background:** Autonomic dysfunction is a distinctive but undervalued feature of hereditary transthyretin amyloidosis (ATTRv) that may predate the onset of polyneuropathy or cardiomyopathy.

**Objective:** To examine autonomic function by means of standardized cardiovascular autonomic reflex test (CRTs) in patients with genetically proven ATTRv, evaluating both symptomatic and pre-symptomatic subjects.

**Methods:** In this cross-sectional study, we analyzed all the ATTRv subjects who underwent CRTs (head-up tilt test; Valsalva manoeuvre; deep breathing; cold face test; handgrip test) under continuous blood pressure (BP) and heart rate (HR) monitoring to our Autonomic Units. ATTRv subjects were divided according to the presence/absence of polyneuropathy in ATTRv-PN and ATTRv-w0PN, respectively. Age- and sex-matched controls (HC) were used for comparison.

**Results:** Thirty-seven ATTRv subjects (19 ATTRv-PN, 18 ATTRv-w0PN) and 41 HC performed CRTs. Four out 37 ATTRv subjects (11%) presented neurogenic orthostatic hypotension during head-up tilt test. According to CRTs results, autonomic dysfunction characterized by either sympathetic or parasympathetic impairment were detected in 37% and 63% of ATTRv-PN patients, respectively.

Also, pre-symptomatic ATTRv subjects (ATTRv-w0PN) presented a significant impairment of autonomic responses to Valsalva manoeuvre (overshoot p = 0.004; Valsalva ratio p = 0.001) compared to HC.

**Conclusion:** Autonomic dysfunctions are frequent in ATTRv subjects when detected by means of standardized CRTs, being relevant also in the pre-symptomatic stage. Cardiovascular functions are affected primarily and more. This may be crucial in defining the proper diagnostic workup for early diagnosis and ameliorating the chance of a prompt administration of disease-modifying treatments.

**Abstract No: EFAS-2022-10**

Rising high, falling low; subjects with strong cardioinhibition in vasovagal syncope have a higher heart rate, already in the supine position

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**Background:** The degree of cardioinhibition (CI) is variable during vasovagal syncope (VVS).

**Objective:** To assess whether subjects with strong and weak CI have different hemodynamic profiles.

**Methods:** We included 149 subjects with complete VVS and CI during a tilt-table test. CI was defined as a sustained decrease in heart rate (HR) before syncope. We defined 3 subgroups of strong, intermediate, and weak CI based on tertile values of the HR decrease during CI. We assessed mean arterial pressure (MAP), HR, stroke volume (SV), and total peripheral resistance (TPR) at the start of CI and in the supine position.

**Results:** At the start of CI, mean (SD) HR was 111 (13) bpm in the strong CI group, 98 (18) bpm in the intermediate group, and 82 (16) bpm in the weak CI group (p < 0.0001). HR increased in the minutes before the start of CI only in subjects with strong CI. MAP at the start of CI was higher in the strong (82 (19) mmHg) compared to the weak (71 (14) mmHg) CI group (p = 0.003), while SV was slightly lower in strong CI (0.045 (0.015) liter (L)) compared to weak CI (0.054 (0.017) L, p = 0.03). Mean supine HR was 76 (10) bpm for strong CI, 73 (10) bpm for intermediate CI, and 64 (9) bpm for weak CI (p < 0.0001). There were no significant differences in supine MAP, SV, or TPR between the groups.
Conclusion: Subjects with strong CI have a different hemodynamic profile at the start of CI as well as a higher HR already in the supine position.

Abstract No: EFAS-2022-11

Cerebral structural alterations associated with cardiovascular autonomic failure in multiple system atrophy
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Background: Early severe autonomic failure in multiple system atrophy (MSA) is a factor of poor survival. Postmortem studies suggest that it is related to the degeneration of preganglionic autonomic neurons of the brainstem and spinal cord.

Objective: To characterize morphological alterations associated in vivo with cardiovascular (CV) autonomic failure.

