

# Cerebellar Ataxia & The Effect of Nicotinamide in Patients with Friedreich's Ataxia

A Research Presented for the National Syrian Center for the Distinguished

Course:

**Biology**

Presented By

**Al-Abbass Mohamed**

Supervised By

**Mr. Nidal Hassan**

**December 2015**

## This Research Includes

<b>INTRODUCTION</b>	<b>3</b>
<b>DEFINITION &amp; DESCRIPTION OF ATAXIA</b>	<b>4</b>
<b>CAUSES OF CEREBELLAR ATAXIA</b>	<b>5</b>
ACQUIRED ATAXIA	5
HEREDITARY ATAXIA	5
<b>TYPES &amp; DIAGNOSIS OF ATAXIA IN GENERAL</b>	<b>7</b>
SENSORY ATAXIA	7
VESTIBULAR ATAXIA	7
FRONTAL ATAXIA	7
<b>CEREBELLAR ATAXIA &amp; ITS TYPES</b>	<b>8</b>
SPINOCEREBELLAR ATAXIA	8
FRIEDREICH'S ATAXIA	9
<b>TREATMENT OF ATAXIA</b>	<b>10</b>
<b>PHYSIOTHERAPY</b>	<b>12</b>
COORDINATION & MOBILITY OF SPINE & SHOULDERS	12
COORDINATION & MOBILITY OF SPINE & SHOULDERS	13
DYNAMIC BALANCE TRAINING/ SAFETY STEPS	14
TRAINING OF HAND-ARM COORDINATION	15
<b>NICOTINAMIDE &amp; THE TREATMENT OF FRIEDREICH'S ATAXIA</b>	<b>16</b>
NICOTINAMIDE	17
<b>CONCLUSION AND RECOMMENDATIONS</b>	<b>18</b>
<b>FINALLY</b>	<b>18</b>
<b>REFERENCES</b>	<b>19</b>
<b>TABLE OF FIGURES</b>	<b>21</b>
<b>TABLES</b>	<b>21</b>

## Introduction

Human Beings are without any doubt the most complex organisms on the planet Earth. Nevertheless, like all the other organisms, they are formed of billions of microscopic units called cells. Each cell has its own identity, and each group of similar cells gather forming a tissue in order to accomplish a certain job. When several tissues work together then we have an organ, such as the stomach or the kidney. Nevertheless, one organ cannot finish its work by its own, so each couple of organs integrate together to do a more complicated function, and this is called an organ system. We have ten organ systems in our body, each with a complex function that guarantees the continuousness of life[1]. One of these functions is balance development and coordination. This function is done by several anatomical structures including: the nervous system, especially the cerebellum, the vestibular system, and the somatosensory system. However, the cerebellum and the spine integrate and coordinate between the vestibular and somatosensory systems. When one of these structures is damaged or severely affected, the function they perform will subsequently be affected as well. The condition where we have a poor coordination or balance is called "Ataxia". This disorder can be divided into several groups according to the structure affected or damaged. But still, researches argue about the types or groups of Ataxia. Some researchers say that Ataxia has two types: Sensory Ataxia and Cerebellar Ataxia. To others, there are three types: Sensory, Cerebellar and Vestibular Ataxia. Moreover, some other claim that Frontal Ataxia is a forth type [2]. However, the symptoms of two or more Ataxia types may occur, this is called Mixed Ataxia.

In this research, we are going to study this disorder, namely the one in the cerebellum through these main questions:

- **What is the Ataxia?**
- **What are the main causes of the Ataxia?**
- **Are there different types of Ataxia?**
- **How can we diagnose it through its symptoms?**
- **What are the treatments?**
- **Is there a cure?**

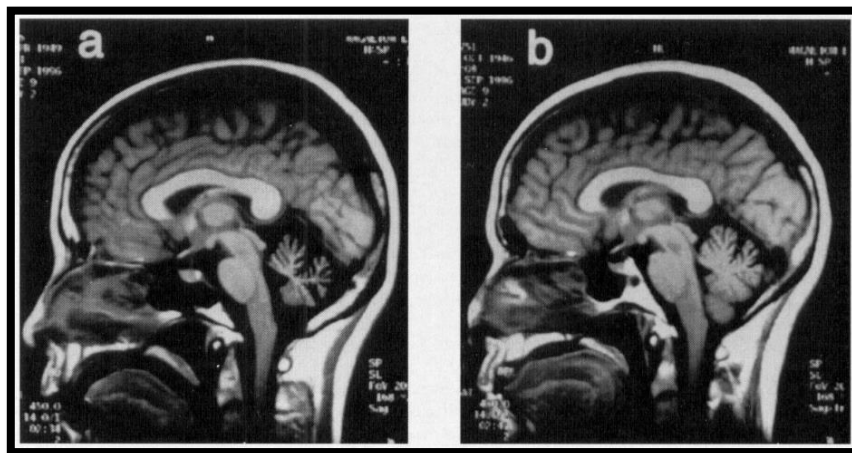
Several studies argue about the efficiency of Nicotinamide (Vitamin B3) towards the treatment of Friedreich's Ataxia.

