DEPRESSION AND ANXIETY IN POLYQ SPINOCEREBELLAR ATAXIA

A literature review

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Foreword

This thesis, titled: “Depression and Anxiety in PolyQ Spinocerebellar Ataxia: A Literature review”, was written as closure of the pre-master Biomedical Sciences at the University of Groningen.

My main reason for choosing this topic is personal interest since my father-in-law has SCA6. By writing this thesis I hope to contribute to the research in this field. I also hope to raise awareness for the influence of the disease on not only the patient’s life, but also the life of relatives.

I want to thank my supervisor, dr. Dineke Verbeek, for the excellent guidance and support during the process. I would also like to thank my husband who supported me by stimulating me to actually get some work done.

I wish you a lot of reading pleasure,

Berdien Maring

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Abstract

Spinocerebellar ataxia (SCA) is a heterogeneous group of neurodegenerative disorders characterized by progressive cerebellar dysfunction. Beyond the well-documented motor impairments, recent studies have shed light on the significant comorbidity of depression and anxiety in individuals with SCA. This review aims to determine what the origin of depression and anxiety in polyQ SCAs is. It is expected that besides the emotional component the underlying pathology of SCA contributes to depression and anxiety as well. Literature shows that depression is present among all types of polyglutamine SCAs with a higher prevalence compared to the general population and that anxiety is most described in SCA3. SCA3 patients are the worst affected by depression. Based on the largest studies, a relation between SARA scores and depression is likely. On the other hand, the length of the CAG repeat is not related to the severity of depression. Despite advancement in understanding the pathology of SCA it is still not clear what the effect of the extended CAG repeats is on the human brain. This also applies to the involvement of the cerebellum in depression and anxiety. Several SCA mouse models are available to study depressive and anxious behavior in SCA. However, the current published studies have to many limitations to draw conclusions from them. When taken all the research in consideration depression and anxiety in polyQ SCAs can be biological or emotionally reactive from origin, or maybe even both. It is possible that an out of cerebellar pathology of SCA may influence depression and anxiety, or that the cerebellum plays a role in depression and anxiety.

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1. Introduction

Spinocerebellar ataxia (SCA) is a group of hereditary neurodegenerative disorders characterized by progressive dysfunction of the cerebellum and its associated pathways. These disorders cause a broad range of motor and non-motor symptoms, including gait disturbances, dysarthria, and impaired coordination. Until to date SCA remains an untreatable disease. Over the years it has become clearer that besides motor impairments, non-motor symptoms are also common under SCA patients. These non-motor symptoms often include psychiatric impairments like depression and anxiety. A growing amount of evidence highlights the influence of psychiatric impairments, like depression and anxiety, on the quality of life (1). Despite that, deciphering the origin of anxiety and depression, is still very difficult in many SCA types.

SCA exhibits remarkable clinical and genetic heterogeneity, with more than 35 distinct subtypes identified to date (2). These subtypes are classified based on the implicated gene mutation, the most prevalent being the polyglutamine expansion repeat disorders, commonly referred to as polyQ SCAs. These disorders are characterized by an abnormal repetition of the trinucleotide CAG, resulting in the production of an expanded polyglutamine (polyQ) tract within the respective protein (3). The polyQ SCAs include SCA1, SCA2, SCA3, SCA6, SCA7 and SCA17. All polyQ SCAs have a different threshold at which they cause full penetrance.

SCA1 has an adult onset that is caused by CAG repeat mutation in the ATXN1 protein (4). Unaffected individuals have 19-36 CAG repeats, SCA1 patients have 43-81 repeats (5). The mutant amount of CAG repeats leads to degeneration of Purkinje cells in the cerebellum (3). Because of the extended CAG repeat, the mutant protein is highly stable and more resistant to degradation (3).

SCA2 is caused by CAG repeat expansion at ATXN2 gene (6). The mutation causes gains of new or toxic functions for the ATXN2 protein. This results in slow Purkinje cell firing frequencies and eventually Purkinje cell loss (3).

SCA3 also known as Machado-Joseph disease is the most common type of SCA. It has a distinct geographical distribution with a peak in certain regions of Brazil, Portugal, and China (3). It is caused by a CAG repeat expansion of ATAXN3.

