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Review Article

Association between spinocerebellar ataxias caused by glutamine expansion and psychiatric and neuropsychological signals - a literature review

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Abstract: The autosomal dominant cerebellar ataxias, also known as spinocerebellar ataxias (SCA), are characterized by cerebellar degeneration and by their afferent and efferent connections. Currently, at least 31 types of SCA are described, among which a subset, comprising types 1, 2, 3, 6, 7, 17 of the disease, is distinguished due to sharing the same form of mutation involving the repetition of the series of CAG triplets, known as polyglutamine diseases (SCA_{polyQ}). Through a systematic literature review using the *Pubmed, PsycoINFO, LILACS* and *SciELO* databases and the keywords *Spinocerebellar Ataxia* in association with the words *neuropsychiatric, psychological, cognitive impairment(s)* and *psychiatric comorbidities* this study aimed to identify the possible associations between SCA_{polyQ} and neuropsychological and psychiatric symptoms/disorders. A greater presence of symptoms of depression and anxiety was evidenced, as well as the existence of cognitive impairments in the patients with SCA_{polyQ} when compared with the general population, with important differences in the profile of these impairments among the types of SCA. It was observed that the findings, in general, indicated greater impairment in the executive functions, verbal fluency and verbal memory and that there was a higher concentration of studies for SCA2 and SCA3. However, there is a need for a greater number of studies using a more homogeneous methodology, which perform direct comparisons between the types of ataxias and that explore some of the still little evaluated neuropsychological functions and the different psychiatric disorders in their amplitude.

Keywords: Spinocerebellar ataxia, cognitive aspects, psychiatric aspects, cognitive function

Introduction

Hereditary ataxias comprise a complex group of genetic diseases, which constitute an extensive field of research in the clinical, anatomopathologic and genetic areas. Although rare, this group of disorders is highly heterogeneous in the way they are clinically and genetically manifested, complicating their recognition [1]. The multiple forms of manifestation of the ataxias led researchers to question the uniformity of these diseases and to seek criteria that could favor their recognition, discrimination and more accurate forms of classification [2].

Among the classifications suggested for this group of diseases, the proposition of Pierre Marie in 1893 stands out, considering two distinct groups of hereditary ataxias: one with standard autosomal-recessive inheritance and the other of late onset with distinct clinical findings and a pattern of autosomal-dominant inheritance. In 1982, Harding proposed a classification separating the autosomal dominant cerebellar ataxias into groups based on their clinical manifestations, which is still an important parameter in the current clinical practice [2].

The autosomal dominant cerebellar ataxias, also known as spinocerebellar ataxias (SCA), the focus of this study, are characterized by cerebellar degeneration and their afferent and efferent connections [3]. Currently, at least 31 types of SCA are described [4]. Among these, a specific SCA subgroup is highlighted for con-

Table 1. Main clinical symptoms of the different types of CAG ataxia, according to Subramony (2012)

Type of SCA	Main symptoms
SCA1	Ataxia, dysphagia, sensory neuropathy, loss of tendon reflexes, extrapyramidal signs such as dystonia and cognitive decline.
SCA2	Ataxia associated with slow saccades, prominent neuropathy leading to generalized areflexia, parkinsonism, cognitive dysfunction (executive function), dysphagia, facial atrophy and fasciculation.
SCA3	Ataxia associated with spasticity, ophthalmoparesis, slow saccades, facial and tongue atrophy, fasciculations, sensory neuropathy, amyotrophy, cognitive problems (frontal cognitive dysfunction), sleep problems and dystonia.
SCA6	Slowly progressive cerebellar ataxia and downbeat nystagmus.
SCA7	Ataxia associated upper motor neuron signs, degeneration of the retina up to evident visual loss.
SCA17	Ataxia, extrapyramidal signs and dementia.

taining the highest quantity of known ataxias and sharing a mutation involving the repetition of the series of CAG (glutamine) trinucleotides in different parts of the deoxyribonucleic acid (DNA), which is referred to in this study as SCA_{polyQ}. Such ataxias, also known as polyglutamine diseases, refer to types 1, 2, 3, 6, 7, and 17 of the disease [5, 6].

According to Durr [5], the SCA_{polyQ} are neurodegenerative diseases with diffuse neurological dysfunction, leading to death due to brainstem failure. Although the different types present varied manifestations they all present cerebellar syndrome, with corticospinal syndrome, extrapyramidal syndromes, dysfunction of the brainstem, peripheral neuropathy and amyotrophy also being common [6, 7]. Furthermore, although all are progressive, the rate of progression varies widely.

The phenotypic heterogeneity within each type of ataxia and the overlapping of manifestations between the different types makes its differentiation based strictly on the clinical evaluation impossible, so that the family history, appropriate imaging and particularly the genetic test become essential instruments in the diagnosis [6].

