Parkinsonism and Related Disorders 103 (2022) 73–76

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Short communication

A Bayesian approach to Essential Tremor plus: A preliminary analysis of the TITAN cohort

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ARTICLE INFO

Keywords:
Differential diagnosis
Soft signs
Gait
Cognitive
Dystonia

ABSTRACT

Background: The construct of Essential Tremor plus (ET-plus) refers to patients who also have rest tremor and/or mild neurologic signs of unknown significance. It is unclear whether soft signs represent confounding factors or are useful in suspecting an alternative condition.

Methods: Using a Bayesian approach to ET-plus patients recruited in The ITAlian tremor Network (TITAN), we analyzed the probability that these patients do not have ET.

Results: The data of 274 ET-plus patients were extracted from the TITAN database. The majority of patients (240/274; 87.5%) had a single soft sign. The post-test probability of not having ET was different according to the specific soft sign: namely, 0.64 (rest tremor); 0.46 (questionable dystonia); 0.85 (questionable bradykinesia); 0.19 (soft gait impairment); and 0.09 (questionable cognitive issues). In patients with multiple soft signs, the post-test probability of not having ET was higher than 50% for 7 out of 11 combinations, accounting for 44.1% of subjects. Overall, the post-test probability of not having ET was higher than 50% in up to 71.5% of ET-plus patients.

Discussion: We have here shown that: 1) the soft signs differently contribute in modulating the probability that a patient does not have ET; and 2) the effect of multiple soft signs are not always addictive. Future studies are needed to collect prevalence figures of soft signs in different neurological disorders as well as in the elderly and to calculate their value in predicting the development of an alternative tremor syndrome.

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https://doi.org/10.1016/j.parkreldis.2022.08.030
Received 14 June 2022; Received in revised form 20 July 2022; Accepted 19 August 2022
Available online 29 August 2022

Although Essential Tremor (ET) is considered the commonest movement disorder, there is a lack of consensus about its epidemiology, defining clinical features, neurophysiologic markers, prognosis and pathology [1]. This has been attributed to the fact that ET has been loosely defined in the literature, with some authors including in its definition additional features such as dystonia and other subtle neurological signs of uncertain significance [2]. Therefore, a new tremor classification has been recently released and the ET-plus construct was proposed to classify patients fulfilling the criteria of ET but manifesting with additional neurologic "soft signs" of uncertain significance (e.g., impaired tandem gait, questionable dystonic posturing, memory impairment, etc.) that do not suffice to make an alternative tremor diagnosis [3]. This departure from previous ET definitions has generated an enlightened debate, with some researchers questioning the usefulness of ET-plus [1]. However, it has been also suggested that detailed phenotyping of patients with ET and the use of the ET-plus construct will ensure more robust research results [1].

One way to address the relevance of such soft signs is to apply a Bayesian approach, by which it is possible to estimate the probability that a patient with ET-plus has an alternative tremor syndrome rather than ET [4]. In fact, soft signs might either represent findings unrelated to the tremor syndrome, for instance related to aging, or might be useful in suspecting an alternative condition [4]. Differently from traditional frequentist statistics that address how likely is a positive/negative sign in a population given a known disease status by calculation of sensibility/specificity values, Bayesian analyses use likelihood ratios (LRs) which contain information about both sensitivity and specificity of a test (e.g., in our case of a clinical sign), to adjust the probability of disease in individual patients. LRs can be considered corrective factors applied to a pre-test probability (p_{PRE}) of having a certain condition to generate a ''revised'' post-test probability (p_{POST}), which can be therefore seen as a proxy of certainty of having the condition when disease status is unknown.

Here, we applied a Bayesian approach to ET-plus patients recruited in The ITAlian tremor Network (TITAN) to explore the possibility that they do not have ET and to calculate the possible cumulative effect of different soft signs when present in combination.

1. Methods

The TITAN is a multi-center, prospective study with the aim to assess the phenomenology and natural history of tremor syndromes. The study protocol and the preliminary findings have been published elsewhere [5]. Briefly, patients aged >18 years with any tremor syndromes, but the ones combined with parkinsonism, were eligible for recruitment [5]. The study has been approved by the ethic committee of the coordinator center (approval n.33_r.p.s.o._02/10/2020). The diagnosis of ET-plus was based on the current tremor classification [3] and the investigators were asked to list the soft signs for each patient. For the current work, we extracted from the TITAN platform data of ET-plus patients.