- **Would the Nicotinamide really be a cure for Friedreich's Ataxia in the future?**
- **What are the approaches of these studies?**

All of these questions will be answered at the end of this research.

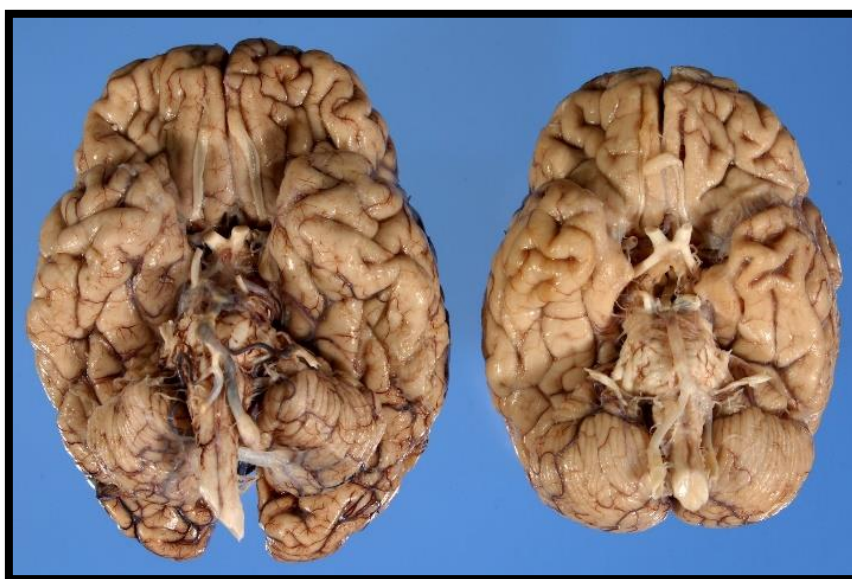
## Definition & Description of Ataxia

Ataxia in general is poor coordination, balance, speech and lack of control over muscles during voluntary movement that is not caused by muscle weakness. It is described as a symptom more than a disease or diagnosis, but sometimes it is also used to refer to a family of disorders. Ataxic people have difficulties with eye movement, swallowing, tasks that require high degree of control, like writing or eating, and have bad vision. These symptoms and their severity vary depending on the type of Ataxia a person has.[2, 3] There are two main categories for Ataxia: Acquired Ataxia that usually result from an environmental factor such as a brain injury, a tumor or chemical exposure and Hereditary Ataxia that is passed on in family. Most disorders that result in Ataxia cause cells in the cerebellum and sometimes the spine to degenerate, and then we have a Spinocerebellar Atrophy.[4]



**Figure 1** Spinocerebellar Atrophy (MRI)

**a.** Cerebellum and spine shrinkage **b.** Normal Cerebellum and spine



**Figure 2** Spinocerebellar Atrophy (Anatomy)

**Left:** Cerebellum and spine shrinkage **Right:** Normal cerebellum and spine

## Causes of Cerebellar Ataxia

As mentioned, some damage in the neurons in the cerebellum may results Ataxia. Diseases that damage the spinal cord and peripheral nerves that connect your cerebellum to your muscles also may cause Ataxia. In this case, we may have two main possible causes of this damage: Either it is an acquired damage resulting from an injury or illness, or it is hereditary and the reason is a faulty gene.[3]

### Acquired Ataxia

Acquired Ataxia is noticed when there's no clear genetic cause for the condition and the patient has recently undergone a severe injury or an illness that affects the nervous system or the peripheral muscles.[5, 6] Most common causes of Acquired Ataxia:

1. **Head Trauma:** damage to the central nervous system can cause sudden-onset Ataxia (Acute Cerebellar Ataxia).
2. **Lack of Blood Supply:** When the blood supply to a part of the brain is interrupted (by a stroke, haemorrhage or an external injury) or severely reduced (internal bleeding or Transient Ischaemic Attack), depriving the brain tissue of Oxygen and nutrients, brain cells die.
3. **Bacterial Brain Infection:** such as meningitis or encephalitis.
4. **Tumor:** whether it was malignant or benign, it can damage the cerebellum.
5. **Cerebral Palsy:** Here, the brain develops abnormally or is damaged before, during or shortly after birth.
6. **Viral Infection:** In very rare cases of the Chickenpox or measles, the infection might spread to the brain, which appears in the healing stages of the infection and last for days or weeks, and this is temporary.
7. **Multiple Sclerosis:** A chronic, potentially debilitation disease that damages the nerve fibers of the central nervous system.
8. **Exposure to Certain Toxic Chemicals:** Ataxia can be a potential side effect to some medication, especially barbiturates, such as phenobarbital, and sedatives, such as benzodiazepines. Other chemicals like Lead or Mercury may cause Ataxia if a person is exposed to enough of them. In addition to sustained long-term consumption of Alcohol.
9. **Certain Vitamins Deficiency:** Lack of Vitamin E or Vitamin B12 because of the absorbing deficiency or other reasons can lead to Ataxia.[5, 6]