Table 1 describes the main clinical characteristics of SCA_{polyQ}, according to Subramony [6].

According to Schöls et al. [8], studies on the prevalence of spinocerebellar ataxias are restricted to a few isolated areas, not reflecting the actual occurrence of the disease. However, the same authors point out that, in general, a prevalence of approximately three cases of the disease for each 100,000 people is estimated, although they believe that this frequency underestimates the actual occurrence. The polyglutamine ataxias are the best known group of ataxias and among them SCA3, also known as "Machado-Joseph Disease", stands out due to having a higher worldwide prevalence [5].

Clinically an important association can be seen between this group of diseases and neuropsychological and psychiatric symptoms. More recently, cerebellar degeneration has been indicated as the cause of cognitive impairments, however this association is still controversial with different clinical findings among the studies. Recently, there has been growing interest among the scientific community in evaluating the psychiatric and neuropsychological alterations in patients with $SCA_{polyQ,}$ which is evidenced by the increased number of studies, especially in the last two years. To our knowledge, no review study has been conducted aiming to systematize these findings, which justifies the present study.

The aim of this study is to conduct a systematic review of the literature, aiming to identify possible associations between the spinocerebellar ataxias caused by glutamine expansion (SCA_{polyQ}) and neuropsychological and psychiatric symptoms/disorders.

Materials and methods

A systematic search was performed in the main databases: PubMed, PsycoINFO, LILACS and SciELO, using the key words Spinocerebellar Ataxia in association with the words neuropsychiatric, psychological, cognitive impairment(s) and psychiatric comorbidities. The following inclusion criteria were adopted: a) studies