The sensitivity and specificity of each soft sign were calculated based on published literature and on a database of 116 de-novo patients with Parkinson's Disease (PD) of one of the authors (RE). Namely, the sensitivity/specificity of rest tremor (0.65 and 0.84, respectively) were calculated based on the results published by Bologna et al. [6] on 90 ET patients, of whom 14 had rest tremor, and by reviewing the data of 116 de-novo PD patients, of whom 40 did not have rest tremor. From the same sources, the sensitivity/specificity of questionable bradykinesia were calculated as 0.93 and 0.93, respectively. Namely, these figures are based on the presence of a scoring ≥1 on the item 3.4 (e.g., finger tapping) of the Unified PD Rating Scale (UPDRS), motor sub-scale, in 6/90 ET patients [6] and on a scoring equal to 0 on the same item in 7/116 de-novo PD patients. The sensitivity/specificity of subtle gait impairment were calculated to be 0.27 and 0.5, respectively [8], whereas the sensitivity/specificity of subtle cognitive impairment were calculate to be 0.1 and 0.57, based on its reported frequency in ET [9] and in elderly healthy subjects [10]. Finally, for questionable dystonic posturing the values of sensitivity/specificity were calculated as 0.2 and 0.9, respectively [4]. In the supplemental material there are available the formulas for calculating LRs and p_{POST} as well as additional references about Bayesian analyses. The latter have been performed using the spreadsheet available in Ref. [4], the p_{PRE} of not-having ET being conservatively set as 0.3 based on the evidence that about one third of patients with ET might have an alternative condition [7]. Given that the LRs of any soft signs have been calculated in the literature either against a particular syndrome (dystonia, parkinsonism, etc) or against elderly healthy subjects, the effects of the soft signs here reported, especially when in combination, indicate the estimated p_{POST} of not having ET, rather than suggesting a specific diagnosis.

2. Results

Out of 653 subjects recruited in the TITAN study by January 2022, the data of 274 (157 M/117 F) patients with ET-plus were extracted for the current work. They had a mean age of 69.61 ± 11.71 years, a mean age at onset of 55.32 ± 18.93 years, a mean disease duration of 15.72 ± 15.61 years and a mean TETRAS severity score of 27.42 ± 11.56. The majority of patients (240/274; 87.5%) had a single soft sign. Namely, 156 patients (56.9%) had rest tremor, 31 (11.3%) questionable dystonia, 25 (9.1%) questionable bradykinesia, 15 (5.5%) subtle gait impairment, and 13 (4.7%) questionable cognitive issues. The remaining 34 patients (12.5%) had multiple soft signs; Fig. 1 depicts their combination. The p_{POST} of not having ET for patients with a single soft sign was as follows: 0.64 (rest tremor), 0.46 (questionable dystonia), 0.85 (questionable bradykinesia), 0.19 (soft gait impairment), and 0.09 (questionable cognitive issues). The addictive effects of multiple soft signs is detailed in Table 1. In brief, for 7 out of 11 combinations, accounting for 44.1% of patients with multiple soft sings, the p_{POST} of not having ET was higher than 0.5, whereas for the remaining, in which there were subtle gait impairment and/or questionable cognitive issues, it was lower than 0.5. Overall, for 196 patients (71.5%) out of 274, the p_{POST} of not having ET was higher than 0.5.

3. Discussion

In this study we applied a Bayesian approach to ET-plus, which was found to account for about 42% of the entire TITAN cohort, confirming that ET-plus is one of the commonest tremor syndromes when patients are classified according to the new classification [5,11].

By using this approach, we have here shown that: 1) individual soft signs contribute with a different weight in modulating the probability that a patient does not have ET; and 2) the effect of multiple soft signs are not necessarily addictive. For instance, the p_{POST} of not having ET for a patient with ET-plus rest tremor lowers from 0.64 to 0.29, if questionable cognitive issues are also present. This scenario was observed especially for those soft signs that have been formerly associated with ET, but are also relatively frequent in the elderly, otherwise healthy, population, such as minor cognitive or gait issues. Therefore, given that the p_{POST} of not having ET was lower than 0.5 for these single soft signs and for their combination, we cannot claim whether these signs are part of the ET spectrum or represent confounding features, given their relative frequency in the elderly [4]. In either case, it suggests that some patients we label today with ET-plus have in fact ET. This seems to support the criticisms raised by some authors against the construct of ET-plus [1]. However, for other soft signs (e.g., rest tremor and questionable bradykinesia) the p_{POST} of not having ET exceeded 0.5. This highlights the importance of deep clinical profiling of these patients and would suggest that the construct of ET-plus as a whole might not be meaningful if one does not consider the particular soft sign(s) associating to the core phenotype of ET.