SCA6 is a late onset ataxia characterized by pure cerebellar dysfunction (7). Genetically, SCA6 is caused by a CAG repeat at the C-terminus of the α1A subunit of the P/Q voltage-gated calcium channel CACNA1A (7). Healthy people have 4-18 repeats, while patients have 19-33 repeats (7). Neuropathological studies show loss of cerebellar Purkinje cells and morphological changes in the remaining Purkinje Cells (8).

SCA7 is caused by an unstable repeat expansion of the ATXN7 gene (9). Toxic properties of the ATXN7 gene lead to neuronal degradation in the cerebellum, the brain stem, and the retina. Due to the founder effect the frequency of SCA7 is higher in Scandinavia, Korea, South Africa, and Mexico.

SCA17 is caused by an abnormal CAG repeat expansion in the TATA-box binding protein (10). Interestingly SCA17 has an extensive phenotypic variability, with an age of onset that spans several decades.

The extended CAG repeat causes several features which are common between the polyQ SCAs. First, there is an inverse relationship between the age at onset and the number of repeats in the expansion. Besides that, more CAG repeats cause a more severe disease. In addition, the different amount of CAG repeats causes variability of phenotypes within the same genotype.

The exact pathological molecular mechanism of the extended CAG repeat remains unclear, but it is suggested that the extended polyQ tract develops an altered protein folding (11). Experiments indicated that the misfolded proteins are prone to aggregate (11). These aggregates interfere with normal functioning of neurons. Various cellular processes are disrupted including, protein degradation, RNA processing, cellular transport, and mitochondrial function. The misfolded proteins accumulate particularly in the cerebellum, where it causes degradation of the cerebellar neurons, primarily the Purkinje cells. As the cerebellum is responsible for coordinating movement and maintaining balance these are particularly affected in SCA (2).

Despite that every year more knowledge about the pathology and molecular mechanism behind SCA is discovered, deciphering the origin of anxiety and depression in SCA is still difficult. This is mainly because of two reasons: first, having a progressive untreatable disease imposes a huge emotional burden. This stress alone may even be the reason to be depressed. Second, in most types of SCA the neuropathology is not limited to the cerebellum but extends to multiple brain regions (2). Moreover, even patients with the same type of SCA do not always have the same distribution of brain damage. Besides that, not all SCAs are very common, and recorded data is often clustered within a few families.

Altogether, it remains unclear whether psychiatric symptoms like anxiety and depression have a biological origin based on SCA specific pathology or are an emotional response of chronic illness. In this study the cause of depression and anxiety in polyQ SCAs is investigated based on current available literature. The expectation is that anxiety and depression in polyQ SCAs can be related in multiple ways. First, if depression/anxiety and SCA are connected a higher prevalence of depression is expected compared to the general population. Second, each type of SCA has a specific genotype and phenotype, so depression and anxiety will not be equally present among different types of SCA. Third, if depression and anxiety are an emotional response to having a chronic degenerative disease it is likely that patients with more severe ataxia have more change to develop depression. Fourth, since there is an inverse relationship between CAG repeats and age of onset, and a larger repeat expansion causes a more severe disease, it is expected that a larger number of CAG repeats causes more severe depression and anxiety. In addition, since the exact pathology of SCA remains unclear, it can be possible that out of cerebellar pathology of SCA may contribute to the development of anxiety and depression. Or that the cerebellum is involved in depression. The last question is whether mouse models can contribute to the research to determine whether anxiety and depression are related to SCA.

2. Depression and anxiety in polyQ SCA

Depression in polyQ SCAs was described in 22 studies and anxiety in 10 studies (Table 1). In these studies, 42 patient groups were analyzed for depression symptoms and 17 patient groups for anxiety symptoms. Two studies used a population of mixed SCA subtypes, the remaining studies analyzed the genetic subtypes separately. Among them 9 studies analyzed depression in SCA1, 12 for SCA 2, 14 for SCA3, 7 for SCA6, and 2 for SCA7. The size of the patient groups differed from 1 to 227 patients. Nine of the studies took place in Europe, followed by 7 studies in Brazil, 3 in Asia, 2 in the USA. And one study used a combined population form the USA and Europe. However, the largest studies were conducted in the USA and Europe.