### Hereditary Ataxia

The hereditary Ataxias are genetic, which means that a certain faulty gene causes them. This defect or faulty gene that causes the production of abnormal proteins that hamper the function of the neurons, especially in the cerebellum and the spinal cord, causing them to degenerate.[3, 6, 7] The faulty gene is autosomal, so the chance of developing Ataxia is not related to gender. It can be inherited in two ways: a dominant gene from one parent or a recessive gene from two parents.

### ▪ Autosomal Dominant Ataxias:

In dominant patterns, the faulty gene can develop the disorder or condition when receiving a single faulty gene from one parent. This happens because the faulty gene is strong enough to dominate over the other normal gene. Which means that the children of the carrier parent have 50% chance of developing Ataxia. The first Ataxia gene identified for a dominantly inherited type[6]. It was called "Spinocerebellar Ataxia type1 (SCA1)". Subsequently, as more and more dominant genes were found they were called SCA2, SCA3, etc. Therefore, the number behind the SCA refers to the order in which the gene was found. About 36 different gene mutations have been found. Most common types inherited in this pattern are Spinocerebellar Ataxia and Episodic Ataxia.[3, 7]

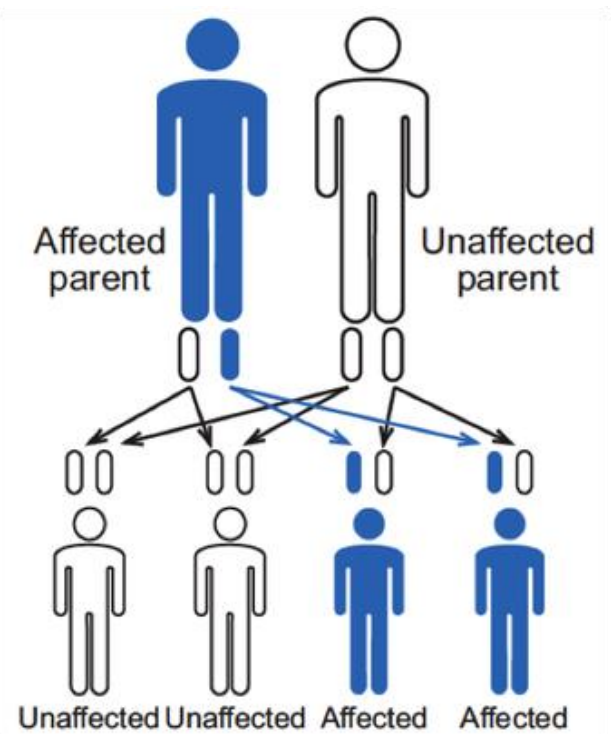


Figure 3 Autosomal Dominant Inheritance

### ▪ Autosomal Recessive Ataxias:

In recessive patterns, the affected person must inherit the faulty gene from both parents. One faulty gene is not enough to trigger the Ataxia because the other normal gene is strong enough to hamper it. Still, the person with one recessive faulty gene is considered a carrier of the gene. Approximately, one in every 85 people are carriers of the gene that causes Friedreich's Ataxia, and one in every 100 are carriers of the gene that causes Ataxia-telangiectasia. The chance of developing the condition is 25% in this inheritance pattern.[3, 5]

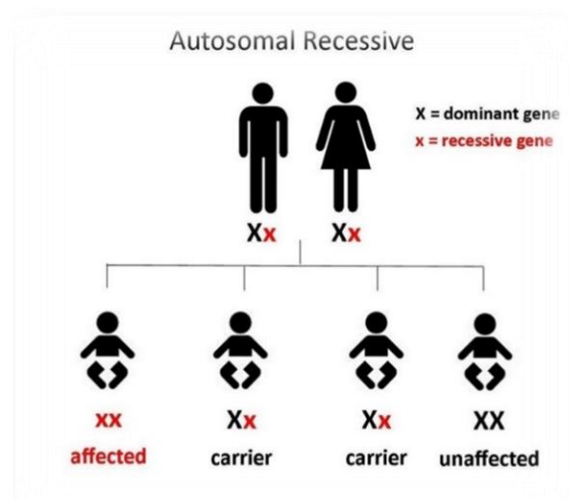


Figure 4 Autosomal Recessive Ataxia



## Types & Diagnosis of Ataxia in General

Ataxia is categorized mainly by the part of the body that the damage occurred in and caused the Ataxia. There are two conventional types of Ataxia, Sensory and Cerebellar Ataxia, and two nonconventional types, Vestibular and Frontal Ataxia. Nevertheless, when we have the symptoms of two or more Ataxia types, then we have mixed Ataxia.[2, 8]