The advantage of Bayesian approaches is in the quantification of the

degree of certainty of an event happening (e.g., disease status to be present), even when the values of sensitivity or specificity of individual soft signs might appear high to not require further analyses. For instance, the specificity of questionable dystonia was calculated as 0.9 [4], which implies from a frequentist statistical perspective that 90% of subjects would be true positive for dystonia. However, as mentioned above Bayesian analyses use LRs, instead of single values of sensitivity/specificity, and therefore the p_{POST} of not having ET is in this case of 0.46 only.

Nonetheless, Bayesian approaches also suffer from limitations. First, there is a paucity of data about the prevalence of soft signs in the elderly as well as in those neurological conditions to consider in the differential diagnosis of ET. For instance, the values of sensitivity/specificity for rest tremor (0.65 and 0.84, respectively) were calculated based on PD as a comparator. However, it has also been shown that more than one third of dystonic patients with arm tremor have rest tremor [12]. If one were to use these data [12], the specificity of rest tremor in ET (and against dystonia) would drop to 0.41, with the p_{POST} lowering to 0.32. Second, LRs of any soft signs may vary as a function of the disease duration. In fact, some of them, for instance rest tremor, have been suggested to be late manifestations of ET [11]. Accordingly, future studies might attempt to calculate differential LRs of individual soft signs based on *when* they develop during the disease course. Similarly, LRs of individual soft signs might be different according to the age of the patient: for example, impaired tandem gait might suggest an alternative diagnosis more strongly in young than in old ET cases. Third, Bayesian analyses depend on the estimation of the p_{PRE} of a certain condition. We conservatively adopted a p_{PRE} of 0.3 [7], but this might vary depending on the epidemiology of the specific conditions, being higher for PD and lower for dystonia in a given age range. Notwithstanding these limitations, which call for the need of collecting robust "normative" data on the presence of soft signs in different neurological conditions as well as in the elderly, we endorse the proposal made by Elbe to apply a Bayesian approach to ET-plus [4]. In fact, this approach might be proven useful for prognostication as well as for recruitment in research studies depending on the specific purpose. One might in fact choose to include patients with only one soft sign in studies of ET if the soft sign has low LRs for an alternative tremor classification. On the contrary, one might exclude a patient with a soft sign with high LRs for an alternative tremor classification from research studies that require comprehensive phenotyping or from invasive procedures with significant risks (e.g., deep brain stimulation) [4].

In summary, despite being preliminary, our results show the feasibility of a Bayesian approach to ET-plus, highlight the importance of deep clinical phenotyping of ET-plus patients, and remark on the need of collecting robust, large data about the presence of soft signs beyond the ET spectrum. It is clear that, although tremor evaluation was performed according to a standardized protocol [5], the interpretation of the soft signs was left to the investigators [3], since there are no operational criteria for their quantification. This obviously represents a source of uncertainty that might be overcome in the future by obtaining objective measures of the soft signs with the use of sensors, for instance quantifying the degree of motor halts without clear bradykinesia during the finger tapping. Future longitudinal studies are also warranted to calculate the value of each soft sign and their combination in predicting the development of an alternative tremor syndrome.

Table 1
Post-test probability of not having Essential Tremor based on the combination of soft signs
Cog: subtle cognitive impairment; gait: subtle gait impairment; dyt: questionable dystonia; slowing: questionable bradykinesia.

Comination of soft signs	Post-test probability (of not having ET)
Rest tremor + cog	0.29
Rest tremor + gait	0.48
Rest tremor + dyt	0.78
Rest tremor + slowing	0.96
Rest tremor + dyt + slowing	0.98
Rest tremor + gait + cog	0.18
Rest tremor + gait + cog + dyt	0.30
Rest tremor + gait + cog + slowing	0.74
Slowing + dyt	0.92
Slowing + gait	0.75
Slowing + cog	0.57

Author roles

1. Conception and design of the study, or acquisition of data, or analysis and interpretation of data;
2. Drafting the article or revising it critically for important intellectual content;
3. Final approval of the version to be submitted.

