IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

ATAXIA-A RARE GENETIC DISORDER

NIKHIL.N.NAVINDGIKAR[1], RIYA HAKE[2] , SHASHANK LIGADE[3]

Author[Assistant Professor][1],Co-author[2],Co-author[3]
Department of Pharmaceutics[1],

Amepurva Forum Nirant Institute collage of pharmacy, Boramani, solapur-413002, Maharashtra, India[1,2,3].

Abstract: One type of outward sign that the human body experience balance issues and poor coordination is ataxia. It indicates often disease in certain part of the body many internal factors may causing Ataxia. Ataxic symptoms are caused by a variety of illness affecting cerebellar function known as cerebellar Ataxias . Cerebellar ataxia has a heterogeneous etiology that encompasses both an incurable condition and a readily recognized, frequently reversible cause (drug poisoning). Review article discuss the causes, symptoms, types, & treatment of cerebellar ataxia. The main purpose of this update review the causes & possible mechanism of action of ataxia & lead to improved treatment strategies for this challenging group of patients.

***Key word*:** Cerebellar Ataxia, Spino cerebellar Ataxia, Dysfunction

INTRODUCTION

The Greek roots of the word ataxia, which means “without order,”are “a-,’’ which is a negative prefix, in a medical sense. This is a non-specific clinical symptoms that suggest a malfunction of the cerebellum and\or its associated systems,including the visual, vestibular, proprioceptive, and there linkages. This patterns of neurological dysfunction have multiple potential explanation .In light of the research , this review and “taxia ,” which means to place in order. It describes inadequate postural and a lack of coordination discusses the neuro anatomic basis, kinds, causes, and treatment of ataxia.[1]

In addition to its primary symptoms of impaired speech, balance, and coordination, ataxias can also occasionally present with extrapyramidal movement abnormalities, pyramid indications, seizures, cognitive affective symptoms, and peripheral neuropathy .Because both non genetic and genetic reasons must be taken into account, sporadic adult-onset ataxias present unique challenge .A significant GALT deficit is the cause of classic Galactosemia, an un common autosomal recessive hereditary conditions of galactose metabolism.[2]

The purpose of this study was to look into how self reported depressions, anxiety, exhaustion, cognitive deficits, and the severity of symptoms were affected by the kinds of ataxia(hereditary, acquired, or idiopathic). To facilitate comparisons, a healthy control group devoid of ataxia was also added. The purpose of the supplemental analysis was to investigate associations between the length, non motor symptoms, and self-reported severity of ataxia symptoms.[3]

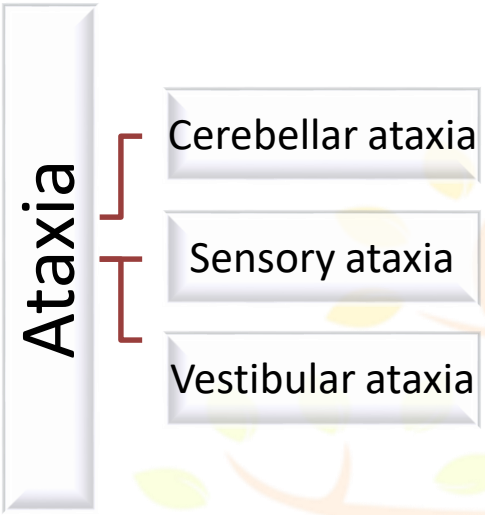
Over the hundred genetic causes have been found for the ataxias, a complicated group of uncommon neurological disorders. A patient’s cerebellum or its connections might be damaged, leadings toa variety of symptoms in ataxia patients. Characteristics of gaits instability, peripheral neuropathy, double vision, tremor, pyramidal and extra pyramidal symptoms, and cognitive impairment are among the symptoms of ataxia that might vary in associations. According to global epidemiological research, the incidence of ataxia in children is estimated to be 26 instance per 100000 while the prevalence of hereditary cerebellar ataxia is predicted of hereditary cerebellar ataxia is predicted to be 2.7-3.3 cases per 100000. The most prevalent inherited ataxia is Friedreich’s ataxia, which is estimated to affects 3.4 out of every 100000 people.[4]

