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Genetic Mutations and Treatment of Spinocerebellar Ataxias

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Abstract

Cerebellar diseases and disturbs cause speed, amplitude and strength deficiency. Among cerebellar dysfunctions, the spinocerebellar ataxia is a pathology characterized by the presence of progressive cerebellar ataxia. Spinocerebellar ataxia has as its initial clinic manifestations the deterioration of equilibrium and coordination, beyond eye disturbances, progressive postural oscillation associated with dysarthria, dysphagia and pyramidal and extrapyramidal signs. Cerebellar ataxias are caused by a cerebellum disorder and its connections, which may be attributed by root causes in the cases of congenital and hereditary ataxias. This review brings a brief historical perspective about cerebellar functions and in addition, a discussion about a specific cerebellar dysfunction, spinocerebellar ataxia, emphasizing its physiology to a better comprehension of the disease, its clinic and the several types of this pathology.

Keywords: Ataxia; Cerebellum; Muscle Atrophy

Introduction

Ataxia in the terminology of Greek origin means "out of control". In medical terms "ataxia" refers to a disorder in the control of body posture, motor coordination, speech and eye movements. The term locomotor ataxia is being employed since the XIX century, often meaning "lack of motor coordination" [1]. Cerebellar ataxias are caused by a cerebellum disorder and its connections, which may be attributed by root causes in the cases of congenital and hereditary ataxias [1].

This review brings a brief historical perspective about cerebellar functions and in addition, a discussion about a specific cerebellar dysfunction, spinocerebellar ataxia, emphasizing its physiology to a better comprehension of the disease, its clinic and the several types of this pathology.

Cerebellar Dysfunction

Studies of patients with cranial trauma since the First World War leaded to an initial understanding of cerebellum functionality. Holmes in 1917 performed detailed descriptions about cerebellar injuries, in which he attested that after the injury there were alterations in the patients' ability of performing sequential complex and gentle movements [2].

Cerebellum presents great importance to Central Nervous System (CNS), since it performs interrelations and essential functions. The main functions of cerebellum involve the coordination of motor activity, equilibrium and muscular tonus [3,4]. In addition, cerebellum is a great integrator of information, as it receives upgrades all the time referring to spinal medulla activity and the ongoing movements. Cerebellum also coordinates a great number of afferent signs and alerts the appropriate motor centers to perform the necessary correlations in order to obtain a coordinated movement [5].

Cerebellar diseases and disturbs cause speed, amplitude and strength deficiency. Among cerebellar dysfunctions, the spinocerebellar ataxia is a pathology characterized by the presence of progressive cerebellar ataxia. Spinocerebellar ataxia has as its initial clinic manifestations the deterioration of equilibrium and coordination, beyond eye disturbances, progressive postural oscillation associated with dysarthria, dysphagia and pyramidal and extrapyramidal signs [6].

Progressive disturbs are characterized by the degenerations of spinocerebellar tracts. Among the neurological manifestations present, the visual loss and nystagmus are the most frequent characteristics of these diseases [7] Hereditary cerebellar ataxias may be classified based on the pattern of inheritance (autosomal recessive, autosomal dominant, x-linked and mitochondrial).

Autosomal Dominant Cerebellar Ataxias (ADCA)

The ADCA are known as hereditary spinocerebellar ataxias, which have a vast classification of neurodegenerative disorders,

but all have in common the ataxia. The etiology, in most of the cases, is explained by the mutations that occur in the evaluated gene, characterized by the presence of a repeat, expansive and unstable CAG trinucleotide [7].

After the description of the first defective gene caused by ADCA, each new defective gene discovered received a numeration and ADCA started to be called spinocerebellar ataxia.

The clinical signs presented by the patients with this disease are, march progressive ataxia, members' progressive ataxia, eye movements abnormalities, dysarthria, dysphagia, facial atrophy, tongue fasciculation, pyramidal and extrapyramidal signs, peripheric neuropathies, deafness and visual loss. The patient's clinic depends on what type of ADCA he has and which modified gene is involved. The clinical characteristics are better stablished to ADCA in which a specific genetic defect is identified.

Spinocerebellar Ataxia (SCA) Types

The most common spinocerebellar ataxias are characterized by an increased number of repetitions of a certain nucleotide sequence, above the number normally found in people without disease background. The enhancement of CAG trinucleotide repetitions is the most frequent cause of SCAs. These mutations are called dynamic expansions and arise from the instability of repeated DNA in the same locus. This fact causes a greater propensity to alterations in polymerase DNA enzyme, triggering an insertion of more nucleotides in this segment, favoring an expansion.

In his study, Takiyama [8] reported that the biological basis of repetitions in expansion disorders is the instability of these repetitions during cell division, in meiosis as well as in mitosis, and that this instability causes, by the process of contraction and genic conversion, different cellular populations with different numbers of repetitions, forming a mosaic of cells. The instability in meiosis causes gonadal mosaicism, observed in patients' sperm. During transmission, these patients tend to present greater expansion dimension through generations. When this mosaicism occurs during mitosis, it is detected in somatic cells (somatic mosaicism), including lymphocytes, muscular cells and central nervous system, however, it is less significant than the gonadal mosaicism.