Methods: 62 MSA patients followed at the French Reference center were retrospectively included, aged 67.3 ± 8.6 years, 69.4% MSA-P, symptoms duration 4.2 ± 2.1 years. Assessment of sympathetic and parasympathetic CV failure was respectively based on changes (i) in systolic and diastolic blood pressure during tilt-test (ASBP and ΔDBP), and (ii) in heart rate (ΔHR) using a composite score that combines HR response to deep breathing and root-mean-square of the difference between two successive R waves (rMSSD). Voxel-based morphometry (SPM12), volumetry, and cortical thickness measurements (FreeSurfer 7.0) of T1-weighted anatomical images were used to assess the atrophy of the subentorhinal gray matter (GM). Multivariate analysis included age, disease severity (UMSARS), and total intracranial volume as confounding factors.

Results: A decrease in GM volume in the left anterior cingulum and in the deep nuclei of the cerebellum was associated with a more severe sympathetic CV dysfunction. GM loss in the dentate nuclei was correlated to greater parasympathetic CV failure. Medulla oblongata atrophy was correlated to ASBP and ΔDBP.

Conclusion: Cerebellar degeneration may contribute to the severity of CV autonomic failure in MSA by affecting baroreflex responses. Medulla oblongata impairment could contribute to altered sympathetic responses to the baroreflex.

Abstract No: EFAS-2022-12

Cardiovascular autonomic involvement in acute SARS-CoV-2 infection, post-COVID-19 Syndrome and COVID-19 vaccination—a systematic review
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Background: Cardiovascular autonomic nervous system (ANS) seems to be affected during severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, in the post-COVID-19 phase, and after SARS-CoV-2 vaccination.

Objective: To summarize and describe the cases reported in the literature with cardiovascular ANS involvement in the context of COVID-19.

Methods: Systematic review of cases with cardiovascular ANS involvement described in the context of SARS-CoV-2 infection, post-COVID-19, and SARS-CoV-2 vaccination by screening both published and preprint articles.

Results: One hundred and thirty-nine cases were identified (81 in acute SARS-CoV-2, 53 in post-COVID-19, and 5 after SARS-CoV-2 vaccination). Post-COVID-19 cases were younger than those with acute infection (p = 0.002) and had female predominance (p = 0.028). The primary autonomic diagnosis was significantly different in acute and post-COVID-19 conditions: reflex syncope in acute SARS-CoV-2 (p = 0.005) and postural orthostatic tachycardia syndrome in post-COVID-19 (p = 0.001). Autonomic function tests were performed in the majority of patients with post-COVID-19 (91% vs 61% with acute infection, p = 0.0001). Treatment included several non-pharmacological and pharmacological measures in both acute and post-COVID-19, but the first ones were more used in the latter (p = 0.001). Despite (limited) mortality associated with acute SARS-CoV-2, the outcome was generally better compared to post-COVID-19 patients regarding cardiovascular autonomic dysfunction, with greater frequency of full recovery (p = 0.002) and fewer instances of partial (p = 0.045) or no recovery (p = 0.043).

Conclusions: Different phenotypic clusters of cardiovascular ANS involvement may arise depending on the clinical phase of COVID-19 with reflex syncope predominating in the acute illness and POTS in the post-COVID-19 phase. The association between ANS dysfunction and COVID-19 vaccination remains controversial.

Abstract No: EFAS-2022-13

Cardiovascular autonomic dysfunction as a marker of progression and conversion in isolated REM Sleep Behavior Disorder
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Background: Cardiovascular autonomic dysfunction is a common marker of neurodegeneration in iRBD, with the greatest impairment in sympathetic function. However, prospective data are limited.

Objectives: To objectively assess cardiovascular autonomic function in patients with isolated REM sleep behavior disorder (iRBD), its longitudinal progression, and value for conversion.

