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Spinocerebellar Ataxia Type 2 and its Association with Amyotrophic Lateral Sclerosis

Abstract

All the neurodegenerative diseases seem to have a few common patterns. Recent studies have discovered similarities between Amyotrophic Lateral Sclerosis (ALS) and a sub-type of the Spinocerebellar Ataxia (SCA) diseases. SCA is characterised by different sub-types; the sub-type Spinocerebellar Ataxia Type 2 (SCA2) is particularly related to ALS. Similarities in both diseases with other types of neurodegenerative diseases make it difficult to diagnose at onset and hence symptomatic treatment, not cure, is usually started later on in the progression of the disease.

In this article, a brief description of both diseases and an overview of the genetics of the individual diseases are outlined. In particular, reference is made to studies which have shown that the pathological number of CAG trinucleotide repeat-expansions in the ATXN2 gene are causative of SCA2 or even ALS.

Amyotrophic Lateral Sclerosis

ALS involves progressive motor neuron loss in the spinal cord and in the brain, affecting both lower motor neurons (LMNs) and upper motor neurons (UMNs). It is a neurodegenerative syndrome and not a neuromuscular disease, sharing pathobiological characteristics with frontotemporal dementia (FTD) (Van Es et al., 2017). ALS is a fatal type of motor neuron disorder (Zarei et al., 2015). Symptoms usually emerge in patients aged between 50 and 65 (Logroscino et al., 2009), however, young-onset ALS has been diagnosed and observed clinically (Artemiadis et al., 2016).

ALS can be divided into two forms:

- Familial ALS (FALS);
- Sporadic ALS (SALS).

The sporadic form is the most common form. 90%-95% of all cases reported are of the sporadic type. The sporadic form has no evident genetically acquired component.

The other type, FALS, represents the rest of the 5%-10% of cases (Ticozzi et al., 2011). The latter have a genetically dominant inheritance factor with 30 or more affected genes (Renton et al., 2013).

To date no one has developed a cure for ALS. Patients suffering from ALS more often than not, complain of fatigue, which may eventually cause distress and impair quality of life (QoL) (Gibbons et al., 2018).

Slowing down disease progression is the current aim of clinical trials. This is done by testing those drugs that work on the processes that come about after the onset of the disease. Current novel therapies that are in trial include (Gordon, 2011):

- Vaccine therapies;
- Injections of stem cells;
- Neuroprotective agents with different acting mechanisms; and
- Diaphragmatic pacing.

ALS patients have an approximate life expectancy of 3 years following onset of symptoms. In approximately 5% of patients, however, there is a range of survival between a few months and ten years or longer (Gordon, 2011). At the last stages of life the only available comfort to patients is palliative care.

Spinocerebellar Ataxia

SCAs are a subgroup of a group of autosomal dominant cerebellar ataxias which are hereditary. Ataxias and SCAs share the same clinical features. Cerebellar ataxias are the progressive type of neurodegenerative diseases affecting primarily the cerebellum with progressive degeneration but also affecting other regions which are connected, including the brainstem.

CAG repeat expansions coding for polyglutamine are observed in many SCAs suggesting that the disease involves the polyglutamine protein (polyQ), which is the toxic type (Sullivan et al., 2018).

The disease is mostly adult onset (Klockgether et al., 2019). In particular, SCA type 2 is caused by CAG nucleotide repeat expansions in the gene ATXN2, which codes for the ataxin-2 protein. Patients with this disease present with slow saccades and progressive ataxia (Scoles & Pulst, 2018).

To date no treatment to stop or slow SCAs has been found, many of which terminate in premature death. Patients suffering from SCA receive clinical care which manages the disease's symptoms.

Genetics of ALS

In approximately 60% to 80% of FALS patients, mutations of genes of grand effect are identified, in particular, mutations in the below tabulated genes (Renton et al., 2013):

Genes:	Percentage of patients:
Chromosome 9 open reading frame 72 (C9orf72)	40%
Superoxide dismutase 1 (SOD1)	20%
Fused in Sarcoma (FUS)	1.5%
TARDBP-43 (Trans-active response DNA-binding protein 43 [TDP-43])	1.5%

Table 1: Patient Percentages of Gene Mutations in FALS. Most patients (40%) with FALS present with a gene mutation in C9orf72. Second most common mutation (20%) is in the SOD1 gene, followed by roughly equal lesser presentations (1.5%) of FUS and TDP-43 gene mutations.