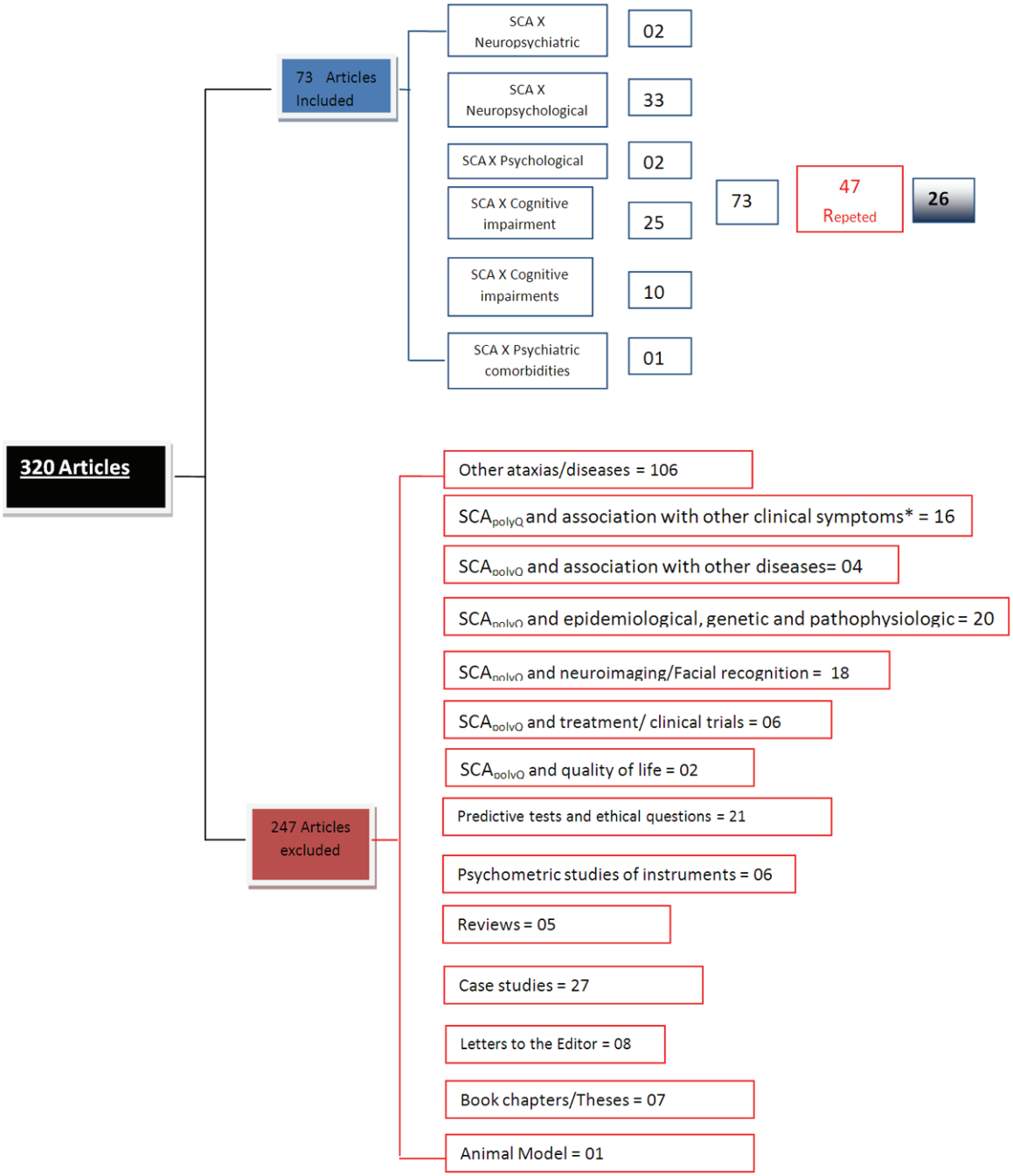

Figure 1. Process of inclusion and exclusion of the articles of the study. SCA: spinocerebellar ataxia in general; *other clinical symptoms: for instance, olfactory impairment, saccadic latency, parkinsonism.

regarding the association between SCA_{polyQ} and psychiatric and neuropsychological alterations; b) in English, Portuguese and Spanish; c) without a time limit; and d) studies conducted with humans; over the age of eighteen. Exclusion criteria used were studies that involved: a) other ataxias/diseases; b) association of SCA_{polyQ} with other diseases and clinical symptoms; c) epidemiological, genetic and pathophysiological aspects; d) neuroimaging/facial recognition; e) clinical drug trials; f) quality of life; g) genetic predictive tests and ethical issues; h) psychometric studies of instruments; i) reviews, case studies, letters to the editor, book chapters/theses; and j) animal models. Additionally, through a manual search, it was

Table 2. Main results of the studies that evaluated indicators of depression and anxiety

Psychiatric Symptoms		
	Main Instruments Used X	Most significant findings X
Depression (N = 13)	*Beck Depression Inventory* (N = 05)	SCA_{polyQ} > GP [12, 13]
	Specialist Clinical Evaluation (N = 04)	SCA1 > GP [15]
	Hamilton Rating Scale for Depression (N = 02)	SCA2 = GP [15, 24, 30]
	Hospital Anxiety and Depression Scale (N = 02)	SCA3 > GP [9, 10, 20, 18, 26]
		= GP [15]
		= *at risk [34]
		> *at risk [18]
		> SCA1, 2, 6 [19]
		< SCA1, 6 [15]
		< Multiple Scales [18]
		SCA6 = GP [17]
		> GP [15]
Anxiety (N = 05)	*Hospital Anxiety and Depression Scale* (N = 02)	SCA3 > GP [9, 10, 20, 26]
	Hamilton Anxiety Scale (N = 02)	SCA6 < GP [17]
	State-Trait Anxiety Inventory (STAI) (N = 01)	

(>) Main depressive/anxious symptomatology; *X* not exclusive categories; GP: general population; *individuals at genetic risk for SCA3; N: number of studies; between [ ]: reference of the studies.

sought to identify possible studies to be included in this review from the references of the selected articles. Only one article was selected through this criterion.

The process of inclusion and exclusion of the studies can be better visualized in **Figure 1**.

Results

Considering the parameters used for this review, 26 articles were selected [9-34], which were independently evaluated regarding the relevance of their inclusion by two psychologists and a psychiatrist, researchers in the area. These articles were the objects of analysis in this review.

Regarding the origins of the studies, 58% of these were from European countries, 19% from Latin America and the remaining 23% evenly divided between Japan, the U.S.A. and Australia. The studies included were published between 1993 and 2012, with a more recent increase in publications, from 2010. In relation to the design methodology, 27% of the studies were descriptive (N=7) [13, 14, 23, 25, 26, 29, 33] and 73% used comparison groups. The comparison groups were established from convenience samples (people with similar social and demographic features from the group of patients) arising from the general population [9-12, 15, 17, 18, 20-22, 24, 27, 28, 30, 32], or from clinical population, namely: patients with different SCA_{polyQ} ataxia [15, 16, 19, 21], patients at different stages of the same disease type [31], patients with genetic risk for SCA3 [18, 34] and multiple sclerosis patients [18]. These comparison groups were always similar concerning the sociodemographic characteristics of the clinical group.

The sample sizes ranged between six and 526 participants, however, observing this in greater detail, shows that the median of the sample is 22.5 participants, with most of the studies composed of samples from six to 40 participants (N=22). All the studies included individuals of both sexes in the sample, with age at the date of evaluation ranging from 42.3 to 61 years and age at the onset of the disease between 28.8 to 48.6 years. Concerning the duration of the disease, the range was from 8.2 to 15 years. The results regarding the association between SCA_{polyQ}, psychiatric disorders and neuropsychological alterations will be presented considering the most significant findings and taking into account the different functions evaluated.