Anxiety in SCA is not as extensive researched as symptoms of depression in SCA, it has only been investigated in 10 studies. Signs of anxiety were analyzed in one genetically mixed population of SCA1 and SCA2, and one population of SCA1 patients, 1 of SCA2, 7 of SCA3 and 1 of SCA6. None of the studies examined anxiety in SCA7 patients.

In most studies standardized rating scales were used for the assessment of anxiety and depression in SCA. All scales are not intended to provide a diagnosis of depression, but rather assist in evaluating the presence and severity of symptoms. The methods all use a different rating scale and investigate different items and each method has its own limitations.

The severity of ataxia was most measured with the Scale for Assessment and Rating of Ataxia (SARA) and in one case with the International Cooperative Ataxia Rating Scale (ICARS). The Scale for SARA is a widely employed clinical rating scale that quantifies the severity of ataxia across different domains, including gait, stance, sitting, speech, and fine motor skills. It provides a comprehensive assessment of ataxia severity and aids in monitoring disease progression (12). The ICARS is another established rating scale used to evaluate the severity of ataxia. It encompasses a broader range of motor and non-motor functions, such as posture, limb coordination, and oculomotor control, offering a comprehensive evaluation of disease progression (13).

2.1. Prevalence of depression and anxiety in SCA

To determine whether depression and anxiety in SCA are a problem, it is important to know if anxiety and depression have a higher prevalence in SCA compared to the general population.

The prevalence of depressive symptoms in SCA varies widely, ranging from 4.5 – 75% (Table 1). However, the largest study, including 282 SCA patients, reports a prevalence of 17-26% based on measurements by the PHQ-9 (1).

Most studies describe significant more depressive symptoms in patients with SCA compared to the healthy control group, although, two studies find no significant differences (14, 15). A study on 20 Italian SCA2 patients, originating from Middle Easter Sicily, gave no significant higher BDI score compared to sex and aged matched healthy controls (15). Another study on 18 SCA2 patients from Middle Eastern Sicily showed no differences in depressive symptoms compared to the healthy control group based on Hamilton Depression scale (14).

Significant more anxiety symptoms were found in 8 out of 10 studies compared to the general population. The prevalence of anxiety was only described in one study on SCA3 patients, with a prevalence of 42.3% (Table 1).