The inheritance in FALS patients follows a Mendelian genetic pattern and is autosomal dominant (He et al., 2014). The C9orf72 gene mutation in FALS is referred to as a hexanucleotide repeat expansion (HRE). This mutation causes degeneration of neurons in 3 ways (Brown & Al-Chalabi, 2017; Balendra & Isaacs, 2018):

- Loss of function;
- Ribonucleic acid (RNA) toxicity - which leads to toxic gain of function; and
- Dipeptide repeat proteins (DRPs) – which also lead to toxic gain of function.

Mutations in the SOD1 gene cause cell cytotoxicity. It primarily affects RNA and deoxyribonucleic acid (DNA) metabolism.

Adenosine triphosphate (ATP) production and free calcium release in the mitochondria are also impacted. Astrocytes and microglia that are associated with motor neurons are also impaired and hence cause progression of the ALS disease. This disease progression is caused because of the astrocyte cells' reduced uptake of glutamate resulting in the accumulation of glutamate - which is toxic to the motor neurons (Pasinelli & Brown, 2006).

Both FUS and TDP-43 are genes which are responsible for gene regulation and gene expression. In particular, RNA splicing, transcription, translation, transport and the processing of regulatory RNA (Kiernan et al., 2011).

Genetics of SCA2

SCAs are genetically grouped according to repeat expansions. In most SCAs, damage is caused to the Purkinje neurons in the cerebellum which results in atrophy of the cerebellum. The damage is not only limited to the cerebellum, however, damage may also be caused to the brainstem pontine nuclei, basal ganglia and the spinal cord (Klockgether et al., 2019).

In particular, SCA2 disease is caused by a trinucleotide CAG expansion of 31 or more repeats in the gene that codes for the ataxin-2 protein, i.e. ATXN2. The trinucleotide repetitive sequence of (CAG)8(CAA)1(CAG)4(CAA)1(CAG)8 found in the amino-terminus of the gene codes for repetitive glutamine residues. CAA trinucleotides also code for glutamine, however, their presence in the repetitive sequence allows for stability of the expansion and has an effect on the secondary structure of RNA (Sobczak & Krzyzosiak, 2005). These observations are said to possibly contribute to the disease's phenotypic variability (Antenora et al., 2017).

Ataxin-2 in ALS and SCA

The ataxin-2 protein is expressed in normal human brain, in particular, in the midbrain, trochlear neurons, Purkinje neurons and large neurons found in the substantia nigra. Wild-type protein ataxin-2 is limited to the cytoplasm, but it can also be found in the endoplasmic reticulum and Golgi apparatus (van de Loo et al., 2009). The pattern of ataxin-2 expression was the same both in the brains of SCA2 patients and in unaffected individuals (Antenora et al., 2017).

The exact function of ataxin-2 is still not known. A study conducted on mice deficient of ataxin-2 showed that they remained viable and only gained weight when fed on a fat-enhanced diet, indicating that its function in development is not essential (Kiehl et al., 2006). Other studies showed evidence that it is involved in the regulation of the amount of calcium released from endoplasmic reticula, involved in RNA processing and also in stress granules assembly as well as epidermal growth factor receptor (EGFR) endocytic trafficking (Antenora et al., 2017).

Alleles are said to be 'normal' if they have CAG repeats in the ATXN2 gene which amount to 31 or even lower. SCA2 is seen in patients with an expansion of CAG repeats in the ataxin-2 gene. A CAG repeat expansion in the ATXN2 gene greater than or equal to 34 is causative of SCA2 (Pulst et al., 1996).

Elden et al., (2010) suggested that 29 to 34 repeat expansions of the trinucleotide CAG repeats at the ATXN2 polyQ locus present a risk factor for ALS. This type of ATXN2-associated ALS is referred to as classic ALS because it presents with a number of UMN and

LMN signs. In this particular type of ALS it is reported that in the cerebellar vermis there is remarked loss of Purkinje cerebellar cells which is not present in other forms of ALS (Tan et al., 2016).

This link is in line with the study that many risk genes in ALS, in particular TDP-43 are involved in RNA metabolism hence further enhancing the observed link between the proteins ataxin-2 and TDP-43. TDP-43, like ataxin-2, is involved in certain RNA processes especially in RNA stability, alternative splicing and transcription all of which are associated with RNA metabolism (Paulson et al., 2017).