Regarding the evaluation of psychiatric symptoms/disorders, **Table 2** presents a synthesis of the main findings.

As can be observed in **Table 2**, the studies were restricted, for the most part, to the evaluation of symptoms of depression and anxiety, mainly through the use of different screening scales.

Table 3. Main results of the studies that evaluated the global cognitive aspects

Neuropsychological Aspects		
	Main Instruments Used X	Most significant findings X
Global Cognitive Aspects (N = 14)	*Mini-Mental State Examination (MMSE)* (N = 08) *Wechsler Intelligence Scale* (N = 04)	SCA1 > GP [16, 21] = GP [27] SCA2 > GP [11, 16, 28, 31] = GP [21, 29, 30] SCA3 = GP [10, 20, 26, 21] SCA6 = GP [14, 17, 22] SCA7 > GP [16]

(>) Greater impairment; *X* not exclusive categories; GP: General Population, N: number of studies; between [ ]: reference of the studies.

In the case of depressive symptoms, a more significant prevalence was generally noted in the group of patients with SCA_{polyQ}, compared to the general population group, which is most evident for SCA3. Regarding SCA2, there was a greater consistency of findings indicating the absence of differences in relation to the general population. Comparisons of the prevalence of depressive symptoms among the different ataxia groups proved to be inconsistent, not allowing a conclusion.

The five studies that evaluated symptoms of anxiety exclusively used self-applied screening scales. Again, SCA3 was the most investigated, with four studies indicating a higher frequency of anxiety symptoms when compared with the general population. Also in relation to the psychiatric aspects, a descriptive study [25] indicated a high prevalence of psychiatric disorders in patients with SCA2 (about 90%), highlighting the adjustment disorders with depressive mood, suicidal ideation and sleep disorders. Another descriptive study with patients with SCA17 reported the presence of symptoms such as personality changes, aggressiveness, depression, hallucinations and alcoholism [23].

Regarding the neuropsychological aspects, these will be presented in two groups, namely: a) global cognitive functions and b) specific cognitive abilities. Among the specific cognitive abilities, the aspects evaluated were: visuospatial ability, motor function, executive function, verbal fluency, language, memory, attention and working memory, verbal memory, and visuospatial memory.

Table 3 presents the main findings related to the global cognitive aspects.

As can be seen in **Table 3**, the instruments used to evaluate the global cognitive aspects varied in terms of sensitivity and refinement with a predominance of the M*ini-Mental State Examination screening scale* (N = 08) and, to a lesser extent, the *Wechsler Intelligence Scale test* (N = 04), which can be considered of greater complexity and accuracy due to providing a more thorough evaluation of the general intelligence, through specific subtests.

The results showed a trend toward greater impairment in the patients with SCA2 and SCA1 and no significant differences compared to the control group for the patients with SCA3 and SCA6.

Regarding the specific cognitive functions, **Tables 4**, **5** and **6** present the main study results.

With respect to the visuospatial skills, it was observed, as shown in **Table 4**, that different subtests of the *Wechsler Adult Intelligence Scale* were used. The patients with SCA3 were the most studied (N = 04), presenting findings, in the majority of the studies [9, 10, 20], that indicate greater impairment compared to the general population. The studies involving patients with SCA1 (N = 02), found no significant differences with respect to the general population, in this function. The studies for the other SCA_{polyQ} are unique or inconclusive, not allowing generalizations regarding this ability.

Motor function, as can be seen in **Table 4**, was one of the least studied of the specific skills, restricted to the four studies, in which less variation between the techniques used can be observed. The studies involving patients with SCA3 are prominent, the findings of which evi-

Table 4. Main results of the studies that evaluated visuospatial ability and motor function

Neuropsychological Aspects		
	Main Instruments Used X	Most significant findings X
Visuospatial ability (N = 07)	*Wechsler Adult Intelligence Scale* (Picture Completion) (N = 05) *Wechsler Adult Intelligence Scale* (Block Design) (N = 03) *Wechsler Adult Intelligence Scale* (Spatial span) (N = 02) *Rey-Osterrieth Complex Figure* (N = 02)	SCA1 = GP [21, 27] SCA2 > GP [11, 24] = GP [21] SCA3 > GP [9, 10, 20] = GP [21] SCA6 = GP [17]
Motor Function (N = 04)	*Purdue Pegboard* (N = 02) Motor sequencing task adopted from Luria (N = 02) *Cambridge Neuropsychological Test Automated Battery (CANTAB)* (N = 01)	SCA1 > GP/Gross and Fine♦ [15] SCA2 = GP/Gross♦ [15] > GP/Fine♦ [15] > GP [29] SCA3 > GP [26, 32] = GP/Gross♦ [15] > GP/Fine♦ [15] < SCA1, SCA6 [15] SCA6 > GP/Gross and Fine♦ [15]

(>) Main difficulty in the function; *X* not exclusive categories; GP: General Population; ♦Gross and Fine motor function, N: number of studies; between [ ]: reference of the studies.