### Sensory Ataxia

In this type of Ataxia, the cause is the loss of proprioception (Sensitivity to joint and body part position responding to stimuli from within the body), generally caused by damage or dysfunction in the dorsal columns of the spinal cord, since they carry proprioceptive information to the brain. Sometimes the problem or damage may be in parts of the brain that receive this information such as the thalamus, and the parietal lobes.[2, 8]

Sensory Ataxia can be diagnosed by the unsteady stomping with heavy heel strikes, and postural instability. These symptoms worsen by time due to the lack of proprioception, especially in the dark where the brain cannot even depend on the visual input to coordinate the muscles into an organized successful move.

Sensory Ataxia can be observed in types of hereditary Ataxia such as Friedreich's Ataxia and Spinocerebellar Ataxia. In addition, it may accompany some diseases such as diabetic neuropathy and multiple sclerosis.[2, 8, 9]

### Vestibular Ataxia

The vestibular system is the composed of three organs: the utricle, the saccule and the semicircular canals. It is connected to the brain (vestibular nucleus) primarily with the cranial nerve VIII. Vestibular Ataxia result when the vestibular nuclei and/or the afferent or efferent connections of the vestibular nuclei are damaged or diseased.[2]

Mainly, it is diagnosed by the disturbance in balance in standing and sitting, the instability when walking and the motion of the head and the trunk, and subsequently the arm, is decreased. [2, 8, 9] In some cases, Vestibular Ataxia may be accompanied by vertigo, nausea, vomiting, blurred vision and nystagmus (involuntary movement of eyeball) due to the vestibular system's role in sensing and perceiving self-motion and stabilizing gaze via the vestibulo-ocular reflex.

### Frontal Ataxia

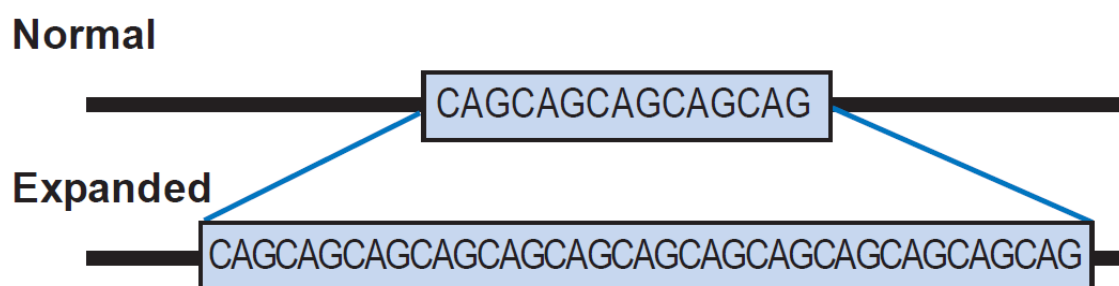
Also known as Gait Apraxia. Frontal Ataxia when the frontal lobe is damaged or pressured by a tumor, abscess, or normal hydrocephalus. Usually, it is diagnosed by the hyperextension in the patient's movement, the instable walking, the incoordination between the legs and the trunk [2, 8].

## Cerebellar Ataxia & its Types

Cerebellar Ataxia results from damage to or atrophy of the cerebellum, or the nervous connections to or from the cerebellum. This type of Ataxia is often accompanied with other damages in other organs in the body, especially the spine and the medulla oblongata [2, 3]. There are two common types of Cerebellar Ataxia:

## Spinocerebellar Ataxia

[3] Spinocerebellar Ataxia is one of the most common types of Cerebellar Ataxia. It is a hereditary Ataxia and caused by a faulty gene. Generally, the change or mutation within the faulty gene that causes most of SCA types is repeat expansion. It means that a certain chromosome pattern is repeated too many times, which disrupts the normal function of the protein made by the gene. [3]



**Figure 5** CAG repeat expansion

The schedule below shows the types of SCA and the chromosome repeat expansion responsible for the disorder:

### Table 1 Genetic Aspects of SCA

Type	Chromosome location of gene	Normal repeat size	Expanded repeat size	DNA pattern repeated
SCA1	6	6-36	39-83	CAG
SCA2	12	15-31	34-220	CAG
SCA3	14	12-40	55-86	CAG
SCA6	19	4-18	21-33	CAG
SCA7	3	4-19	37-300	CAG
SCA8	13	16-34	80-800	CTG
SCA10	22	10-22	280-4500	ATTCT
SCA12	5	7-28	66-78	CAG
SCA17	6	25-42	46-63	CAG

The progression of all Spinocerebellar Ataxia types is slow and the symptoms, especially the incoordination of walking, worsen gradually over years, though some types of SCA progress faster than other types. [3] However, once the atrophy has advanced, it cannot be retrieved or cured, and the damage is permanent.