Methods: We enrolled 34 consecutive videopolisomnography-confirmed IRBD patients and followed them longitudinally for a mean of 2.35 ± 1.27 years. Each patient underwent Ewing’s battery of cardiovascular reflex tests. Procedures were performed at baseline, and annually for a total of 103 observations (range 2–6 per patient).
Results: Patients (24 males–71%) had a mean age of 69.69 ± 6.42 years. At baseline 21 iRBD (62%) showed a pathologic Valsalva Maneuver, of them 8 showed neurogenic orthostatic hypotension (nOH). Handgrip (HG), Cold face (CF), and deep breathing (DB) tests were abnormal in 16, 12, and 10 patients respectively. At follow-up 9 iRBD presented nOH (p = 0.617), and the frequency of abnormal VM, HG, CF, and DB did not significantly change over the years. Seven patients converted to an alpha-synucleinopathy, and patients with nOH at baseline had a higher risk of conversion (p = 0.010). Considering blood pressure and heart rate (HR) responses, systolic blood pressure decreased at the 3rd minute (p = 0.013) and 10th (p = 0.006) minute of tilt significantly increased in magnitude. Valsalva Ratio (p = 0.013) and DB HR (p = 0.034) change decreased.

Conclusions: Not only is cardiovascular autonomic impairment in iRBD already manifest, but it also worsens over time impacting conversion, and justifying its value as a marker of progression.

Abstract No: EFAS-2022-14

Hemodynamic determinants of supine hypertension in neurogenic orthostatic hypotension

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Background: Patients with classic orthostatic hypotension (cOH) often exhibit supine hypertension. The underlying mechanisms of this complication are poorly understood.

Objective: To investigate the hemodynamic mechanisms of supine hypertension in patients with cOH.

Methods: We performed a retrospective analysis of continuous blood pressure (BP) patterns in 65 patients with cOH (53 neurogenic OH [nOH]) and 39 controls who underwent a tilt test. Supine rest and three minutes after the head-up tilt were compared. Mean arterial pressure (MAP) and its constituent heart rate, stroke volume (SV), and total peripheral resistance (TPR) were analyzed. Both groups were split based on the median supine SBP of 150 mmHg, dividing them into a high and a low supine SBP group.

Results: Patients with cOH and high supine SBP had a higher supine TPR and MAP than those with a lower supine SBP, while supine heart rate and SV did not differ between groups. The upright position yielded a more pronounced MAP fall and smaller SV decrease in patients with a higher supine BP. Notably, the larger BP fall upon tilting was not accompanied by a more marked TPR response, suggesting a ceiling effect of TPR. Interestingly, when comparing the high and low supine SBP groups in healthy controls, we did not find contrasts in supine or standing TPR.

Conclusions: Supine hypertension in cOH is primarily driven by a high TPR in the supine position and a larger BP fall caused by an inability to increase TPR beyond supine levels. Supine hypertension in nOH may result from long-term influences affecting BP homeostasis.

Abstract No: EFAS-2022-15

Autonomic failure is a frequent and early prognostic marker of disease progression in hereditary/variant transthyretin amyloidosis: a single center experience

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Background: Hereditary or variant transthyretin amyloidosis (ATTRv amyloidosis) is a rapidly progressive proteinopathy resulting in deposits of extracellular fibrillary misfolded β-sheets in the heart, gastrointestinal tract, and peripheral nerves.

Objective: We described autonomic features, performed quantitative cardiovascular autonomic function testing (AFT), and explored whether autonomic dysfunction could serve as a prognostic marker of disease progression in a population of ATTRv amyloidosis.

Methods: Symptoms of orthostatic intolerance, gastrointestinal, genitourinary and sudomotor dysfunction, as well as neuropathic and cardiac features, were collected at two different time points, namely at disease onset (retrospectively) and at the time of AFT. This included head-up tilt table testing, standing test, Valsalva maneuver, pressor stimuli, and deep breathing. The severity of quantitative autonomic impairment detected at AFT was stratified into 3 stages: autonomic stage 0—no cardiovascular dysfunction; autonomic stage 1—isolated parasympathetic or mild mixed sympathetic and parasympathetic autonomic dysfunction; autonomic stage 2—widespread autonomic cardiovascular dysfunction. The polyneuropathy disability (PND) staging was used to stratify the severity of peripheral neuropathy and its progression rate (time to reach PND stages 1–2 and further progression to stages 3–4).