TABLE 1: OVERVIEW OF STUDIES THAT DESCRIBE DEPRESSION AND ANXIETY IN SCA

Title	Location	Methods	Patients	Severity of ataxia	Depression	Anxiety	Prevalence of depression/anxiety
Agata et al., 2011 (16)	Italy	Zung SDS, STAI-Y	SCA2 (n = 9) SCA6 (n = 5) SCA7 (n = 2) SCA8 (n = 4)	ICARS 46	0	0	45%
Braga-Neto, Dutra et al., 2012 (17)	Brazil	BDI, HAMA	SCA3 (n = 29)	SARA 13.3 ± 8.4	+	+	NA
Braga-Neto, Pedroso et al., 2012 (18)	Brazil	BDI, HAMA	SCA3 (n = 38)	SARA 13.2 ± 9.1	+	+	NA
Chen, Lee, Chien, Hwu, & Lin, 2019 (19)	Taiwan	BDI, BAI	SCA1 (n = 5) SCA2 (n = 33) SCA3 (n = 48) SCA6 (n = 1)	NA NA NA NA	0 + + 0	0 0 0 0	NA NA NA NA
Fancellu et al., 2013 (20)	Italy	HAMD, HAMA	SCA1 (n = 20) SCA2 (n = 22)	SARA 12.53 ± 6.4 SARA 14.29 ± 56	+ +	0 0	5% 4.5%
Gigante et al., 2020 (21)	Italy	BDI	SCA2 (n = 22)	SARA 10.4 ± 4.5	0	NA	NA
Hengel et al., 2023 (22)	EU + USA	PHQ-9	SCA3 (n = 227) Pre ataxic mutation carriers (n = 42)	SARA 12 SARA 1	+ 0	NA NA	NA
Jacobi et al., 2020 (23)	West Europe	PHQ-9	SCA1 (n = 173) SCA2 (n = 207) SCA3 (n = 172) SCA6 (n = 125)	SARA 9.0 SARA 12.0 SARA 11.5 SARA 13.0	NA	NA	NA
Kawai et al., 2004 (24)	Japan	HADS	SCA3 (n = 16)	NA	+	+	NA
Klinke et al., 2010 (25)	Europe	BDI	SCA1 (n = 6) SCA2 (n = 3) SCA3 (n = 3) SCA6 (n = 8)	SARA 12.5 ± 4.7 SARA 3.8 ± 1.4 SARA 8.2 ±6.4 SARA 12.6 ± 4.8	+ 0 0 +	NA NA NA NA	50% 33% 13% 75%
La Pira et al., 2002 (14)	Middle Eastern Sicily	HAMD	SCA2 (n = 18)	NA	0	NA	NA
Lo et al., 2016 (1)	North America	PHQ-9	SCA1 (n = 49) SCA2 (n = 46) SCA3 (n = 123) SCA6 (n = 64)	SARA 14.2 ± 8.5 SARA 16.9 ± 7.4 SARA 15.0 ± 8.8 SARA 14.3 ± 7.5	+ + + +	NA NA NA NA	24.5% 21.9% 30.9% 21.9%
Lopes et al., 2013 (26)	Brazil	BDI, BAI	SCA3 (n = 32)	SARA 13.6 ± 6.3	+	+	NA
Martins, Martinez, Abreu, Lopes-Cendes, & França, 2015 (27)	Brazil	BDI	SCA1 (n = 12)	NA	+	NA	NA
McMurtray, Clark, Flood, Perlman, & Mendez, 2006 (28)	USA	Clinical interview	SCA1 (n = 12) SCA2 (n = 22) SCA3 (n = 20) SCA6 (n = 22)	NA NA NA NA	+ + + +	NA NA NA NA	25% 23% 60% 27%

Title	Location	Methods	Patients	Severity of ataxia	Depression	Anxiety	Prevalence of depression/anxiety
Moriarty et al., 2016 (29)	United Kingdom	PHQ-9	SCA1 (n = 2) SCA2 (n = 2) SCA3 (n = 2) SCA6 (n =4) SCA7 (n = 3)	SARA 10.5 ± 0.35 at baseline, 19.75 ± 6.01 at follow up SARA 9.5 ± 0.71 at baseline, 14.5 ± 0 at follow up SARA 20.25 ± 4.6 at baseline, 24.75 ± 4.6 at follow up SARA 13.13 ± 2.56 at baseline, 17.38 ± 3.54 at follow up SARA 13.5 ±4.27 at baseline, 19.5 ± 5.77 at follow up	+ 0 + + 0	NA NA NA NA NA	NA
Moro et al., 2017 (30)	Brazil	BDI, HAMA	SCA3 (n = 28)	SARA 15.7 ± 7.3	+	+	NA
Pedrose et al., 2017 (31)	Brazil	BDI, HAMA	SCA2 (n = 33)	SARA 16.80 ± 12.22	+	+	NA
Saute et al., 2010 (32)	Brazil	BDI	SCA3 (n = 19)	SARA 14.5 ± 7.5	+	NA	63.3%
Tamaš et al., 2021 (33)	Serbia	HAMD, HAMA	SCA1 (n = 12) SCA2 (n = 6)	SARA 15.3	+	+	NA
Yuan et al., 2019 (34)	China	HAMD, HAMA	SCA3 (n = 68)	SARA 11.01 ± 4.97	+	+	48.5%/42.6%

*Notes: **BAI** = Beck Anxiety Inventory, **BDI** = Beck Depression Inventory, **HAMA** = Hamilton Anxiety Scale, **HAMD** = Hamilton Depression Scale, **HADS** = Hospital Anxiety and depression scale, **PHQ-9** = Patient Health Questionnaire, **STAI-Y** = The State-Trait Anxiety Inventory, Zung **SDS** = Zung Self Rating Depression Scale, 0 = no significant differences between a patient group and control group, **+** = significant differences between a patient group and a control group*

2.2. Depression and anxiety in different SCA types

Considering that each type of SCA is caused by a repeat expansion in a different gene, anxiety and depression might have a different prevalence in each subtype. Therefore, it is critical to determine whether patients with a certain type of SCA have more depressive symptoms.

