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Cerebellar Signs in Spinocerebellar Ataxia Type 37 at the Start of Follow up

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Abstract

Background: Spinocerebellar ataxia 37 (SCA37) is a new type of pure spinocerebellar ataxia (SCA) with important alteration of vertical eye movements described by our group. The clinical cerebellar phenotype is still to be carefully explored. The objective of the study was to analyse the SCA37 phenotype using SARA scale. SARA rates cerebellar signs excluding oculomotor functions.

Methods: Twelve affected patients were recruited from two different SCA37 families in Spain. Cerebellar affection was assessed by SARA scale at the beginning of the follow up. Sex, referred age at onset and time from onset (TO) evolution were also collected. Relationships between SARA items and these variables were studied by the use of network analysis. Patterns of affection were examined by hierarchical clustering after multiple correspondence analyses.

Results: Sitting appeared normal in all patients. The rest of the items were positively correlated, as expected. A tight relation was found between gait, speech and stance items and these three items strongly correlated with TO. Three patterns of patients were defined according to the severity of the affection.

Conclusions: This study adds new clues for SCA37 clinical suspicion. Network analysis identifies a main clinical module (formed by speech, gait and stance SARA items) in SCA37. Heat map shows the different patterns of cerebellar signs, allows classification and provides with objective gradation of SCA37 patients in three severity groups. These two novel and multivariate analysis techniques allow an objective and reproducible clinical description based on the same pattern recognition approach clinicians use in a subconscious way. These data may be useful for clinicians to recognize more cases of SCA37, may allow meta-analytic approaches in future research and improve eventual therapeutic trials.

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Introduction

Autosomal dominant spinocerebellar ataxias (SCAs) are a heterogeneous group of neurodegenerative disorders whose clinical spectrum widens from pure ataxia to complex phenotypes with involvement of extrapyramidal system, peripheral neuropathy, dementia, pyramidal signs or seizures. Several loci have been linked to this group of diseases and more than 40 genes have been already identified [1,2]. Spinocerebellar ataxia 37 (SCA37) has been recently described by our group [3]. It is a new SCA subtype characterized by pure cerebellar ataxia with abnormal vertical eye movements. Disease onset is usually in the late forties and progression is slow in the early stages of the disease. Brain magnetic resonance imaging shows cerebellar atrophy with brainstem preservation. Genetic studies have linked this disease to a locus in a 11- Megabase interval on 1p32 [3]. Different scales have been designed to measure the severity of ataxia. The most widely used is the Scale for Assessment and Rating of Ataxia (SARA) [4-6]. SARA shows interesting properties such as easy performance, construct validity, internal consistence, external reliability and good correlation with quality of live scales [5,7]. The scale has eight items, yielding a total score of 0 (no ataxia) to 40 (most severe ataxia). Although SARA was initially designed to summarize information in a final single score, each item of this scale rates the degree of abnormality found in different ataxia-related symptoms except for the ocular motor functions.

Interestingly, the distribution of abnormalities among SARA items has been previously used to disclose different clinical ataxia patterns in other SCAs. This approach allows a precise understanding of the clinical phenotypes and their related disability and help for clinical suspicion of particular genotypes [8].

We initially used both electro-oculographic studies and SARA total scores to assess patients with SCA37 and detailed clinical data from a single family was reported [3]. Following the description of this family and its linkage to 1p32, a second Spanish family with ataxia linked to the same region has been recently identified (unpublished data).

The aim of this new study is to describe the clinical spectrum detected in the two identified families with SCA37 at different stages of the disease. We particularly focused on coordination using single SARA items, their internal relationships and their relations with other clinical variables, such as age of onset or time from onset.

Patients and Methods

Patients

Twelve patients from two distinctive Spanish SCA37 families were included in this study (6 men and 6 women). Evaluation was performed at the start of follow up. All patients underwent a complete neurological assessment and none of them presented with motor or sensory deficits, extensor plantar reflexes, fasciculations, epileptic

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seizures, or cognitive impairment. Magnetic resonance imaging scans were available for 5 patients, and general cerebellar atrophy with sparing of the brainstem was detected on the scans of all 5 patients. No hot cross bun sign or other pathological findings were identified [3]. The SARA evaluation was applied by a single neurologist (CS). The English version of the scale was used. Scores from each SARA item (gait, stance, sitting, speech disturbance, right and left finger chase, right and left nose-finger test, right and left fast alternating hand movements and right and left heel-shin slide) and total SARA scores were collected. Considering the possibility of side asymmetry in cerebellar signs and to avoid loss of information, we collected and analyzed left and right tests independently. A careful interpretation of asymmetries should be done because they could simply indicate biased expression of the disease in one specific side in our sample at the time of the neurological exam. Most SCA37 patients will develop a progressive, complete and symmetrical cerebellar syndrome, as previously reported in other SCAs. Time of evolution, age at the evaluation, age at onset and sex were assessed as clinical variables.