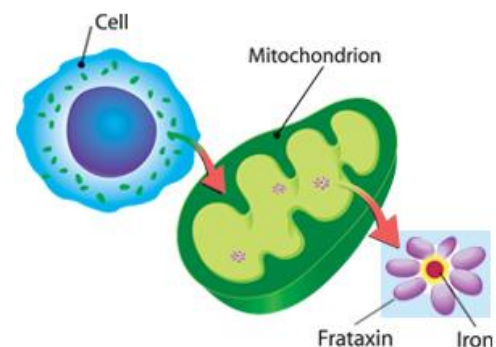


Spinocerebellar Ataxia mainly causes irregularities in the rate, rhythm, amplitude, and force of voluntary movements, especially at initiation and termination of motion, resulting in irregular trajectories (dysnergia), terminal tremor, and overshoot (dysmetria) in limbs.[2, 9]

### Friedreich's Ataxia

Friedreich's Ataxia is a genetic, neurodegenerative, rare disorder that causes progressive damage to the nervous system. Although it's rare, Friedreich's Ataxia is the most common form of recessively inherited Ataxia. It is sometimes confused with Spinocerebellar Ataxia which is dominantly inherited[10-12].

Friedreich's Ataxia is caused by defects, or mutations, in the Frataxin (FXN) gene located on chromosome 9. This gene is responsible of making of the Frataxin protein, which is believed to regulate the level of iron in the mitochondria by playing the role of a storage depot, releasing it when needed[11]. If the Frataxin was not present, then the iron would float freely in the mitochondria triggering oxidative stress, the buildup of oxygen-based free radicals that damages the mitochondria[10].



**Figure 6** Frataxin in the Mitochondria

The mutation in the Frataxin gene is caused by the trinucleotide repeat expansion in the "GAA" DNA pattern. In normal people, it is repeated from 5 to 30 repeats, but in FA patients it ranges from 100 to 1300, but in most cases it is 500 and more[13]. Short expansions (<400 GAA repeats) are often associated with later age of onset, slower progression of clinical features, and absence of or mild cardiomyopathy. The repeat expansion results in gene silencing and reduction in capacity to produce Frataxin protein. The severity of FXN gene silencing is proportional to the length of the expanded "GAA" repeat mutation, in addition to the variability of associated symptoms and findings. In 95% of people with FA, both copies of the Frataxin gene contain expanded repeats[12]. In the rest, just a copy of the Frataxin gene is expended and the other is point mutated, so the Frataxin gene made from these instructions is not normal[13].

The symptoms of FA begin usually between the ages of 5 and 15, but can be as early as 18 months and as late as 30 [14]. Some way how similar to the ones in other types of Ataxia in the first stages, beginning from muscle weakness, unsteady posture, frequent falling, and progressive difficulties in walking due to impaired ability to coordinate voluntary movements. Advanced symptoms may include speech problems, and irregular lateral or sideways curvature of the spine (scoliosis). The last stage of symptoms includes heart diseases that may lead to heart failure which can be observed by the shortness of breath upon exertion and chest pain [11, 13, 15].

## Treatment of Ataxia

Ataxia has no cure for now. There are no medications that can specifically treat and cure the symptoms of Ataxias. However, it is sometimes possible to treat the underlying cause of the condition so it improves, or stops getting worse, but in most cases this is not possible, and the only applicable treatment is by easing the symptoms or managing the co-existing conditions such as muscle cramps, stiffness, tremor, spasticity as well as depression, anxiety, sleep disorders, and more. The most common and efficient treatment is physiotherapy[16, 17].

When treating Ataxia, a team of specialists must follow up the whole treatment, each of them takes care of a group of symptoms relating to his/her specialization. These are the therapies for each group of symptoms and the specialist responsible for treating it[16-18]:

- 1. A Neurologist:** to keep up with the progression of the disease.
- 2. Speech & Language Therapy:** At some point of Ataxia, slurred speech (dysarthria) and swallowing problems (dysphagia) may occur. Thus, the therapist helps the patient to make his/her voice sound clearer by the following methods: changing the posture to improve the quality of the voice, carrying out exercises to strengthen the muscles used when speaking, speaking more slowly to emphasize each word, and using some breathing techniques to improve the speech. In very advanced phases of Ataxia, speaking aids may be used such as a laptop computer, a keyboard connected to a voice synthesizer. As for the dysphagia, some exercises are available to stimulate the nerves used to trigger the swallowing reflex and strengthen the muscles used when swallowing. At a certain phase, the patient won't be able to eat any food, so a dietitian may advise him/her with some easy-to-swallow food.
- 3. Occupational Therapy:** Occupational therapy aims to teaching the patient how to adapt to the gradual loss of mobility and develop new skills that can be used to carry out normal daily life activities. An occupational therapist teaches the patient to use wheelchair and other mobility devices sufficiently, nevertheless suggesting modifications that can be done on the house to help make the life easier, such as installing guide rails or a stair lift.
- 4. Fatigue:** Due to the disturbed sleep and the physical efforts of having to cope with the loss of coordination, many Ataxic people suffer from feeling extremely tired and lethargic. This symptom can be managed with physiotherapy that increases stamina, and advises about how to adapt daily activities to help coping with fatigue, given by an occupational therapist.
- 5. Cardiomyopathy:** Cardiomyopathy is a common condition that follows several types of Ataxia, especially Friedreich's Ataxia. It can be very serious as it effects the affects the normal blood flow in the heart, and causes heartbeat irregularities. This problem cannot be completely treated, but regular check-ups by a cardiologist can be done to keep up with the patient's status.