In scientific literature, authors affirm that for most part of expansion disorders, there are differences related to clinical manifestation severity and age of symptoms' appearance. These differences depend from whom the expanded allele was inherited.

Among SCAs, when the transmission is paternal, an increased number of repetitions in children is verified, unlike when the expanded allele is maternal, in which this tendency is not observed. Therefore, paternal transmission involves worse clinical manifestations. In these cases, patients usually present the symptoms earlier than their father did. Normally, the more serious are the symptoms and the earlier they appear, the greater is the number of repetitions. This observation is known as symptoms anticipation and it is common in expansion disorders [9].

Genetic Mutations and Treatment

Among all spinocerebellar ataxias, the most common characteristic is cerebellum neurodegeneration. SCAs are differentiated by the involvement of extra cerebellar regions and genetic mutations during disease progression. This genetic involvement is what makes the disease propagate through generations, due to phenotype gap and the heterogynid that arises from expansions of DNA repetition.

Until the last decade there was a great difficulty in identifying the type of genetic mutation when symptoms appeared, therefore the difficulty of specifying the course of the disease was also a difficult task. In dominant disease, the clinical observation of younger ages at onset and increasing severity in successive generations is referred to as genetic anticipation. Variability in age at onset, especially the anticipatory decrease in age at onset in successive generations, is regarded as a hallmark of polyglutamine expansion SCAs. The discovery that the CAG repeat length changes in size during transmission, germline mosaicism, is the molecular explanation for this finding. Whereas normal alleles are transmitted to off spring without modification, pure expanded alleles are unstable and the number of CAG repeats tends to increase during transmission. Paternal expansions are more likely to be unstable during transmission. This paternal bias is often attributed to the increased number of mitotic divisions preceding male gametogenesis, but could also be attributable to alterations in the activity and concentration of DNA repair proteins. another genetic characteristic is the so called polyglutamine expansion SCAs. The polyglutamine expansion SCAs share a mutational mechanism with other polyglutamine expansion diseases, such as Huntington disease and spinal bulbar muscular atropy, and perhaps a pathogenic process, even though most of the proteins involved in polyglutamine expansion diseases have unknown or unrelated functions [10].

The polyglutamine expansion SCAs caused by translated CAG repeat expansions are the most well studied group of ADCAs. They share the same mutation, a CAG repeat, which manifests above a threshold of CAG repeats that varies according to the gene-usually above 37-40 repeats, but repeats are much smaller in the gene for SCA6 (>19)28 and much larger for SCA3 (>51) [10].

After the description of the first defective ACAD-causing gene, each newly discovered defective gene was numbered and ACAD was renamed Spinocerebellar Ataxia (SCA). The current classification based on genetic alterations comprises 31 types of SCA4. Its prevalence ranges from 0.9 to 3: 100,000, varying by type and continent. SCA1, 3 and 6 are the most frequent in the world. In Brazil, SCA3, also called Machado-Joseph Disease, is the most prevalent type [11].

Nowadays, genetic tests can be performed in commercial laboratories in order to obtain more accurate diagnostics, thereby, it is also possible to find available treatments and present a prognostic to each type of ataxia. With all this information, patients and their families may receive a better and more complete counseling. Magnetic resonance is an efficient exam to identify cerebellar regions involved in the disorders.

Spinocerebellar ataxias are treated with therapies that aim to alleviate symptoms. These therapeutic techniques utilize the principles of motor learning, with the objective of improving the movement's coordination with the repetition of a functional movement that is specific to a certain task. Thus, the treatment consists in: gaining muscular strength, modulating tonus; improving trunk's stability through exercises; training transferences (from lying to seat, from seated to standing); normalizing the speed of the movements; training the march (utilizing regular and irregular surfaces, ramps, stairs); in a nutshell, it consists in providing the patients the greatest independence possible [12].

Therefore, functional training, also known as motor control exercises, may benefit patients with spinocerebellar dysfunction.

To the present moment, there is no pharmacological treatment to SCAs, however, cholinergic, serotoninergic, gabaminergic and also dopaminergic drugs are being tested for this purpose. Researchers reported that rare cases of episodic SCAs may respond to acetazolamide treatment [13].

As highlighted in recent systematic reviews of randomized controlled trials there is currently a lack of high-quality research studies into the rehabilitation of cerebellar ataxia. Despite this, the literature on the treatment of cerebellar ataxia describes some approaches that warrant further investigation. Approaches may be broadly divided into those that aim to improve functional ability by compensating for the underlying deficit and those that aim to improve function through restorative techniques that involve adaptation and recovery within the neuromusculoskeletal system.

Compensatory approaches include the use of strategies to encourage decomposition of movement into simpler single joint movements; visual and verbal cues to aid walking speed and stride length; the use of assistive technology to aid computer use; and aids such as customized seating and frames to help posture, balance and mobility [14].

Future Research

Few scientific articles focus on therapeutic interventions, or aim to find new methods of treatment to this neurodegenerative disease. Therefore, new researches are necessary to evidence the importance of neurofunctional interventions in the treatment of SCA, as well as to search for new ways to treat this disease.

Conclusion

Autosomal dominant hereditary ataxias, currently called Spinocerebellar Ataxias (SCAs), are progressive neurogenerative diseases that trigger slow degeneration of cerebellum and its connections.

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