Results: A cohort of 120 patients (35 females) had a confirmed diagnosis of ATTRv amyloidosis. Age at onset was available for 88/120 patients, while symptoms at disease onset (any between autonomic, neuropathic, or cardiac) were available for 80/120 patients. At disease onset, symptoms of autonomic dysfunction were present in 24/80 (30%) subjects, while neuropathic and cardiac symptoms were present in 51/80 (63.75%) and 17/80 (21.25%) patients respectively. Ninety seven/one hundred and twenty patients had not received any disease-modifying therapy from disease onset to AFT and were included in our final analysis. 63/97 (64.9%) patients reported symptoms of autonomic dysfunction at the time of autonomic assessment [mean disease duration of 4.27 ± 3.72 (years ± SD)]. Gastrointestinal dysfunction was the most common feature (54/63, 87.5%) followed by orthostatic intolerance (40/63, 63.4%), syncope (25/63, 39.6%), urinary (23/63, 36.5%), sexual (22/63, 34.9%), and sudomotor (10/63, 15.8%) dysfunction. Fifty eight/ ninety seven patients reported neuropathic symptoms. Quantitative AFT was analyzed in a subset of 46/97 patients, who were not treated with antihypertensive medications. Autonomic failure (autonomic
stages 1 and 2) was present in 34/46 (73.9%) patients. Nerve conduction studies were available in a subset of 73/97 patients, showing evidence of large and small fiber neuropathy in 47/73 (64.3%) and 7/73 (9.5%) respectively. Progression rates from PND stage 1 or 2 to 3 or 4 were available for a subset of 23 patients, and it was significantly shorter for patients with autonomic symptoms at onset (median time 2 years; range 1–8 years), compared to patients without autonomic onset (median time 5 years; range 2–12 years).

Conclusion: Autonomic dysfunction is an early, underestimated, and rapidly progressive feature in ATTRv amyloidosis, and it can predict faster disease progression and motor disability.

Abstract No: EFAS-2022-16

Sex-related differences in the clinical presentation of people with multiple system atrophy

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Background: Multiple system atrophy (MSA) is considered to affect both sexes equally without an influence on progression or survival, but it is unclear whether sex influences the clinical phenotype.

Objective: To investigate sex-related differences in MSA clinical presentation.

Methods: We censored the frequency of the motor and non-motor features at disease onset and last-available follow-up in a well-characterized, retrospective cohort (n = 144) of people with probable OR possible MSA, at least 12 months follow-up and 3 years of disease duration at last available visit.

Results: Seventy-three female and 71 male (49%) individuals with MSA were included. Men more frequently reported a disease onset with orthostatic intolerance (14 vs. 4%; p = 0.044). At the last available follow-up, women suffered from greater motor disability [Hoehn-&-Yahr scale 4.0 (4.0; 5.0) vs. 4.0 (2.0; 5.0); p = 0.043], while also showing a higher cumulative prevalence of depression over the disease course (81 vs. 45%; p < 0.001). By contrast, male MSA individuals featured a higher cumulative prevalence of sexual dysfunction (100 vs 82%; p = 0.006), orthostatic hypotension (85 vs. 66%; p = 0.009), severe orthostatic blood pressure falls (i.e., ≥ 30/15 mmHg in 71 vs. 51%; p = 0.021), supine hypertension (53 vs. 33%; p = 0.023), history of syncope (50 vs. 30%; P = 0.014), and cardiovascular comorbidities (48 vs. 30%; p = 0.029).

Conclusion: Cardiovascular autonomic failure, which is known to be associated with increased morbidity and mortality, may have an earlier onset, and be more frequent and severe in male MSA individuals, whereas women appear to suffer from a greater motor disability and higher neuropsychiatric burden.

Abstract No: EFAS-2022-18

Autonomic biomarkers and cutaneous phosphorylated α-synuclein deposition differentiate pure autonomic failure from other α-synucleinopathies

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Background: Pure autonomic failure (PAF), multiple system atrophy (MSA), Parkinson’s disease (PD) and Dementia with Lewy Bodies (DLB) are neurodegenerative diseases characterised by abnormal α-
Objective: We evaluated multiple autonomic biomarkers in a cohort of patients with α-synucleinopathies to identify biomarkers to differentiate between disease groups and predict phenoconversion in patients presenting with PAF.