- 6. Neuropathic Pain:** Neuropathic pain can be subscribed as a burning, aching, or shooting pain, or sometimes tingling in certain parts of the body. Traditional painkillers such as Paracetamol or Ibuprofen are not usually effective, but it can be treated by pain relievers such as amitriptyline, gabapentin or pregabalin.
- 7. Eye Problems:** The muscles that move the eye are sometimes affected by the cause of Ataxia, so Oscillopsia may occur, where there is involuntary movement of the eye balls from side to side or up and down. Some medications such as gabapentin can be used to control the muscles that move the eye. Sometimes, eye problems can be seen as double vision, where the patient sees two images of a single object, which can be treated by attaching wedge-shaped piece of glass or plastic called a prism to the glasses.
- 8. Muscle Problems:** Due to the lack of using of some muscles, problems such as spasms, cramps and stiffness may happen. These problems can be treated with muscle relaxants like baclofen or tizanidine. In some advanced cases where these medications won't work, an injection of botulinum toxin (Botox) would do the job. This works by blocking the signals from the brain to the affected muscles, usually it lasts for about 3 months.

## Physiotherapy

Physiotherapy helps on maintaining the use of the patient's arms and legs, and prevent muscles weakening or getting stuck in one position, also it improves the functional level of the patient through restorative techniques. It is the most common and important type of therapy, because it helps the patient to be more independent and able to do his/her daily activities normally[9, 18].

Restorative physical treatment aims to improve balance and postural reactions against external and gravitational changes, Improve and increase postural stabilization following the development of joint stabilization, develop upper extremity functions, and through developing independent and functional gait, improve the life quality of the patient by increasing the patient's independence while performing daily life activities[2, 9].

A physical therapist must, before starting the treatment, evaluate several aspects in the patient: The range of motion, the strength of everything in the patient's body, foot deformities with the shoes and socks off, scoliosis of the spine caused by muscle imbalance, balance, gait by looking at the speed, quality and safety of the gait[9].

The treatment strategy has a key element, which is for the patient to stop making him/her-self stiff, starting to sway more after the first exercise will make the first achievement. This will help the patient to perform his/her movements more accurately, and when losing balance, to react more flexibly. After a while of training, the patient's movement will become more controlled and accurate. This program strengthens the patient in repeating the daily life oriented exercises[9, 18].

Here are some exercises included in physiotherapy categorized[18]:

### Coordination & Mobility of Spine & Shoulders

**1. Rotation in Lying:** The patient lies down on his/her back, bend the knees and put the feet on the mat, spreads the arms and tilt both knees to one side. This procedure must be repeated 10 times for each side.



Figure 7 Rotation in Lying

**2. Rolling on a mat or in bed:** The patient lies down on his/her back, lifts the arm in the desired direction for rolling, pushes the other arm over the body and lift the leg, so that he/she come to lay on the side, and then the patient rolls back. This procedure should be repeated 10 times to each side.



Figure 8 Rolling on a Mat

**3. Quadruped Position:** The patient brings the left elbow and right knee together below the body, straightens the left arm and right leg and elevate them far up. This exercise should be repeated 5 times for the left arm and the right leg, and 5 times for the right arm and the left leg.

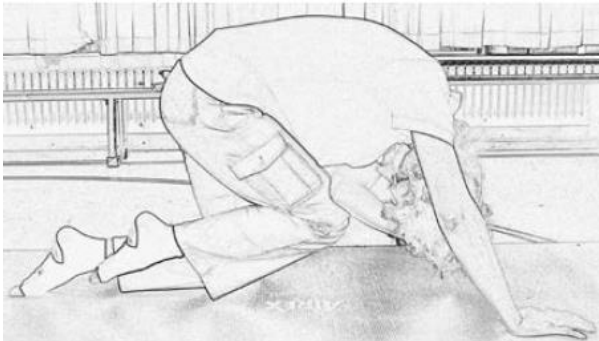


Figure 9 Quadruped Position (1)