RE: 1,2,3; AP: 1,2,3; LM: 1,2,3; EO: 1,2,3; AN: 1,2,3; ADF: 1,2,3; CD: 1,2,3; FDB: 1,2,3; MB: 1,2,3; AT: 1,2,3; ADR: 1,2,3; AFG: 1,2,3; ME: 1,2,3; VM: 1,2,3; LdB: 1,2,3; FV: 1,2,3; MR: 1,2,3; EC: 1,2,3; NM: 1,2,3; AP: 1,2,3; PB: 1,2,3.

Financial disclosures

Roberto Erro receives royalties from publication of Case Studies in Movement Disorders—Common and Uncommon Presentations (Cambridge University Press, 2017) and of Paroxysmal Movement Disorders (Springer, 2020). He has received consultancies from Sanofi and honoraria for speaking from the International Parkinson's Disease and Movement Disorders Society.

Paolo Barone received consultancies as a member of the advisory board for Zambon, Lundbeck, UCB, Chiesi, Abbvie, and Acorda.

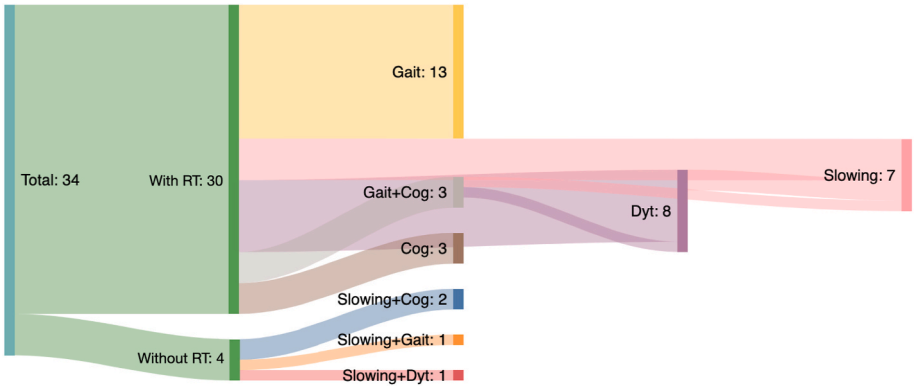

Fig. 1. Sankey diagram showing the combination of soft signs in our cohort.
RT: rest tremor; Cog: subtle cognitive impairment; gait: subtle gait impairment; dyt: questionable dystonia; slowing: questionable bradykinesia.

Anna De Rosa received consultancies from Lundbeck, and from Bial as a member of advisory board.

Andrea Pilotto received grant support from Ministry of Education, Research and University (MIUR) and IMI H2020 Initiative (IDEA-FAST project- MI2-2018-15-06), received research support from Zambon SrL Italy and Bial italy; he received speaker honoraria from Abbvie, Biomarin, Bial and Zambon Pharmaceuticals.

Alessandro Padovani received grant support from Ministry of Health (MINSAL) and Ministry of Education, Research and University (MIUR), from CARIPLO Foundation; personal compensation as a consultant/scientific advisory board member for Biogen 2019-2020-2021 Roche 2019-2020 Nutricia 2020-2021 General Healthcare (GE) 2019; he received honoraria for lectures at meeting ADPD2020 from Roche, Lecture at meeting of the Italian society of Neurology 2020 from Biogen and from Roche, Lecture at meeting AIP 2020 and 2021 from Biogen and from Nutricia, Educational Consulting 2019-2020-2021 from Biogen.

Lazzaro di Biase has received a speaker honoraria from Bial, consultant honoraria from Abbvie and research funding from Zambon, is the scientific director and one of the shareholders of Brain Innovations Srl, a University spinoff of Campus Bio-Medico University of Rome.

All other authors have nothing to disclose.

Acknowledgments

We are extremely grateful to Lucia Faraco and the staff of the “Fondazione Limpe per il Parkinson ONLUS” for the continuing support in the maintenance of the portal and for coordinating the activities between centers.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2022.08.030.

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