Methods: We retrospectively extracted data from the first cardiovascular autonomic testing, plasma catecholamines, and pupillometry of 391 patients with PAF, MSA, and DLB (including PD and DLB) seen at a national autonomic unit between 1987 and 2021. 52 patients recruited to a prospective study between 2018 and 2021 also had skin biopsies processed for phosphorylated α-synuclein (p-syn) and autonomic symptom and quality of life questionnaires.

Results: Amongst the patient groups, patients with PAF had the most severe orthostatic hypotension and lowest supine plasma noradrenaline at initial assessment (P < 0.001), with 64% demonstrating sympathetic pupillary deficits, consistent with greater postganglionic adrenergic denervation. Twenty six percentage of patients initially presenting with PAF converted to MSA/LBD. More preserved orthostatic tolerance, heart rate response to deep breathing ≥ 10 bpm (OR 2.9, P = 0.001) supine noradrenaline ≥ 200 pg/ml (OR 2.4, P < 0.001), and normal pupils (OR 4.7, P = 0.01), predicted future phenoconversion, with younger age and higher supine noradrenaline predicting conversion to MSA rather than LBD. Patients with PAF had significantly greater p-syn deposition in the cutaneous autonomic nerves compared to patients with MSA and LBD (P < 0.01). Cutaneous autonomic p-syn deposition correlated with cardiovascular biomarkers reflecting adrenergic control of total peripheral resistance, including pressure recovery time after Valsalva manoeuvre (P = 0.44, P = 0.03) and orthostatic hypotension on head-up tilt (P = 0.63, P < 0.001) and patient reported orthostatic intolerance (P = 0.57, P = 0.006). Patients with PAF reported more severe orthostatic intolerance than patients with MSA (P = 0.01), but similarly severe physical disability.

Conclusions: Multimodal autonomic biomarkers can help to differentiate between the α-synucleinopathies and predict future phenoconversion in patients presenting with PAF. P-syn deposition in the peripheral autonomic nerves may disrupt adrenergic control of total peripheral resistance leading to symptomatic orthostatic hypotension in PAF. Severe symptomatic orthostatic hypotension is associated with marked physical disability despite an absence of motor symptoms in PAF.

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Abstract No: EFAS-2022-19

Cutaneous synuclein as a diagnostic biomarker in potential pure autonomic failure

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Background: Pure autonomic failure (PAF), multiple system atrophy (MSA), Parkinson’s disease (PD), and Dementia with Lewy Bodies (DLB) are neurodegenerative diseases characterized by abnormal α-synuclein deposition. Twelve to thirty four percentage with PAF later develop other neurological symptoms consistent with MSA, PD, or DLB. Subacute disabling autonomic failure and other atypical features may suggest underlying autoimmune rather than degenerative etiology, even without known auto-antibodies. Early biomarkers to confirm an underlying synucleinopathy could aid prognostication and help tailor treatment strategies.

Objective: To present preliminary results from a cohort study of patients with possible PAF, MSA, and PD and disease controls without non-synuclein pathology from a national autonomic center between April 2018–June 2021.

Methods: All patients had comprehensive autonomic testing and distal leg skin biopsies and were re-evaluated up to June 2022 for possible phenoconversion. Four potential PAF patients with atypical features received a trial of immunotherapy from treating clinicians for possible autoimmune disease without improvement. Skin biopsies were analysed using indirect immunofluorescence to measure intraepidermal and pilomotor innervation and evaluate for phosphorylated synuclein (p-synuclein) on nerves supplying sweat glands, piloerector muscles, vessels, and subepidermal nerves, deeper cutaneous nerves and nerve bundles giving a semiquantitative p-synuclein score out of 6.