Table 5. Main results of the studies that evaluated executive function, verbal fluency and language

Neuropsychological Aspects		
	Main Instruments Used X	Most significant findings X
Executive Function (N = 15)	*Wisconsin Card Sorting Test* (N = 11) *The Stroop Neuropsychological Screening Test* (N = 05) *Verbal Fluency (Semantic/Phonemic/Switching)* (N = 04) *Wechsler Adult Intelligence Scale* (Similarities) (N = 04) *Trail Making Test* (N = 03) *Controlled Oral Word Association* (N = 03) *Wechsler Adult Intelligence Scale* (Symbol Search) (N = 02)	SCA1 > GP [15, 21, 27] = GP [16] > SCA3 [21] < SCA2, SCA7 [16] SCA2 > GP [11, 15, 16, 29, 30] = GP [28] SCA3 > GP [9, 10, 15, 26] = GP [20, 21] SCA6 > GP [14, 15] = GP [17, 22] SCA7 > GP [16]
Verbal Fluency (N = 09)	*Verbal Fluency (Phonemic/Semantic/Switching)* (N = 08) *Controlled Oral Word Association Test (FAS)* (N = 01)	SCA1 > GP [21, 27] SCA2 > GP [11, 21, 24] SCA3 > GP [9, 10, 20] = GP [21] SCA6 = GP [22] > GP [17]
Language (N = 03)	*Western Aphasia Battery* (N = 01) *Verbal Fluency* (N = 01) *Token Test* (N = 01) *CERAD Naming Test* (N = 01)	SCA2 = GP [30] SCA3 = GP [20] > GP [26]

(>) Greater impairment; *X* not exclusive categories; GP: General Population; N: number of studies; between [ ]: reference of the studies.

dence greater impairment compared to the control group [15, 26, 32] except in the gross motor function, in which there were no significant differences. For SCA1 and SCA6, the findings indicate greater impairment, including the gross motor function, both when compared with the general population and with SCA3 patients [15].

Table 5, presented below, refers to the studies that evaluated executive function, verbal fluency and language.

Table 6. Main results of the studies that evaluated memory, attention and working memory, verbal memory, and visuospatial memory

Neuropsychological Aspects		
	Main Instruments Used X	Most significant findings X
Memory (N = 08)	*Wechsler Memory Scale* (N = 03) *Rey Auditory Verbal Learning Test* (N = 01) *Verbal Span Test* (N = 01) *Visual Immediate Memory Test* (N = 01) *Verbaler Lern-und Merkfähigkeitstest* (N = 01) *Diagnosticum für Cerebralschädigung* (N = 01)	SCA1 = GP [15, 16] SCA2 = GP [24, 15, 30] SCA3 = GP [15, 26, 32] SCA6 = GP [14, 15] < SCA1, SCA2, SCA3 [19] SCA7 > GP [16]
Attention and Working Memory (N = 14)	*Wechsler Memory Scale (Digit Span)* (N = 06) *Wechsler Adult Intelligence Scale (Digit Span)* (N = 05) *Wechsler Adult Intelligence Scale (Arithmetic)* (N = 01) *Wechsler Memory Scale (Logical Memory)* (N = 01) *Test of Everyday Attention (Elevator counting task and Elevator counting with distraction)* (N = 01) *Cambridge Neuropsychological Test Automated Battery* (N = 01)	SCA1 = GP [21, 27] > GP [15, 16] > SCA3 [15] SCA2 = GP [15, 28, 24] > GP [11, 16] > SCA1, SCA7 [16] SCA3 = GP [10, 20, 21, 26] > GP [15, 32] > at risk* [34] SCA6 = GP [17, 22] > GP [15] SCA7 = GP [16]
Verbal Memory (N = 09)	*Wechsler Memory Scale* (N = 05) *Word List* (N = 04)	SCA1 > GP [21, 27] SCA2 > GP [21, 24, 28] SCA3 > GP [20, 21] = GP [10] > at risk* [34] SCA6 = GP [17, 22]
Visuospatial Memory (N = 05)	*Rey-Osterrieth Complex Figure* (N = 04) *Wechsler Memory Scale* (N = 01)	SCA1 = GP [21, 27] SCA2 = GP [21, 28] SCA3 = GP [21] SCA6 = GP [22] > GP [17]

(>) Greater impairment in the function; *X* not exclusive categories; GP: General Population; *individuals at genetic risk for SCA3; N: number of studies; between [ ]: reference of the studies.