ATAXIA

Mechanism of Ataxia

Disruption of proprioceptive input from the periphery can also lead to ataxia. Consequently injury to the afferent segments of peripheral nerves(such as large-fiber neuropathies) can cause "sensory ataxia", the dorsal column of the spinal cord, the medial lemniscus of the brain stem, the sensory-receiving areas of the thalamus, and occasionally the parietal cortex are among the dorsal nerves roots that enter the spinal cord(e.g.,tabes dorsalis).[5]

TYPES OF ATAXIA.[6]



CEREBELLAR ATAXIA

Speech, swallowing, balance, gait, and eye movement can all be affected by ataxia, which is defined as then ability to control voluntary muscle movements. That indicates the existence of a problem. The brain region known as the cerebellum, which controls voluntary movements, is typically damaged or diseased when persistent ataxia occurs. moreover, disorders affecting the peripheral nerves and spinal cord might result in ataxia. It encompass conditions like multiple system atrophy and spinocerebellar degeneration.[7]

.list a few ataxia causes that mostly impact the cerebellum.

-Drunkenness from drug, alcohol, or other substance

-long-term alcohol consumption when not drunk

-ischemic stroke, hemorrhagic stroke, or cerebellar stroke

-The neurosyphilis

-A lack of vitamin B_{12}

-Myelopathy linked to the human immunodeficiency virus (HIV)

-Neoplastic disorders

-Atrophy of several system

-Postinfectious cerebellitis, which typically in affects kids

-There are many genetic symptoms.[8]

Classification of cerebellar Ataxia[9] :-

There are mainly two types of cerebellar ataxia and they are classified as following table.

Primary/Hereditary cerebellar Ataxia	secondary/sporadic cerebellar ataxia
a.The Dominant Autosomal cerebellar ataxia - ataxia Episodic (type 1-6) - Subtype of spinocerebellar ataxia (SCA): 1-28 - palidoluysian dentatorubal atrophy	**a. cerebellar ataxia present with symptoms** 1. structural defect and lesions 2. Toxic :- -alcohol - Alcoholic beverage a. Anti-Epileptic Drug b. Benzodiazepines c. Lithium d. Anti-neoplastic e. Others - others a. heavy metals arsenic,Bismuth b. chemicals-solvents,pesticide -
b. Cerebellar ataxias in Autosomal Recessive Families **Families** - detected gene defect -detected gene-locus - as a component of prolonged illness, metabolic disorders - Additional metabolic and degenerative disease that may - Being in childhood or during birth	
c. Cerebellar ataxia associated with genes . -Adrenoleukodysatrophy -Ataxia syndrome with - Ataxia along with hereditary side roblastic, anemia - Additional-X linked congenital and paediatric ataxias	3. endocrine - Hypothyroidism 4.malabsorption -celiac disease (gluten ataxia) - deficiency of vitamins 5. Miscellaneous - paraneoplastic syndrome - demyelinating disorders 6. inflammatory - whipple disease - postviral /immune mediated ataxia
.	
d. Mitochondrial cerebellar ataxia .	**b. Idiopathic** -multiple system atrophy - idiopathic late-ons