Methods

Descriptive analysis: Median and range were used for quantitative and ordinal variables.

Pattern analysis: Two different approaches were applied to study clinical characteristics of SCA37 patients. In order to understand how SARA items are correlated between them and how they are associated with the clinical variables, a *network analysis* of correlations betweenSARA items and clinical variables was represented using bivariate Spearman's correlation coefficients as weighted edges (only correlations with an absolute value higher than 0.5 were shown) [9]. To explore different expression of cerebellar signs measured by SARA scale in the patients and to define the fingerprint of cerebellar signs in SCA37, we performed *two multivariate classifications* for *both patients and cerebellar signs*. To classify patients, we performed a hierarchical clustering analysis. Distances were calculated using the eight first dimensions of a multiple correspondence analysis of SARA items. Cerebellar signs were also classified by hierarchical clustering analysis using as a distance: 1 minus the absolute value of Spearman's correlation coefficient. Average was used as grouping criterion in both classifications. A heat map was used to display the pattern of cerebellar signs for each patient [10]. R language programming was used for data analysis.

Results and Discussion

Results

Descriptive analysis: Clinical characteristics and SARA score are shown in Figure 1 (left side). The median time from onset was 15 years (range: 3-38) and the median age at onset was 50 years (range: 20-64). Median global SARA score at the start of follow up was 14.25 points (range 4-27).

Pattern analysis: Network analysis representation shows the relationship between the clinical variables and SARA scale items (Figure 2). Sitting remained normal in all patients; therefore no relationships with other SARA items or clinical variables were detected. Time from onset (TO) is the central parameter in the network. Although it is also correlated with other cerebellar signs, TO is particularly highly correlated in a positive way with alteration of stance (rho=0.767), gait (rho=0.811) and speech (rho= 0.818). Stance, gait and speech abnormalities are also tightly positive correlated between them (bivariate Spearman's rho from 0.835 to 0.925), which could be interpreted as a module of clinical expression in patients with SCA37. Age at onset is obviously negatively correlated with TO and interestingly, also with finger chase, right and left nose-finger tests and right and left heel-shin slides (which are less correlated with disease duration). This indicates that the earlier onset the patient has, the higher rates in those tests the patient shows. Sex is mildly correlated with TO indicating that in our sample, women tend to have longer disease duration at the start of our follow up. Figure 1 (right) show the different patterns of cerebellar signs in our sample of patients with SCA37. Each patient is represented in a row and each SARA scale item in a column. Three patterns could be defined according to severity of cerebellar signs. All patients have preserved sitting even those in late stages or with severe forms of the disease. Patient number 11 is the

Code	Sex	Age at evaluation	Age at onset	Evolution	Total SARA
P11	F	58 y	20 y	38 y	27
P8	F	74 y	40 y	34 y	23
P5	F	60 y	43 y	17 y	19.5
P3	M	66 y	51 y	15 y	16.5
P4	M	66 y	56 y	10 y	18.5
P10	F	82 y	56 y	26 y	20
P2	M	52 y	45 y	7 y	7.5
P9	M	65 y	50 y	15 y	12
P1	F	62 y	43 y	19 y	11.5
P12	M	52 y	42 y	10 y	10
P6	M	67 y	64 y	3 y	4
P7	F	65 y	62 y	3 y	4

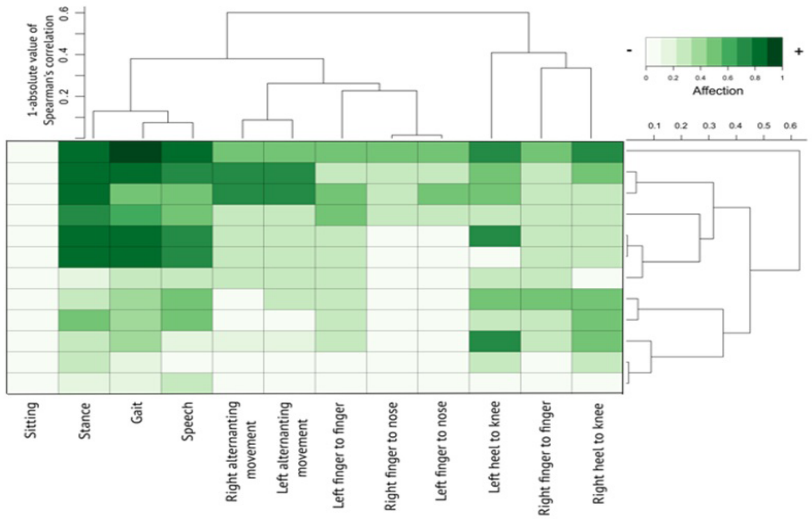

Figure 1: Graphical representation of network analysis. The circles represent each SARA item and the clinical variables. Lines represent correlations between two parameters (green for positive and red for negative relation). The wider the line joining two variables is, the more correlated these two variables are. For this analysis, sex has been transformed into a numerical variable (1 = woman, 0 = man) and has been accordingly represented by WOM.