In a study using a yeast screen, the Pab1p-binding protein (PBP1), which is a yeast homologue of ataxin-2, is shown to increase toxicity which is TDP-43 mediated. This increase in TDP-43 toxicity was also related to the ATX-2 Drosophila homolog of ataxin-2. This concludes that the association between ataxin-2 and TDP-43 is RNA-dependent in both mammalian and yeast cells (Elden et al., 2010). It was also observed that ataxin-2, like TDP-43 is mis-localised to the cytoplasm in motor neurons of ALS patients giving it a toxic gain-of-function. The trinucleotide CAG intermediate-length repeat expansions were observed to be less frequent in normal individuals as opposed to ALS patients (Van Damme et al., 2011). This concludes that the polyQ length in the ATXN2 gene (wild-type as well) affects the function in RNA metabolism, involving both ataxin-2 and TDP-43 (Paulson et al., 2017).

Community Care and Patient Well Being

In Malta, 'Dar Bjorn' is a nursing home for patients suffering from ALS and other neurological conditions. Ever since its setting up in November 2017, it has provided continuous aid and care for the residents of the nursing home.

It has helped in improving the QoL of patients suffering from neurological conditions, many of whom would not have had the same level of comfort from home.

Conclusion

Studies are being done on families to see if there are any families with coexisting ALS and SCA2. A study done by Tazen et al., (2013) showed how two members of the same family, a paternal uncle and his niece, were diagnosed with ALS and SCA2 respectively, both having the full CAG trinucleotide repeat expansion. Their family pedigree is shown in Figure 1. This study showed that the mutation in the ATXN2 gene can present with different phenotypes in the same family, hence strongly suggesting that genetic tests to check for polyQ repeat expansions in the ATXN2 gene should be done in patients suffering from ataxia and coming from an ALS family history.

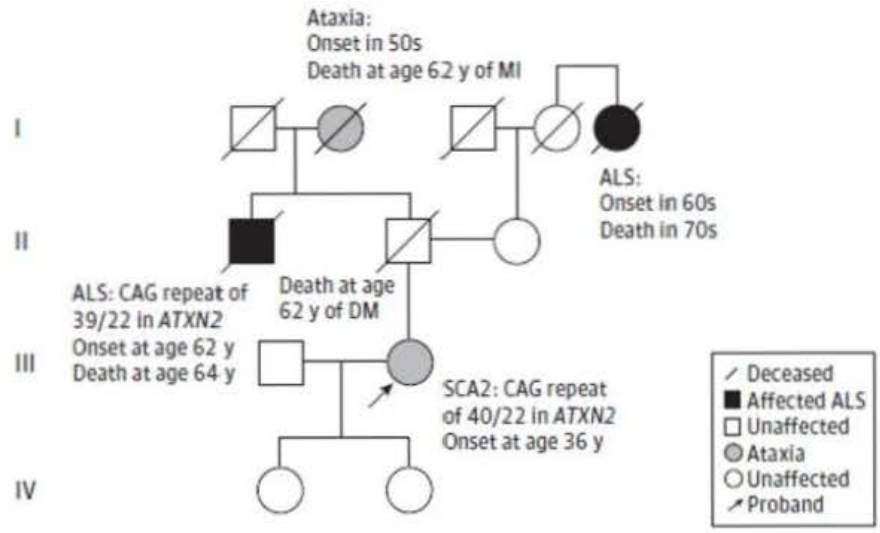

Figure 1:
Family Pedigree (Tazen et al., 2013). The proband – female with SCA2 with an unaffected mother and a deceased unaffected father, having CAG repeat expansions in ATXN2 . The paternal deceased uncle had ALS with the same trinucleotide repeat expansion as the proband but with different lengths.

References

1. Antenora A, Rinaldi C, Roca A, Pane C, Lieto M, Saccà F, Peluso S, De Michele G & Filla A (2017). The Multiple Faces of Spinocerebellar Ataxia type 2. Annals of Clinical and Translational Neurology 4, 687-695.

2. Artemiadis A, Peppas C, Giannopoulos S, Zouvelou V & Triantafyllou N (2016). Case of Young-Onset Sporadic Amyotrophic Lateral Sclerosis. Journal of Clinical Neuromuscular Disease 17, 220-222.

3. Balendra R & Isaacs A (2018). C9orf72-mediated ALS and FTD: multiple pathways to disease. Nature Reviews Neurology 14, 544-558.

4. Brown R & Al-Chalabi A (2017). Amyotrophic Lateral Sclerosis. New England Journal of Medicine 377, 162-172.

5. Elden A et al. (2010). Ataxin-2 intermediate-length polyglutamine expansions are associated with increased risk for ALS. Nature 466, 1069-1075.

6. Gibbons C, Pagnini F, Friede T & Young C (2018). Treatment of fatigue in amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database of Systematic Reviews; DOI: 10.1002/14651858.cd011005.pub2.