STATISTICAL ANALYSIS

The average prevalence of SCA was found to be 2/7 per 1000000 people worldwide, according to a comprehensive review, albeit it was not on the foundation of all-inclusive screening techniques.2 SCA6/CACNA1A(MIM 183086), SCA7/ATXN7 (MIM164500), SCA17/TBP (MIM 607136), DRPLA/ATN1 (Dentatorubral - pallidoluysian atrophy; MIM 125370), AND SCA1/ATXN1 9MIM 164400) are the most prevalent SCA subtype. SCA3 is the most common subtype globally, with founder expression reported in German, Japanese, and Portuguese-Azorean families.3- for SCA2, the most common subtype, founder effect have been documented in the province of Holguin of the French west indies, India, and Cuba. As the third most frequent subtype, SCA6 is particularly widespread in the USA, Germany, Taiwan, Australia, japan, and the UK. South Africa , Russia, and Poland have the highest prevalence rates of 3 SCA1. South Africa, Mexico, and Scandinavian nations have all reported founder effect for SCA7. Even though DRPLA makes up a sizeable portion of the SCA cases in Portuguese, Spanish, and Japanese families, DRPLA and SCA17 are extremely uncommon. Less than 6% of SCAs are caused by point mutations, rearrangements, or non-coding repeat expansions. The frequency of the most recently discovered non-coding repeat expansions, in SCA27B/FGF14, is unknown, hence this proportion may be underestimated. Certain non-coding repeat SCA subtype are common in some areas than others. These includes SCA10 in Mexico and central and south America, SCA12 in India, and SCA31 and SCA36 in Japan.[10]

NEUROPATHY

Ataxia neuropathy spectrum belongs to set of illness known as POLG-related disorders.[11] The core idea of ataxia, which is frequently summed up as incoordination, is the focus of the clinical manifestations of cerebellar dysfunction .The cerebellums extensive significance has led to a growing awareness of the variety of clinical manifestations of cerebellar illness, which may affects a varying numbers of domains including, but not limited to, oculo motor speech, appendicular, gait, and cognition and effect.[12]The queen square group, who identified " cerebellar degeneration" in 7 out of 53 patients with bilateral vestibular failure, probably likely made the initial description by the bilateral vestibular insufficiency condition associated with cerebellar ataxias.[13] A rare hereditary condition that has just been recently described is cerebellar ataxia with sensory neuropathy and vestibular Areflexia syndrome. Due to the impairment of three of the four key props our body uses for balance, it induces gait imbalance.[14]

Motor Function Of Cerebellar Ataxia

The structure that propelled science into the era of the hypothesis-driven experiment is credited to the historian max (1868-1955). The cerebellum, according to Thomas willis (1621-1675),is the centre of vegetative functions and essential for survival.[15] To life cerebellar dysfunction has been linked to the number of ocular motor disorders (cogan. 1995;Daroff and Hoyt, 1971), however it is still unknown how precisely the cerebellum controls eye movements in humans.[16] Since the integration of information from the ocular, proprioceptive , and vestibular system is necessary for skilled motor actions, illness affecting any one of those systems or the cerebellum is a system that combines their data and controls movements(Bastin And Thach, 1955). The primary characteristics of somatosensory ataxia is a noticeable impairment that occurs exclusively while the eyes are closed, as vision is unable to make up for the compromised kinaesthesia perception.[17] 4-Aminopyridine, Ten patient with familial episodic ataxia type 2 (EA2) were administered 4-aminopyridine 15 mg/d in a class I randomized, double blind, placebo-controlled, crossover study. After 3 month of treatment, the in comparisons to median monthly median frequency of 1.65(interquartile range 1.00-4.78)attack frequency of 6.50(interquartile 2.33-13.75) with placebo(p=0.03).[18]

DISCUSION

Sequence of movements that are often invisible to the unaided eye can be understood through movements analysis . After movement analysis has discovered the unique critical components of abberent movements, thid information can be applied to enhance diagnostic abilities in the course of routine clinical practice. Cerebellar ataxia is described by holmes as a concomitant dysmetria, dyssynergia, dysdiadochokinesia, dysrhythmia, and intention tremor.[19]The Training programs was tailored to each participants to maximize difficulty and guarantee security. The programs included sitting balancing exercise since the support surface should could br changed to adjust the degree of challenge. Standing exercise were frequently restricted to trunk and arm movement that were dynamics and executed from a secure starting position. The majority of the participants found that is was too difficult to perform balancing activities safely when walking alone.[20] It seems that participating exercise consistently is necessary to sustain the progress brought about by interventions. Following evaluations, patients of lig et al and miyai , provided there was long term retention, which occurred in every case.[21]For those why mobility impairment, a strategy for physical activity that emphasis increasing light intensity exercise and decreasing sedentary time has been promoted as a potentially effective way to improve metabolic health. The current study participant believe that physiotherapies were primarily concerned with prescribing at home exercise for impairment that would be in line with this significant health promotion paradigm. However participant appreciations for taking on alternative types.[22]