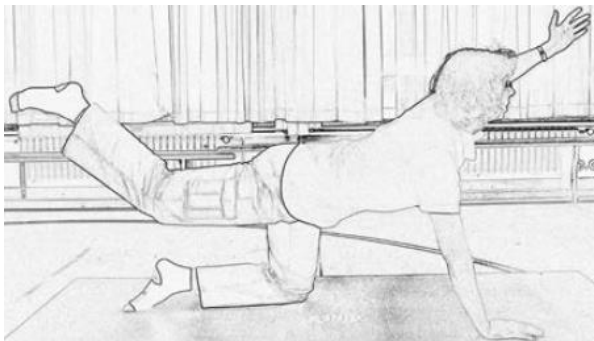


Figure 10 Quadruped Position (2)

Coordination & Balance

**4. Shifting the weight to the side:** The patient sits upright, shifts his/her weight to the side, and sits back up. This exercise should be repeated for 5 times for each side. The difficulty of this exercise can be increased by putting one foot on the bed and back on the ground, and increased even more by putting both feet on the bed over the side.



Figure 11 Shifting the Weight to the side



Figure 12 Shifting the Weight to the side (harder)

**5. Standing Up & Sitting Down:** The Patient mends the spine a bit, shifts his/her weight onto the feet, moves in an upright position, keeps the back and knees slightly bended, and then sits down controlled. This exercise should be repeated 10 times.



Figure 13 Standing Up    Figure 14 Sitting Down



- 6. Kneeling Position:** The patient moves into a kneeling position, moves one leg forward without touching the ground with the toes, and then moves back to the kneeling position. This exercise should be repeated for 5 times for each leg.



**Figure 15** Kneeling Position

- 7. Standing Up from the Ground Using Bear Stand:** The patient stands, bends the knees and spine, touches the floor, that will make him/her in quadruped position, stands on the feet with the hands still on the ground, Straightens the knees, but while keeping them slightly bent; the pressure remains mostly on the forefoot, then the patient lifts the hands off the ground, stands up, and orientates the weight forwards; while keeping the knees slightly bent.



**Figure 16** Standing Up from the Ground Using Bear Stand



**Figure 17** Standing Up from the Ground Using Bear Stand (2)

## Dynamic Balance Training/ Safety Steps

- 8. Side Steps, Steps Forwards & Steps Backwards:** The patient stands upright with the feet hip-width apart, takes a big step to the side, forward, or backwards, and then goes back to the original position. This exercise should be repeated for 20 times with each leg.



**Figure 19** Steps Forwards or Backwards



**Figure 18** Side Steps



- 9. Cross-Step Front:** The patient stands upright with the feet hip-width apart, crosses the legs in the front, and then goes back to the original position. This exercise should be repeated 20 times with each leg.



**Figure 20** Cross-Step Front

### Training of Hand-Arm Coordination

- 10. Exercises with Increasing difficulty:** this includes exercises such as pile building blocks, pile little toy bricks, turn around playing cards, collecting items in a small jar (Marbles, Paper clips), and write half page every day.

- 11. Throwing and Catching a Ball:** The patient throws a ball up in the air with the right hand and catch it with the right hand, does the same for the left hand. it can be more difficult by throwing the ball as far up as the eye height, catching at the height of the wrist, and finally throwing the ball from the right hand to the left and back.



**Figure 21** Throwing and Catching a Ball

- 12. Forearm Rotation:** The patient pours water from one cup in another 20 times.

- 13. Drinking:** The patient should keep calm, move one hand to the chin and back to the table for 10 times, then pour water into the cup, take the cup and move it to the chin and back to the table, for 10 times, finally drink two mouthfuls and put the cup back on the table for 7 times.



**Figure 23** Forearm Rotation



**Figure 22** Forearm Rotation

An effective physical therapy program has several characteristics, such as: Intense strength training, dynamic balance training, cardiovascular training, gait training, stretching, and long-term participation.

Most Importantly to ask about is why physical therapy and exercise important? Simply, because it prevents falls; so much of it is related to safety, it maintains the function the patient currently has, determines if there is a need for adaptive equipment, and it helps to remain as independent as possible[9] . Physical therapy using special equipment prevents scoliosis, and helps support the trunk, which makes the patient have better breathing, talking, swallowing, and using the upper extremities.

## Nicotinamide & the Treatment of Friedreich's Ataxia

As mentioned previously, Friedreich's Ataxia is caused by having abnormally low levels of Frataxin protein due to partial inactivation of the Frataxin gene. The Frataxin regulates the free iron level in the mitochondria motivating the oxidative stress that by its turn increase the level of oxidative free radicals that decompose the mitochondria's components by chemical reactions [11]. However, the goal when treating FA is to avoid and surpass the causes of the disease by increasing the FXN protein levels [19].