Among the polyQ SCAs, SCA3 patients appears to not only have the highest prevalence of depressive symptoms and patients also have the highest depression scores (1, 28). In addition, SCA3 patients have a higher suicidal intention (65%) compared to other types (52%) in general (1). It was suggested that this may result from the neurodegenerative process because the SARA score is not different from the other subtypes. In addition, another study also found significantly greater depressive symptoms in SCA3 patients compared to the other patients with other subtypes (28). It was reasoned that the increased frequency of depression can be subscribed to the involvement of the basal ganglia. When compared to SCA10 patients, SCA3 patients showed significant higher symptoms of depression (30).

However, another study found that SCA1 and SCA6 showed more pronounced depressed mood than SCA3 and controls (25).

Anxiety symptoms were mostly described in SCA3 patients, only in one study on SCA3 patients no significant difference was found between patients and the healthy population (19). Higher symptoms of anxiety only had a correlation with logical memory and verbal fluency (24). Besides that, anxiety in SCA3 patients is correlated with depression (34).

A mixed population of SCA1 and SCA2 participants showed significant more anxiety symptoms compared to the control group based on HAMA scores (33). The same was true for SCA2 participants (35), although this study showed a correlation with smell.

2.3. Influence of disease duration and severity on depression

If depression is an emotional response of having a chronical disease, it is expected that patients with more severe ataxia score higher on depressive rating scales. Besides that, longer disease duration can cause more depressive symptoms.

Whether depressive symptoms are correlated with disease severity or duration is investigated by several studies. In 7 studies no relation between SARA scores and depressive symptoms (20, 21, 24, 28, 31, 33, 34) was found. Depression in these studies was measured by BDI, HADS, Clinical Interview and HAMD. The number of participants varied from 6-68 patients, with most studies around 20 participants. A longitudinal study among 9 SCA1 and 11 SCA2 patients showed no significant deterioration of depressive symptoms over 2 years (20), although at baseline patients had significantly more depressive symptoms than the control group.

Five studies found that depressive symptoms were significant associated with increasing SARA or ICARS scores (1, 16, 22, 23, 32). Depressive symptoms in these studies were measured by BDI, PHQ-9 and Zung SDS. The number of participants varied from 19-667 participants; however, these include the three largest studies (1, 22, 23), with each over 200 participants spread over different types of SCA.

Lo et al. found that depressive symptoms were common among 282 patients with SCA1, 2, 3 and 6, and are associated with higher SARA scores or greater severity of ataxia (1). However, within 2 years observation PHQ-9 scores did not change significantly, even after accounting for age and sex. However, when Generalized Estimated equations (GEE) models were used to investigate factors that affect depressive symptoms, change in SARA scores over time was associated with PHQ-9 scores in SCA1, 3 and 6, but not in SCA2. In addition, higher PHQ-9 scores were associated with longer disease duration in SCA3. Age and sex did not have a significant role in PHQ-9 scores in the models. The GEE models that were used to test whether depressive symptoms would affect ataxia progression showed that increased time varying PHQ-9 scores were associated with higher SARA scores in SCA1, 3 and 6. These effects remained significant even after accounting for age, sex, CAG repeats and time. Summarized, Lo et al., concluded that depressive symptoms remained stable over time for 2 years, and are associated with higher SARA scores or greater severity of ataxia. Considering that the prevalence of depression did not follow the same rank order of progression and that depressive symptoms did not change over time with motor symptoms, it is argued that depression is not only caused by the awareness of disability. So depressive symptoms in ataxia could be due to both the emotional response to suffering and part of the neuropathology of SCA.

On the contrary D'agata et al. noticed that depression is probably linked with the awareness of the disease's worsening (16). This is supported in the study by Saute et al. (2010), in which depression in SCA3 is related to physical incapacity and not primarily to brain involvement (32).

Another study among 227 SCA3 patients concluded that the frequency and severity of depressive symptoms increased in parallel with SARA scores (22). In addition, another study among 677 participants showed that PHQ-9 scores worsened with increased disability stage (23). The disability stage was defined by walking ability and with as last stage death. So PHQ-9 scores were correlated with worsening gait problems. However, these studies did not explain the cause of those relationships.