TREATMENT

Using exercise to address ataxia physical therapy or exercise has be essential in supporting individuals with cerebellar ataxia. Research on intense rehabilitation has demonstrated that physical therapy has enduring benefits. In one study, individuals with degenerative ataxia were divided into two groups and given two different treatment regimens: a 4-week two intense rehabilitation program or a postponed start of the same program. Four weeks after therapy, the immediate rehabilitations groups SARA rating improved more than those of the delayed start group. Given the gradual deterioration of symptoms in degenerative ataxia, it is noteworthy that a large percentage of patient still showed improvement relative to baseline, even though the improvement was diminished at 12 and 24 weeks post-rehabilitation.[23]

CONCLUSION

An approach to Ataxia is predicated on an understanding of its signs and cause. It is necessary to identify. Cerebellar dysfunction patients may be experience slower reaction times, decreased attention modulation, depression and other psychological problems, reduced cognitive ability and flexibility, and decreased automatic "multitasking" skills. These significant facets of higher order behavior affect relationships with others, quality of life, and work and should be acknowledged by the medical community in addition to patients and their families.

ABBREVATIONS

AE- anti-Epileptic,AT Autosomal recessive , BD- Benzodiazepines, AN-Anti-Neoplastic, AS- Arsenic, BI- Bismuth, CD- Celiac Disease, CA- Cerebellar Ataxia,, DD- Demyelinating Disorder, DRPLA- Dentatorudral- pallidoluysian-Atrophy, DACA-Dominant Autosomal Cerebellar Ataxia, HT- Hypothyroidism, IMA-Immune Mediated Ataxia ,MSA- Multiple System Atrophy ,MFCA- Motor function Of Cerebellar Ataxia ,PNS- Paraneoplastic syndrome ,SCA- Spinal Cerebellar Ataxi, ST- statistical Analysis, USA- United State Of America.

ACKNOWLEDGEMENT

A special thanks to Mr.Nikhil.N.Navindgikar sir's excellent experience and endless support and guidance provided during the completion of the review article paper

REFERENCES

1.Anil Tanburoglu ,Mehmet Karatas; Ataxias: pathogenesis, types, causes and treatment ;Medical journal of Mugla sitki kocman university tip Dergisi. Year 2017, Volume: 4 Issue: 2, 32 - 39, 01.08.2017

2.Karafyllis l, ETAL ;Untreated classic Galactosemia- a rare cause of adult-onset progressive cerebellar ataxia: A case report; Available from- https://www.karger.com/CRN

3.Emma Jenkins, Warren Dunger; Impact Of Ataxia Type On Self-Reported Mental Health, Fatigue, Cognition, And Ataxia Symptoms Severity;2023 Oct 27.Research Square.

4.Stephen Morris, Julie Vallortigara, Julie Greenfield, Barry Hunt, Deborah Hoffman , Carola Reinhard et al; Impact Of specialist ataxia centre on health service resource utilization and costs across Europe: Cross- sectional survey ; Orphan journal Of Rare Disease(2023)18:382.

5.[Internet].[Physical Therapy & Rehabilitation Journal]:[Amy J Bastian];Mechanism Of Ataxia;[01 June 1997]. Available form : https://doi.org/10.1093/ptj/77.6.672

6.[Internet].[Medical News Today]:[Heidi Moawad , M.d].- By Yvette Brazier: What is ataxia and what causes it;[9 June 2023]. Available From: https://www.medicalnewstoday.com/articles/162368

7.[Internet].[Barrow Neurological Today]:[Holly Shill, MD,FAAN-By medically reviewed: Cerebellar ataxia;[31 March 2021]. Available From: https://www.barrowneruo.org/conditions/cerebellar-ataxia

8.Giulia coarelli, Marie coutelier, Alexender Durr ;Autosomal dominant cerebellar ataxias:new genes and progress towards treatments; August 2023;The Lancet Neurology 2023;22:735-49 Available Form .https://www.barrowneruo.org/conditions/cerebellar-ataxia/

9.Esther brusse, geboren te Aalten ; Adult-Onset Cerebellar ataxia, a clinical and genetic survey; 4 februari 2011,page no 16.