Results: Thirty-nine patients (14 female, median age 60) were studied: 27 with synucleinopathies, including 11 with potential PAF (9 retained diagnosis by the last review, 1 developed PD, 1 developed DLB), 13 with MSA, 3 with PD, and 12 with non-synuclein pathology, including autoimmune autonomic gangliopathy (8), progressive supranuclear palsy (2), toxic and inherited neuropathies (2). Cutaneous p-synuclein was present in 24/27 synucleinopathy patients: 11/11 with potential PAF, 12/13 with MSA, and 1/3 with PD and 0/12 non-synuclein controls. The average p-synuclein score was significantly higher in patients recruited with PAF (median 4.5, IQR 3.75–4.75) vs MSA (1, 0.5–1.5) and PD (0, 0–0.75), P < 0.01. Intraepidermal and pilomotor innervation did not differ between groups.

Conclusions: Cutaneous p-synuclein is a valuable diagnostic biomarker in patients with potential PAF and appears to be more abundant in PAF vs MSA and PD, consistent with predominant peripheral synuclein deposition. Further larger studies are needed to evaluate if synuclein deposition patterns can predict later phenoconversion.

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Abstract No: EFAS-2022-20

A case report of FAVA syndrome in a young woman carrying PIK3CA gene mutation

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Background: FAVA (Fibro-Adipose Vascular Anomaly) syndrome, first described in 2014, is a pathology characterized by fibrofatty infiltration of muscle, phlebectasia with pain and contracture of the affected extremity. It has been described in young females but also at birth or early adulthood. FAVA is usually sporadic and frequently caused by a mutation involving PIK3CA (Phosphatidylinositol-4,5-bisphosphate 3-kinase) gene.

Objective: To describe an atypical case of FAVA syndrome.

Methods: Case report.

Results: A 34-year-old woman was referred to our Unit in January 2022; the neurological exam showed overgrowth and weakness in the left lower limb with left foot drop and gait imbalance. The physical abnormalities were already present at birth, but weakness progressed slowly over the years. Indeed, she became a Paralympic athlete, although she had to stop when she was 30 due to the impairment of her performance. At the age of 32, a musculoskeletal ultrasound of the lower limbs showed bilateral fibrous infiltration of biceps femoris, gastrocnemius and other muscles; an MRI of the pelvis revealed muscle atrophy with diffuse fatty infiltration. A biopsy of the vastus lateralis muscle did not show histologic evidence of fibrofatty infiltration, while genetic testing on the muscle sample demonstrated PIK3CA gene mutation.

Conclusion: Atypical features of this case lie in the discrepancy between the slow progression of functional impairment and the rapid progression of muscle atrophy, and in the absence of the fibrofatty infiltration at histopathological examination. This suggests that histological alterations are not mandatory for FAVA syndrome diagnosis.

Abstract No: EFAS-2022-21

Heart rate variability in type 2 diabetics and hypertensives compared to healthy volunteers

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Background: Heart rate variability (HRV) is a reliable non-invasive indicator for early detection of cardiac autonomic dysfunction in Type II diabetes mellitus (DM) and hypertension (HTN).

Objective: To evaluate the effect of chronic diabetes and hypertension separately on HRV with respect to age and gender-matched control group.

Methods: Five-minute electrocardiograms from lead II were recorded in 44 diabetic, 39 hypertensive, and 51 age and gender-matched healthy volunteers in a supine position using a 4-channel data acquisition system, the Power Lab (26 T), and LabChart 8.0 software. Frequency and time domain analysis was performed on all 3 groups using an independent sample T-test and Levene’s test was used to establish the statistical significance of variance.

Results: Frequency domain analysis of extracted NN interval data indicated a significant reduction in LF power and LF power % in each patient group (p < 0.001) with a higher decrement in diabetics. Total power of diabetes (\( X = 1470.6, p < 0.001, T = 3.9 \)) was significantly lower than that of hypertensives (\( X = 2145, p < 0.001, T = 3.4 \)) when compared with controls (\( X = 6111.1 \)). In time domain measures, SDNN, RMSSD, and pNN50 showed a greater degree of lowering in diabetics than in hypertensives, when considered with controls (p < 0.001). With regard to non-linear measurements, both SD2 and SD1 were significantly lower in both patient groups compared to controls (SD2: \( X_{DM} = 34.7, X_{HTN} = 49.7, X_{control} = 80.2, p < 0.001 \) (SD1: \( X_{DM} = 18.5, X_{HTN} = 24.2, X_{control} = 35.4, p < 0.001 \)).