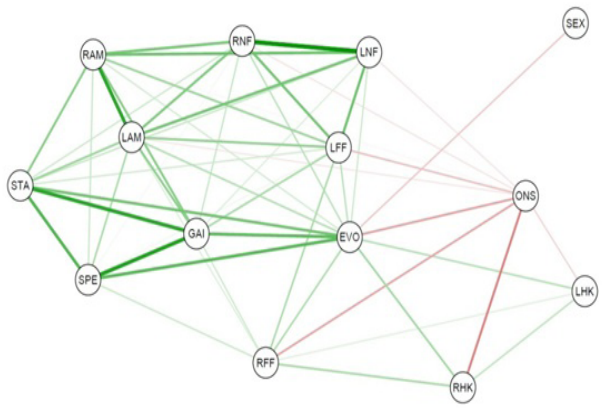

Figure 2: Left: Patients data. Right: Heat map and hierarchical clustering; lateral dendrogram shows the hierarchical classification of patients. Superior dendrogram presents the hierarchical classification of the SARA items. Central heat map represents the affection of each patient. Patients are represented in rows and SARA items in columns: each square represents the value for the SARA item in a particular patient. The darker the square is, the higher score of SARA item this patient has. Three patterns could be defined according to severity of cerebellar signs (patient 11; patients 8, 5, 3, 4, and 10 and patients 2,9,1,12, 6 and 7).

most affected patient and his pattern is striking different from the rest. Patients with a moderate disorder (P8, P5, P3, P4, P10) are grouped together and configure a second pattern. There is a third group formed by patients with milder cerebellar signs (P2, P9, P1, P12, P6 and P7). Although cerebellar signs measured by SARA items are correlated between them, the influence of each item on SCA37 patients' classification differs. The classification of patients mainly depends on impairment of the module of clinical expression formed by speech, gait and stance. Therefore, the higher impairment in speech, gait and stance is, the higher probability of being classified in a group formed by patients with a more severe condition. There is a second set of cerebellar abnormalities present only in patients with moderate and severe disease (such as alternating movements) or in patients with severe disease (such as nose-finger test). Interestingly, there are some other cerebellar signs present in nearly all patients and whose intensity is, in consequence, less relevant for the classification in groups of severity. These are signs related to limb dysmetria measured by left and right heel-shin slide and right finger chase. Patients with milder forms have characteristically higher rates in items related with dysmetria than in the items group formed by gait, stance and speech. The left finger chase cannot be included in any of the models of interpretation we have suggested for the rest of the signs due to the lack of fitting of its distribution among patients with the previous interpretations.

Discussion

The present study uses a multivariate approach to evaluate the pattern of cerebellar signs (assessed by SARA scale) and the correlation with some clinical variables in the first two identified SCA37 families up to date.

We have used a multivariate approach to assess clinical presentation of SCA37. These approaches are consolidated techniques in other disciplines [11], but they are not generally used in the definition of complex ataxia phenotypes. Network analysis representation summarizes relationships between parameters in a single glimpse. Its interpretation is simple and intuitive. Mechanisms or modules can be easily detected [12]. Additionally, classification of patients using multiple correspondence analyses delineates the clinical spectrum in a particular cerebellar disease. With this technique, classification is data-driven and provides with objective gradation [10]. Moreover, presentation of SARA items' scores by heat maps allows understanding of different clusters of signs that are impaired together and the relative contribution of each cerebellar sign to classification. These two statistical tools are complementary. For example, in our heat map left and right finger chase seems not related. However, they do show correlation in the network analysis. This can be attributed to limitations in hierarchical clustering that can be avoided by network analysis. In contrast, heat map offers the opportunity to show complex data from all patients in a single glimpse.

Multivariate approaches seem to be critical to improve pattern recognition in clinical settings and their bases are included in normal diagnostic approach by clinicians in a subconscious way [13]. We think that these novel techniques could help to better define phenotype of different SCAs in research settings. This is an important aim in this era of quick advances in genetics, which need descriptions of clinical phenotypes featured by objectivity and reproducibility and based on pattern recognition approaches. There is a wide spectrum of cerebellar impairment in patients with SCA37. We have grouped patients in three types of severity to illustrate the features of this variability.