2.4. Relation between amount of CAG repeats and depression

Since there is as inverse relationship between CAG repeats and age of onset, and a larger repeat expansion causes a more severe disease, a larger number of CAG repeats can be the cause of more and severe depression and anxiety in SCA patients.

However, of the nine studies that investigate this association (1, 20-24, 32, 34, 36) only two studies found a correlation between CAG repeats and depressive symptoms (22, 34). Nonetheless, Kawai et al., suggest that CAG repeat expansion beyond the normal range may lead to cognitive impairments and that the severity is unrelated to the length of the expansion (24).

A higher rate of psychiatric manifestations was found in patients who had not only a pathological repeat in SCA3 but had an additional intermediate number of repeats in SCA2, compared to patients who only have a pathological repeat of SCA3 (19). Suggesting an additional genetic mutation may be involved.

2.5. SCA neuropathology and anxiety and depression

SCA is classically seen as a cerebellar disease, but researchers are becoming more aware of the possibility that other brain regions are affected as well. Besides that, the question has risen if the cerebellum is involved in cognitive processes, including depression and anxiety.

The so called cerebellar cognitive affective syndrome (CCAS) was already described in 1998 (37). Beside cognitive processes like perception, attention and learning mood problems are frequently described within CCAS. The last few years CCAS has been studied in several SCA types (18, 21, 38) and it has become clear that cognitive functioning is affected in all SCA types.

In addition, several studies have been investigating cerebellar connectivity to identify structural and functional changes of non-motor cerebellar regions in patients with depression (39). However, depression is a clinically and biologically heterogeneous disorder, and only a few studies have been trying to attempt to subtype patients based on clinical, neuropsychological, and neuropsychological features. And most of all, there is a lack of longitudinal brain imaging data of depression. Which makes it hard to answer more fundamental questions, like the involvement of the cerebellum in depression.

More evidence is accumulating that other brain regions, besides the cerebellum, are involved in SCA as well. A recent study investigating altered cerebral blood flow (CBF) in spinocerebellar degeneration patients showed that two clusters, which include the cerebellum and the midbrain, had a decreased CBF (40). Decreased blood flow is in indication for less brain activity and therefore an indication for degeneration of brain tissue. Since the two clusters were negatively correlated with SARA scores, the degeneration in these clusters have an influence are likely related with ataxia. Besides that, one cluster had a negative correlation with the Self-Rating Depression Scale, therefore this cluster is likely involved in both SCA and depression.

2.6. Mouse models to study anxiety and depression in SCA.

Despite that brain imaging techniques like magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) are a powerful resource, they may not always capture the pathological changes of SCA. The only other ways to examine the brain are trough tissue biopsy or autopsy. Since brain tissue biopsy comes with inherent risks, it is not commonly used in research. In addition, autopsy only gives information about the later stages of SCA. Therefore, other ways to determine the neuropathology of SCA are needed, and mouse models may provide a solution.

A way to overcome the difficulties of studying the human brain and its complex relation with emotional behavior, like depression, animal models may provide a solution. The use of mice to test emotional behavior has a long tradition in experimental psychiatry. More recently, they are also used in experiments with mouse models of cerebellar disease (41). Several tests are developed to assess psychiatric related behavior in mice like the *forced swimming test* (FST) in which mice are placed in a container filled with water and left there for up to 10 minutes. Depressive like behavior can be measured by the time a mouse spends immobile (42). Another way to test mice for depression is with the *sucrose preference test* (SPT) in which a mouse is placed separately in a cage with 2 water bottles.

One bottle is filled with 1-5% sucrose where the other contains only water. Subsequently, the water intake is measured for several days and measured. When a mouse shows preference for sucrose this is an indication for anhedonic behavior (43).

The *open field test* (OFT) is a simple test that is widely used because it has multiple outcome measures like overall locomotor activity and anxiety like behavior. The animal is placed in an arena and is led to explorer the arena. Locomotor activity is represented by the distance walked and relative time spent walking. Anxiety like behavior is measured by the % of time spend or % of the distance walked in the proximity of walls, also called thigmotaxis (44).