Conclusions: In contrast to the healthy sample, short-term HRV parameters showed a significant reduction in diabetics and hypertensives, with diabetics having a greater reduction of all parameters.

Abstract No: EFAS-2022-22

The spectrum of autonomic symptoms in Parkinson’s disease

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Background: Autonomic symptoms in Parkinson’s disease (PD) are quite common and are affecting the quality of life.

Objectives: The aim of this study was: (i) to assess the spectrum of autonomic symptoms in PD and (ii) to evaluate the psychometric properties of SCOPA-AUT scale.

Methods: A prospective study on 178 PD patients and 178 sex and age-matched controls. We recorded demographic data, Hoehn and Yahr Scale, Non-Motor symptoms Questionnaire (NMSQuest) and Scale (NMScale), SCOPA-AUT, and the Parkinson’s Disease Questionnaire (PDQ-39).

Results: There were 97 males (54.9%) in each group; the mean age was 63.36 ± 11.23 years for PD group and 62.45 ± 9.34 years for the controls (p = 0.95). The mean duration of disease in PD patients was 7.35 ± 5.71 years. PD patients scored higher than controls in the total SCOPA-AUT score (mean score ± SD was 26.43 ± 9.21 versus 7.9 ± 2.32). The most common domains affected were urinary and gastrointestinal. Among the main items were nocturia, constipation, and salivation. We’ve performed a reliability analysis of the total SCOPA-AUT scale and its domains. Reliability analysis shows a satisfactory Cronbach’s alpha for the total scale (alpha = 0.89), with a very good internal consistency of the scale. The same consistency applied to most of the scale domains, with the exception of the thermoregulatory domain. All scores of the SCOPA-AUT domain had a good correlation with the NMS Scale and PDQ-39.

Conclusions: autonomic symptoms have a high prevalence in PD compared with controls. SCOPA-AUT shows reliable psychometric properties.

Abstract No: EFAS-2022-23

Testing of quality indices for electrocardiogram and blood pressure signals using the EuroBavar dataset

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Background: With an increasing interest in baroreceptor function and combined analysis of continuous electrocardiograms (ECG) and blood pressure (BP) data, quality measurement for BP and ECG data is needed to ensure the reproducibility of studies. Real-Life ECG and BP data are prone to artifacts and extrasystole, possibly contaminating the results of baroreceptor analysis. These artifacts can be visible on ECG or BP signals only or both combined, as it is typical for
extrasystoles. MS-QI was developed as a quality marker for ECG in heart rate variability analysis, as well as PD-QI, both using a modulation-spectrum-based approach.

**Objective:** Due to increasing demand in baroreflex analysis, a quality measurement analogous to already established quality measures of ECG is needed for combined signals of ECG and continuous blood pressure monitoring.

**Methods:** We programmed MS-QI and PD-QI using Matlab R2020b. The initial continuous ECG data is transformed using a short-time Fourier transformation until a modulation spectrum is achieved and a power modulation spectrum can be calculated. MS-QI is given by the ratio of the power of R-peaks in comparison to the remaining power of the modulation spectrum. PD-QI, on the other hand, is based on the peak distance of R-peaks in the modulation spectrum. We further computed the MS-QI and PD-QI for ECG and continuous BP of the EuroBaVar dataset.

**Results:** We documented a correlation between MS-QI and PD-QI of ECG with a correlation coefficient of 0.74, as well as a correlation coefficient of 0.8 for PDQI for ECG and BP.

**Conclusion:** These results indicate that MS-QI and PD-QI are comparable for ECG data, but due to differences in signal components, this correlation was not shown for bp data. This could be explained by the different amplitude spectrums for ECG and BP, as well as different frequencies. PD-QI appears to be less affected by these differences and can be used for ECG and BP data as well. Additional analysis using real-life data is necessary to determine the utility of these indices in blood pressure monitoring.