10.Giulia Coarelli, Marie Coutrlier, Alexandra Durr; Autosomal dominant cerebellar ataxias; new genes and progress towards treatments; Lancet Neurol. 2023 Aug;22(8):735-749.
doi: 10.1016/S1474-4422(23)00068-6.

11.Ataxia Neuropathy Spectrum. Available From- https://medlineplus.gov/genetics/copndition//ataxia-neuropathy-spectrum/

12.Leslie J. Robert et al; Overview of the Clinical Approach to Individuals With Cerebellar Ataxia and Neuropathy; October 2022, Neurology: Genetics, Volume 8, Number5.

13.D.J.Szmulewicz,MBBS (Hons), et al; Sensory neuropathy as part of the cerebellar ataxia neuropathy vestibular arflexia syndrome; may 31, 2011, Neurology 76, 1903-1910.

14. Maria Fernandez-Rueda, Alfredo Garcia-Fernandez, Joaquin Jesus De Vergas-Gutierrez; Variability in the Result of Vestibular Assessment in Patient with Genetically Confirmed Cerebellar Ataxia, Neuropathy, and Vestibular Areflexia Syndrome; September 29, 2023, journal of international advanced Otology 2023; 19 (5): 383-387.

15. Jeremy D. Schmahmann , MD ;Disorders of the cerebellum;Ataxia, Dysmetria of thought, and the cerebellar cognitive Affective Syndrome; Summer 2004; jounal of Neuropsychiatric and clinical Neuroscience 2004;16 :367-378.

16.David S. Zee, Robert d. Yee, David G. Cogan, David A. Robinson and W. King Engel; Ocular Motor Abnormalities in Hereditary Cerebellar Ataxia; Brain, Volume 99, issue 2, June 1976,pages 207-234. Available From-https://doi.org/10.1093/brain/99.2.207

17. M. FerrianM. Gironi L. Mendozzi R.NEmni P. Mazzoleni M. Rabuffeti; Procedure for the quantitative evaluation of motor disturbance in cerebellar ataxic patients; 5 january 2005, Medical & Biological Engineering & computing 2005, volume.43, 349-356

18. Theresa A. Zesiewicz, MD, et al; comprehensive systematic review summary: Treatment of cerebellar motor dysfunction and ataxia; 9 february 2018, Neurology volume 90 ,number 10, march 6, 2018

19. H Stolze, S Klebe, G Petersen, Jraethjen , R. Wenzelburger , K K witt et al; Typical Features of cerebellar Ataxia Gait; J neurology psychatry2002;73:310-312

20. Jennifer L. Keller ,PT, MS, and Amy. J. Bastian, PT, PHD; A Home Exercise programe Improving Walking In People With Cerebellar Ataxia; February 2014, volume 28, Issue 8, Available From-https://doi.org/10.1177/1545968314522350

21.Camila Polonium Martins , Erika de carvalho Rodrigues , Laura Alice santos de oilveria; Physical therapy approach to spinocerebellar ataxia; September 2013, fisioter pesq.2013;20(3):286-291.

22. Elizabeth Cassidy, Sandra Naylor And Frances Reynolds; The meaning of physiotherapy and exercise for people living with progressive cerebellar ataxia: an interpretative phenomenological analysis; Disability And Rehabilitations, 2018 vol 40, No 8,894-904.

23.Kimberly Tsu Kwei, M.d., Ph.D. and Sheng-Han Kuo, M.D; An overview Of THE Current State And The Future Of Ataxia Treatment; 27 February 2020, Neurol Clin. 2020 May;38(2): 449-467.