The *elevated plus maze test* (EPM) is another test that is used for anxiety like behavior. The test field is a plus shaped arena with two "open" and two "closed" arms. Mice with anxious behavior tend to explorer both the open and closed arms but will spend relative more time in de closed arms compared to mice without anxious behavior (45).

Besides the possibility to test for anxiety and depressive like behavior in mice, suitable mouse models for SCA are needed. Several SCA mouse models are already known and used in research (3). However, until to date only SCA1 mouse models have been used to examine depression and anxiety.

A SCA1 mouse model that contains a long CAG repeat in the mouse SCA1 locus was used in the research depressive and anxiety like behavior of SCA1 (41, 46, 47). These knock-in mice carry 78 CAG or 154 CAG repeats in the mouse SCA1 locus (48). Since the mice with 78 CAG repeats showed no behavioral changes until late in life, it was hypothesized that the short life span of the mouse does not allow sufficient time for its neurons to accumulate significant damage. Therefore, a model with a repeat of 154 CAG, larger than the average human repeats, was created. It is proven that these mice developed a progressive neurological disorder, resembling human SCA1 (48).

A study that used the knock in mouse model with 154 CAG repeats in the *Atxn*1 gene demonstrated the possibility of out of cerebellar pathology in SCA and its relationship with depression and anxiety (47). The mice exhibited increased anxiety and depressive like behavior in OFT, EPM, FST and SPT. Moreover, it was found that non-motor deficits were already present in younger mice, before ataxia signs became visible. Therefore, non-motor deficits may characterize the early stage of SCA1 better than ataxia does. This was subscribed by the results of histological examination and mitochondrial respirometry. The histological examination revealed hippocampal atrophy that commences earlier than cerebellar degeneration. Also, mitochondrial dysfunction was found in the hippocampus, but not in the cerebellum of young SCA1 mice. Altogether, this suggests that non-motor symptoms may be independent of the motor deficits and that mitochondrial dysfunction in the hippocampus may be the cause of behavioral deficits.

That the loss of *Atxn1* causes neurodegeneration in the hippocampus of mice was also investigated by another study (49). The depletion of *Atxn1* caused a decrease in hippocampal neurogenesis in mice. Over the last few years, a growing amount of research provided evidence that hippocampal neuroplasticity is implicated in depression pathogenesis (50).

The same SCA knock-in mice with 154 CAG repeats in *Atxn1* showed anxiety like phenotype in EPM (41). When looking at the effects of the length of the polyQ repeats, it was found that mice fewer polyQ repeats (78 CAG repeats) do not show anxiety like behavior. This indicates that anxiety correlates with increased CAG repeats. However, no significant difference between WT and SCA1 mice was found regarding depressive-like behavior.

3. Conclusion and discussion

To answer the question whether anxiety and depression in SCA patients a biological origin have based on SCA specific pathology or are an emotional response of chronic illness available literature has been reviewed.

Results of the studies on depression in polyglutamine SCAs support the hypothesis that depression is present among all types of polyglutamine SCAs and is significantly more present in patients with SCA compared to the general population. The two studies that did not find significant more depressive symptoms in SCA patients are both executed on Sicily. It is possible that other factors, like culture, may have had an influence on depression and anxiety. Despite the different methods that are used to determine the severity and prevalence of depression, the general conclusion is that SCA patients score higher on questionnaires on depressive symptoms. However, none of these studies confirmed the diagnosis depression via the golden standard, Structured Clinical Interview of the DSM IV. Besides that, some symptoms of depression, like inactivity, are shared with SCA. At the moment no method is recommended for measuring depression in SCA. Although a new measurement method has been developed for measuring motor ataxia, quality of life and mental health (51). It stands out that most patients are not aware of the severity of their depressive symptoms and therefore do not receive treatment.

Most studies describe a higher prevalence of anxiety in SCA patients compared to the general population. Since the number of patients that are used in these studies are small, it is likely that they do not represent the whole SCA population. Therefore, in the future it is important that anxiety is researched among more SCA patients.

It seems that depression is not equally distributed among the different SCA types. Patients with SCA3 are the most and the worst affected. However, this can be influenced by the fact that SCA3 is the most and extensively researched, because SCA3 is the most frequent genotype (2). While 14 studies used patients with SCA3, SCA7 was only 2 times used as patient group. Of the polyglutamine SCAs, SCA7 has probably the lowest prevalence worldwide, and in some geographical region no cases of SCA7 are known.