The first type is built by a single patient, who is the more affected, and the subject with longer evolution of illness and earlier onset. This patient represents an extreme form of the disease and this is the reason to be classified on her own. The second group is formed by patients with severe affection of gait, stance and speech and moderate affection of right and left finger chase, right and left nose-finger test, right and left fast alternating hand movements and right and left heel-shin slide. The third group is constituted by those patients with shorter evolution whose alteration of finger-to-finger and heel-to-knee tests are higher than affection of gait, stance and speech. We interpret this classification as it follows. At the beginning of the disease, gait, stance and speech are spared but they quickly get worse as illness progresses. This is also consistent with the results from network analysis where TO is a central parameter highly correlated with gait, stance and speech in a positive way. However, the variability of cerebella dysfunction in SCA37 is not totally explained by illness duration since other signs show less intense relationship with TO. Interestingly, signs of dysmetria of upper and lower limbs could be affected early in the disease and they do not clearly progress or relate with the groups of severity we have defined. Another significant finding is the Preservation of sitting, which can be also a clinical clue to detect this type of ataxia. Up to date, only two families with SCA37 have been identified. A defined pattern of altered vertical eye movements was detected in two patients at onset of the disease. Basically, abnormalities consisted on saccade dysmetria with normal saccade velocity and impaired pursuit and optokynetic nystagmus velocity. Surprisingly, these vertical abnormalities clearly preceded the impairment of horizontal eye movements in both patients and one of them showed severe eye movement abnormalities far before ataxia developed [3]. A similar pattern of vertical eye movement abnormalities was found in all affected patients from both families and in two young at-risk asymptomatic subjects who inherited the risk haplotype on 1p32. We have not found this pattern of abnormalities in controls or patients suffering from other SCAs and they have not been previously reported either. This is mostly relevant for those subtypes with pure cerebellar

phenotype and abnormal vertical eye movements, i.e. SCA6, SCA26 and SCA30. Thus, SCA6 shows vertical dysmetria associated to slow saccades and pursuit, and nistagmus can be an early sign (14), SCA26 presents slow vertical pursuit but vertical dysmetria has not been reported [15] and SCA30 has shown vertical and horizontal dysmetria although detailed information whether isolated vertical dysmetria can be found in SCA30 is not available [16]. We therefore proposed these vertical eye abnormalities may be considered a pre-symptomatic or early sign in SCA37 and may help to identify SCA37 patients among those with SCA and negative standard genetic test for most common subtypes. However, the sensitivity and specificity of these findings are not known yet since more SCA37 families are needed to address these questions.

The present study adds new and different clues for SCA37 clinical suspicion, provides additional data about cerebellar signs prognosis and may help to choose appropriate clinical variables and end points in future therapeutic trials.

Essentially, SCA37 patients are expected to have a normal sitting even in advances cases; tremor measured by nose-finger test seems to appear only in moderate and severe cases and dysmetria assessed by finger chase test and heel-shin slide could begin early but is not expected to excessively progress with the disease. Multivariate pattern techniques also contribute to clinical diagnosis with additional information. The degree of alteration in a sign should be interpreted in accordance with the alterations in others. This fact has clinical relevance. For instance, a patient with an important dysmetria shown by finger-to-finger test with a relatively preserved gait or stance is not consistent with the pattern found in SCA37 and a different diagnosis should be considered.

We acknowledge the main concern of this study is the small number of patients, since this type of ataxia has just been recently discovered. However, all available clinical data have been included and robust techniques of multivariate statistical analysis have been used to overcome this limitation.

Conclusion

SCA37 patients show a main clinical module, formed by speech, gait and stance, by network analysis of SARA items, and heat map discloses the different patterns of cerebellar signs, allows classification and provides with objective gradation of SCA37 patients in three severity groups. These two novel and multivariate analysis techniques offer an objective and reproducible clinical description based on the same pattern recognition approach clinicians use in a subconscious way. We do expect the detailed clinical description provided by the present work to be useful for clinicians to recognize more cases of SCA37, it may also allow sharing data for meta-analytic approaches in future research and improve the design of eventual therapeutic trials.

Competing Interest

The authors declare that they have no competing interest.

Author Contributions

I.P.V and D.G.A performed the statistical analysis and contributed in the writing of the manuscript.

V.V.B. obtained funding, designed and performed the refined linkage analysis.

A.M.D. obtained funding, designed and performed the refined linkage analysis and contributed in the writing and revision of the content of the manuscript.

C.S.M obtained funding, designed and applied the clinical protocol, and analyzed the clinical data. She contributed to the writing and revision of the content of the manuscript.

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Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declarationand its later amendments or comparable ethical standards.

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