As presented in **Table 5**, a wide variety of instruments were used for the evaluation of executive function, which is among the most evaluated of the neuropsychological aspects (N=15). However, the *Wisconsin Card Sorting Test* was predominant, being used in over 70% of the studies. For this function, it was observed that the group of patients with SCA_{polyQ} generally presented greater impairment, highlighting the most consistent number of findings for SCA2 [11, 15, 16, 29, 30], SCA3 [9, 10, 15, 26] and SCA1 [15, 21, 27]. In relation to SCA6, the findings were inconclusive, divided equally between studies that indicated the presence [14, 15] or not [17, 22] of significant differences in comparison with the general population.

Verbal fluency was evaluated predominantly through the Verbal *Fluency test* (N=08), with findings also indicating greater impairment for the group of SCA_{polyQ} patients. The patients with SCA3 and SCA2 were the most studied respectively, with the most significant findings regarding impairments for SCA2 [11, 21, 24] and SCA3 [9, 10, 20], when compared to the general population. Only two studies evaluated SCA1 [21, 27], both of which indicated impairments. For SCA6 the number of studies is limited and inconclusive [17, 22].

Language, similar to motor function, was the least evaluated specific skill and, in addition, each of the studies used a different measurement instrument. The findings for this function should be analyzed with caution, given that only one study evaluated SCA2 [30] and the other two evaluated SCA3 [20, 26], with diverging results. This aspect, coupled with the small

number of studies and the use of different instruments, does not permit the establishment of conclusive evidence regarding this function.

Table 6 presents the studies related to memory, attention and working memory, verbal memory, and visuospatial memory.

To evaluate the general memory, as presented in **Table 6**, various instruments were used with emphasis on the Wechsler Memory Scale. In relation to the main findings, no differences were observed between the groups of SCA_{polyQ} patients and the general population, except in SCA7, for which only one study was conducted with results indicating greater impairment [16].

With regard to attention and working memory, there was a tendency to use the *Digit Span* subtests of the *Wechsler Memory Scale* or the *Wechsler Adult Intelligence Scale* as the main evaluation instrument. The results varied little, with the lack of differences regarding the impairments for the SCA3 [10, 20, 21, 26], SCA2 [15, 28, 24] and SCA6 [17, 22], in comparison with the general population predominating. However, these findings are more consistent for SCA3 (N=04), being that for SCA1, SCA2, SCA6 and SCA7 a greater number of studies seem to be necessary.

Verbal memory was evaluated using the *Wechseler Memory Scale* and *Word List* in the majority of the studies. The main findings for this function indicated greater impairment in the group of SCA_{polyQ} patients, especially for the SCA1 [21, 27] and SCA2 [21, 24, 28] types. In the case of SCA3, the most studied type (N=04), the findings proved inconclusive with two studies indicating impairments [20, 21] and one study indicating an absence of statistically significant differences in relation to the general population [10]. All the studies involving SCA6 [17, 22] presented results indicating an absence of impairments when compared to the non-clinical control group.

Regarding visuospatial memory, it can be seen that the instrument most used was the *Rey-Osterrieth Complex Figure*. In the majority of the studies, the performance of the group of SCA_{polyQ} patients [21, 22, 27, 28] presented no significant difference compared to the general population, except in one study involving SCA6 [17], the findings of which diverged from those of the other studies.

Discussion

This review aimed to evaluate the psychiatric and neuropsychological changes in individuals affected by SCA_{polyQ}, from the analysis of studies without imposing a time restriction. A total of 26 articles were selected, the first having been published in 1993, from which point an increase in interest was observed in this field of knowledge, particularly in the two years prior to this review.

Regarding the origins of the studies, it was observed that more than half of them were from European countries. This has special importance, considering that some SCA genotypes are more typical in a particular world region and ethnicity [7]. In this sense, a larger body of studies, including different ethnic groups, could clarify eventual phenotypic differences between the types of ataxia, and even within a specific type.

From the methodological point of view, 73% of the studies used comparison groups, this being the most appropriate design for the evaluation of the theme studied. The majority of the control groups, 79%, were composed of healthy individuals from the general population [9-12, 15, 17, 18, 20-22, 24, 27, 28, 30, 32] and similar in relation to the sociodemographic characteristics of the clinical group, which provides greater uniformity and reliability to the findings. The sample size was expressive in more than half of the studies, which allows the generalization of the findings.

With regard to the types studied, more than two thirds of the articles exclusively studied one specific type of SCA and only 19% of the studies conducted comparative analyses between SCA_{polyQ} types. Among the most studied ataxias was SCA2, evaluated in 54% of the articles, followed by SCA3 (42%) and SCA1 (31%). The least studied types were SCA7 and SCA17, with only one publication each.