7. Gordon P (2011). Amyotrophic Lateral Sclerosis. CNS Drugs 25, 1-15.

8. He J, Mangelsdorf M, Fan D, Bartlett P & Brown M (2014). Amyotrophic Lateral Sclerosis Genetic Studies. The Neuroscientist 21, 599-615.

9. Kiehl T, Nechiporuk A, Figueroa K, Keating M, Huynh D & Pulst S (2006). Generation and characterization of Sca2 (ataxin-2) knockout mice. Biochemical and Biophysical Research Communications 339, 17-24.

10. Kiernan M, Vucic S, Cheah B, Turner M, Eisen A, Hardiman O, Burrell J & Zoing M (2011). Amyotrophic lateral sclerosis. The Lancet 377, 942-955.

11. Klockgether T, Mariotti C & Paulson H (2019). Spinocerebellar ataxia. Nature Reviews Disease Primers; DOI: 10.1038/s41572-019-0074-3.

12. Logroscino G, Traynor B, Hardiman O, Chio A, Mitchell D, Swingler R, Millul A, Benn E & Beghi E (2009). Incidence of amyotrophic lateral sclerosis in Europe. Journal of Neurology, Neurosurgery & Psychiatry 81, 385-390.

13. Pasinelli P & Brown R (2006). Molecular biology of amyotrophic lateral sclerosis: insights from genetics. Nature Reviews Neuroscience 7, 710-723.

14. Paulson H, Shakkottai V, Clark H & Orr H (2017). Polyglutamine spinocerebellar ataxias — from genes to potential treatments. Nature Reviews Neuroscience 18, 613-626.

15. Pulst S, Nechiporuk A, Nechiporuk T, Gispert S, Chen X, Lopes-Cendes I, Pearlman S, Starkman S, Orozco-Diaz G, Lunkes A, DeJong P, Rouleau G, Auburger G, Korenberg J, Figueroa C & Sahba S (1996). Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2. Nature Genetics 14, 269-276.

16. Renton A, Chiò A & Traynor B (2013). State of play in amyotrophic lateral sclerosis genetics. Nature Neuroscience 17, 17-23.

17. Scoles D & Pulst S (2018). Spinocerebellar Ataxia Type 2. Polyglutamine Disorders 175-195.

18. Sobczak K & Krzyzosiak W (2005). CAG Repeats Containing CAA Interruptions Form Branched Hairpin Structures in Spinocerebellar Ataxia Type 2 Transcripts. Journal of Biological Chemistry 280, 3898-3910.

19. Sullivan R, Yau W, O'Connor E & Houlden H (2018). Spinocerebellar ataxia: an update. Journal of Neurology 266, 533-544.

20. Tan R, Kril J, McGinley C, Hassani M, Masuda-Suzukake M, Hasegawa M, Mito R, Kiernan M & Halliday G (2016). Cerebellar neuronal loss in amyotrophic lateral sclerosis cases with ATXN2 intermediate repeat expansions. Annals of Neurology 79, 295-305.

21. Tazen S, Figueroa K, Kwan J, Goldman J, Hunt A, Sampson J, Gutmann L, Pulst S, Mitsumoto H & Kuo S (2013). Amyotrophic Lateral Sclerosis and Spinocerebellar Ataxia Type 2 in a Family With Full CAG Repeat Expansions ofATXN2. JAMA Neurology; DOI: 10.1001/jamaneurol.2013.443.

22. Ticozzi N, Vance C, LeClerc A, Keagle P, Glass J, McKenna-Yasek D, Sapp P, Silani V, Bosco D, Shaw C, Brown R & Landers J (2011). Mutational analysis reveals the FUS homolog TAF15 as a candidate gene for familial amyotrophic lateral sclerosis. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 156, 285-290.

23. Van Damme P, Veldink J, van Blitterswijk M, Corveleyn A, van Vught P, Thijs V, Dubois B, Matthijs G, van den Berg L & Robberecht W (2011). Expanded ATXN2 CAG repeat size in ALS identifies genetic overlap between ALS and SCA2. Neurology 76, 2066-2072.

24. Van de Loo S, Eich F, Nonis D, Auburger G & Nowock J (2009). Ataxin-2 associates with rough endoplasmic reticulum. Experimental Neurology 215, 110-118.

25. Van Es M, Hardiman O, Chio A, Al-Chalabi A, Pasterkamp R, Veldink J & van den Berg L (2017). Amyotrophic lateral sclerosis. The Lancet 390, 2084-2098

.

26. Zarei S, Carr K, Reiley L, Diaz K, Guerra O, Altamirano P, Pagani W, Lodin D, Orozco G & Chinea A (2015). A comprehensive review of amyotrophic lateral sclerosis. Surgical Neurology International 6, 171.