Anxiety is also most common described in SCA3, although only a small number of studies describe anxiety in SCA. To answer the question how anxiety is distributed among the different types of SCA more data is needed.

The results of the studies by Jacobi et al. and Lo et al. suggest that depressive symptoms in SCA patients are correlated with disease severity. It is interesting to note that when PHQ-9 was used to measure depressive symptoms, always a relation was found between SARA scores and depressive symptoms. Most studies have a fixed timepoint when measuring depression in SCA, only two studies used a longitudinal design. Besides that, only one study investigated signs of depression in pre-ataxic patients. Without the knowledge if depression is already present in pre-ataxic SCA patients and if depressive symptoms worsen over time, it is hard to conclude how depressive symptoms and disease progression are related. Future research is required to determine whether the correlation between disease severity and depression is biased by using PHQ-9.

Because of the inverse relation between the length of the CAG repeats in polyQ SCA, the onset of the disease and disease progression a relation between the length of the CAG repeats and depression is expected. However, in only two studies a correlation between CAG repeats and depression is found. Therefore, it seems unlikely that the length of the CAG repeat explains the differences in depressive symptoms that can be found in SCA patients. Interestingly, in several SCA3 patients suffering from depression an intermediate number of repeats in SCA2 was found. Together with the recent developments in molecular techniques, like next generation sequencing, that still reveals unknown genetic abnormalities in SCA patients, the influence of a genetic factor is still a possibility.

Whether SCA pathology contributes to depression and anxiety, remains unclear. It is possible that the cerebellum has a role in cognitive processes, as suggested by several studies on CCAS. Reasoned from the side of depression, a role for the cerebellum in depression has not been established yet. As shown by reduced CBF in the midbrain and the cerebellum that is correlated with both SARA scores

and depression, neuropathology that reaches beyond the cerebellum can be an explanation of depression and anxiety. Although the study had a small sample size and each measurement was only performed once, this might be an interesting approach for future studies.

If out of cerebellar pathology plays a role in the origin of depression and anxiety, it is expected that other neurodegenerative diseases also show signs of depression and anxiety. Depression is described in several neurodegenerative diseases including Alzheimer's, Parkinson, and Huntington's disease (52). Depression in Huntington's disease was compared with depression in cerebellar degenerative diseases. Huntington's disease is mostly caused by basal ganglia degeneration whereas the cerebellum is relatively spared. Psychopathology in cerebellar degenerative disease is nearly as common as in Huntington's disease, although less severe and somewhat different in type (53).

To overcome the limitations of brain imaging techniques when studying the human brain mouse models can be used. Depressive and anxiety like behavior can be measured in mice. And several SCA mouse models are available. But it remains questionable whether the results from mouse studies can be directly translated into human patients. Although it has been proven the SCA1 mouse model with 154 CAG repeats in *Atxn1* shows SCA pathology, the model has more CAG repeats than humans with SCA1. When translating the age of onset in the mouse model to humans, it is most likely that the 154 CAG repeats cause an infantile onset of SCA1 in humans (48). Besides that, the two studies on depressive behavior in mice showed opposite results in the same mouse model. Therefore, no conclusion can be drawn from this data. In addition, the effect of the CAG repeat that is larger in mouse models than in humans must be investigated first. Besides mouse models, zebrafish can be used to study the neuropathology of SCA since the central nervous system of zebrafish is anatomically similar to humans (54). Also, the zebrafish gene has high homology with the human genome.

This review has a few limitations. First, there is more literature available than is described in this study. Because not all articles where accessible, only the ones with access were used. Second, it is not clear whether depression and anxiety can be seen separately of other psychiatric diseases and cognition. Therefore, it is recommended that in the future psychiatric conditions are investigated in its entirety.

Taken together, based on the current published studies it is not possible to determine what the nature of depression and anxiety in SCA is. It can be biological or emotionally reactive from origin, or maybe even both. It is possible that an out of cerebellar pathology of SCA may influence depression and anxiety, or that the cerebellum plays a role in depression and anxiety.

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