In general, many of the studies (42%) aimed to evaluate the psychiatric and neuropsychological aspects jointly. The neuropsychological functions prevailed as the main area of interest, being evaluated in approximately 85% of

the studies, with emphasis on the executive function (58%) and attention/working memory (54%). Regarding the psychiatric aspects, evaluated in approximately half of the studies, it was observed that most of the studies were restricted to the investigation of indicators of depression and anxiety, with the association with the Axis 1 psychiatric disorders, as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [35] not being explored, which needs to be done in future studies.

With regard to the instruments used for the evaluation of the depression/anxiety symptoms, it should be highlighted that none of the studies used an instrument endorsed as the gold standard for the diagnosis of psychiatric disorders, such as the Structured Clinical Interview of the DSM IV (SCID IV) [39]. Therefore, the limitations involving the use of screening scales should be considered, namely: a) they rely on the self-perception of the subject, and b) there is an overlap and bias in the perception of the psychiatric and clinical symptoms, which favors inaccurate or even erroneous conclusions regarding the aspect evaluated. Nevertheless, the data indicated a higher prevalence of these indicators in the group of patients with SCA_{polyQ}, which is in agreement with previous literature regarding patients with other neurodegenerative diseases, such as multiple sclerosis [36], Huntington's disease [37] and Parkinson's disease, in which the depressive disorder is considered a prominent factor in the clinical presentation of these conditions [36-38].

Also in relation to the psychiatric aspects, it is worth noting that among the SCA_{polyQ}, the presence of such indicators was not homogeneous, being more evident in type 3. The hypotheses for the presence of greater depressive symptomatology in SCA patients are still quite divergent with studies that tend to consider the depressive symptoms as a reactive aspect, considering the losses characteristic of the evolution of the disease [13, 15, 18], or as an intrinsic organic aspect of the disease [12, 26]. Regarding these two hypotheses, an interesting issue was raised from this review, in the sense that although SCA2 presents a pattern of cognitive impairments and clinical symptoms that approximate that of SCA3, for type 2 of the disease, depressive symptomatology greater than that of the general population was not encountered. This seems to reinforce the second hypothesis, with the occurrence of the depressive symptomatology being a factor more connected to the phenotypic expression of SCA3.

With respect to the global cognitive aspects, there was a divergence in the findings depending on the types of SCA, with tendencies toward impairment in types 1 and 2 and an absence of impairment in types 3 and 6. However, there is one important factor to be highlighted with respect to the global cognitive evaluation. As can be seen from the results, the SCA types tend to present impairments in certain specific cognitive abilities and not an overall deficit. With this, a more general evaluation of cognition may tend to mask more circumscribed impairments, especially when screening instruments are used, such as the *Mini-Mental State Examination*.

The findings related to the visuospatial ability proved inconsistent, without a substantial body of studies that demonstrate significant differences between the group of patients and the general population. Therefore, this variable needs to be explored further, also considering that different instruments were used in the evaluation of this function, which complicates point to point comparisons.

Motor function was covered by a very small number of studies (N=04), which presented exploratory findings that tend to indicate impairments for the group of SCA_{polyQ} patients. It is noteworthy that one of the studies described [15] established a differential in the evaluation of this function, considering the fine and gross dimensions of the motor function which, if employed in future studies, can provide greater knowledge about the nature of the impairments involving this function.

The findings related to executive function, one of the most studied neuropsychological aspects, point to greater impairments for the group of SCA_{polyQ} patients, with more consistent results for SCA2 and to a lesser extent for SCA1 and SCA3. Since this function is rather complex, a wide variety of instruments was used. However, despite this diversity, the impairments remained constant. The findings regard-

ing impairment for the patients in this function are confirmed by the literature [7], mainly for SCA2 and SCA3.

In many studies verbal fluency was considered to be an aspect of executive function and even in the studies in which this function was evaluated separately, the findings were coincident. Greater impairments were evidenced for almost all the types of ataxia studied, with the exception of SCA6. In this group of studies, there was homogeneity in the choice of neuropsychological instruments used, which further supports these findings.

With language being one of the least studied neuropsychological aspects and with findings evaluated by means of different instruments, the results for this skill are neither conclusive nor indicative of a possible trend. Thus, future studies are needed to develop the issue.

With respect to general memory, the diversity of techniques used is highlighted, which limits point to point comparisons between the studies. However, despite this, the findings indicate the absence of significant differences between the SCA group and the general population. Although, when memory is evaluated taking into account its various dimensions, the findings point in another direction. This seems to indicate the importance of evaluating this function more specifically.

Attention and working memory were evaluated together in 78% of the studies. In general, the data presented tended to indicate the absence of impairments between the different SCA groups and the general population, especially regarding SCA3 (N=04). It is worth highlighting that in the studies in which no differences were found between the clinical and control group, the instrument predominantly used was the *Digit Span* subtest of the *Wechsler Memory Scale* or the *Wechsler Adult Intelligence Scale*. This instrument is among the most used in the evaluation of these functions [40]. Conversely, the studies that showed significant differences relative to the general population made use of different instruments that exclusively evaluated attention [15, 16, 32]. These aspects should be considered when comparing these findings, setting a limit for the comparison of the results of the different studies.

For the evaluation of the verbal memory, there was less variability in the choice of instruments, which produced greater consistency for the comparison between studies. However, the findings were different among the types, with greater impairments for SCA2 and SCA1 and no significant impairment for SCA6. For SCA3 the need for further studies was revealed, in view of the controversial findings for this SCA type.

The findings for the evaluation of visuospatial memory showed no significant differences in relation to the general population in the majority of the studies except in the case of SCA6, where one study indicated differences [17]. It should be noted that this study used a different instrument from other studies as a form of evaluation, a subtest of the *Weschsler Memory Scale*, which may have influenced the results. Thus, considering the small number of studies, further exploration of this function is necessary to search for more evidence about the presence or absence of dysfunctions in this dimension of the memory.

In general, as already mentioned, the memory, in its different dimensions, was one of the most studied neuropsychological aspects and with well established impairment differences among its specificities. The presence of impairments in the verbal memory was evidenced, as well as a trend in the absence of impairments in the attention/working memory and, in a more marked way, in the visuospatial memory.

Regarding the comparison between the types of SCA_{polyQ}, considering that a minority of the studies carried out such comparisons, it is not possible to say whether there is a type in which the impairments are more or less evident. However, comparing the studies indirectly, it can be seen that SCA2, SCA3, SCA1, tended to present a higher level of impairments compared to the other types (which, as already emphasized, were less studied). Only from direct comparative studies, or from further evidence regarding the neuropsychological and psychiatric aspects of the other types, can conclusions be drawn in this regard.

Given the results of this review, and considering the differences between the types of SCA, it can be observed that the specific cognitive abilities that present more indicators of impairment were executive function, verbal fluency

and verbal memory. This pattern of impairment suggests involvement of the cerebral cortex and especially the frontal lobe, a structure already well recognized as related to the executive functions.

Furthermore, a recent meta-analysis article that included 88 articles about neuroimaging in healthy subjects showed cerebellar activation in the higher cognitive functions, involving emotion, executive functions, language, music, time and working memory [41]. In this regard, many studies involved in this review indicated the close functional relationship between the cerebellum and the cerebral cortex [11, 15, 16, 21, 27, 29, 30], which may suggest that the changes described are linked to dysfunctions in the cerebro-cerebellar circuit. This hypothesis offers a promising path for future comparative neuropsychological studies that could involve patients with different types of SCA_{polyQ} and functional neuroimaging examinations.

The hypotheses proposed up to now regarding the nature of the cognitive alterations present in this group of diseases must be considered with caution, because the heterogeneity of the phenotypes and the lack of homogeneity in the cognitive evaluation methods employed have sometimes resulted in contradictory findings that may compromise generalizations of the results.

Regarding the correlation between clinical variables and cognitive impairments, it was observed that very few studies carried out these analyses, so that it was not possible to establish conclusions regarding the influence of the age at the onset of clinical symptoms, duration of the disease, or size of the CAG expansion on the cognitive impairments. In some studies a negative correlation was found between disease duration and cognitive impairments [12, 14, 28] and in others, this correlation was not confirmed [11, 24, 27, 31], or found only for some subtests [17, 22].

Conclusions

Based on the analysis of the studies, the present work, in general, revealed the existence of more psychiatric symptoms and greater cognitive impairment in patients with SCA_{polyQ} when compared with the general population. Furthermore, there seems to be differences in the profile of cognitive deficits among the types of SCA, with some cognitive functions more likely to be impaired in a specific type, which, added to the clinical specificities characteristics of each type, can be a factor that helps in the clinical differentiation between these ataxias. However, there is a need for a greater number of studies that use a more homogeneous methodology, which perform direct comparisons between the types of ataxias and that explore some of the still little evaluated neuropsychological functions (such as motor function and language) and the different psychiatric disorders in their amplitude and complexity.

Comprehending the neuropsychological and psychiatric changes associated with SCA_{polyQ}, has great importance for the clinical monitoring of these patients, contributing to the establishment of clinical procedures, with specific therapies, that can minimize the impact on the adaptation and emotional suffering of these patients. Furthermore, a better understanding about the cognitive impairments and psychiatric alterations present in SCA_{polyQ} can lead to advances in knowledge about the neurobiological mechanisms underlying the genetic alterations and the functioning of the central nervous system as a whole.

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