In a new clinical trial at the Imperial College London, the ability of Nicotinamide was tested to increase levels of FXN. How? Vitamin B3 is a very important vitamin in our bodies for its role in processing fat and proteins, also for its ability to inhibit the removal of activation marks which occurs on the abnormally silenced Friedreich's Ataxia gene. In FXN deficiency, the coding region of the mRNA and the amino acid sequence of the protein are normal, but the amount of protein produced is reduced [19].



**Figure 24** Structure of Nicotinamide



**Figure 25** Vitamin B3

In order to reverse these epigenetic changes, might be a starting point. So when there is gene hamper due to a mutation, such as in FA, histone protein in the faulty gene in the DNA is deacetylated, and in order to activate it again, histone deacetylase should be hampered. This is possible with histone deacetylase inhibitors (HDAC) in which are present in Nicotinamide and effective when given in high concentrations. Nevertheless, HDAC have been reported to increase FXN concentration in cell culture and in animal models of Friedreich's Ataxia. Nicotinamide is classified as a classical class III HDAC inhibitors [20-22].

When this drug was first tested on patients with FA, researchers noted an increase in FXN mRNA expression and FXN protein concentration in peripheral blood mononuclear cells. This study included ten adult patients with FA. In phase (1), patients were given single doses of up to 8 g (about 200 times higher than, the typical recommended daily allowance (RDA)) as a Vitamin B3, which led to an increase in FXN concentration in peripheral blood mononuclear cells, and this effect increased with increasing dose. In phase (2) daily repeated doses of 2-8 g of oral Nicotinamide were given for 5 days, but in phase (3), it went on for 8 weeks [21, 23].

Nicotinamide is able to cross the blood-brain barrier, but the researcher concerned doing the study did not address whether Nicotinamide affected FXN level in the nervous system and other affected tissues such as the heart. The study only showed an increment of FXN levels in peripheral blood mononuclear cells, which are not affected by FA [21].

The biological effect of Nicotinamide lasted for 2 months in the previous study, which is relatively short to the life of a person with FA. No effects on Ataxia were noted in the study, it is unknown if it is due the patient's notability to respond or by the short duration of the study.

Although Nicotinamide was given in high concentrated doses that proceed the RDA of Vitamin B3, the side effects were mild such as nausea (100% during phases 2 and 3) and vomiting (50%). In long term treatment, the effects can be managed [21].

### Nicotinamide

Vitamin B3 is one of 8 B vitamins. Like all B vitamins, it helps the body to use fat and proteins as a source of energy, and it is highly soluble in water, so the body doesn't store it. B-complex vitamins are needed for a healthy liver, skin and hair, and healthy eyes. Also it helps the nervous system function normally[24].

High doses of B3 can be toxic, and it should not be taken more than the RDA unless it is under a doctor's supervision. Nicotinamide should not be given to people with low blood pressure because it may cause a dangerous drop in blood pressure. Taking one of the B vitamins for a long period of time can result in an imbalance of other important B vitamins. For this reason, the taken B-complex vitamin should include all B vitamins [24, 25].

## Conclusion and Recommendations

Nicotinamide would not work as a treatment for Friedreich's Ataxia because of its many side effects that would be a threat on the patient's life, especially that it reduces blood pressure which may lead to problems with patients with FA because of the cardiomyopathy. In addition, the result of the studies did not include any clear approach to treating Ataxia or even reducing the symptoms but only affected non-related organs and tissues.

I recommend NOT to continue trying to treat Friedreich's Ataxia with Nicotinamide for the previously mentioned reasons.

## Finally

Ataxia is a progressive neurodegenerative group of symptoms accompanied with balance dysfunction that is caused by damage or deficiency in balance-monitoring anatomical structures. It can occur due to external causes (Acquired Ataxia) or can be passed on in families (Hereditary Ataxia). The most common types are Spinocerebellar Ataxia, and Friedreich's Ataxia. Friedreich's Ataxia carriers are 1 to every 85 normal people, so it is considered a prevalent condition. There is no cure for Friedreich's Ataxia for now, but researches are trying their best in order to stop and treat this painful condition for the patients and their families.

## References

1. *SEER Training Modules: Anatomy & Physiology*. 2015 [cited 2015 18 September]; Available from: <http://training.seer.cancer.gov/anatomy/>.
2. Armultu, K., *Ataxia: Physical Therapy and Rehabilitation Applications for Ataxic patients*, in *International Encyclopedia of Rehabilitation*. 2010, Center for International Rehabilitation Research Information and Exchange (CIRRIE). p. 19.
3. Corrine O'Sullivan Smith, S.J.M., Robin L. Bennett, Thomas D. Bird, *Spinocerebellar Ataxia: Making an Informed Choice About Genetic Testing*. 2014: Medical Genetics and Neurology University of Washington Medical Center. 24.
4. *NINDS Ataxia and Cerebellar or Spinocerebellar Degeneration Information Page*. 2015 July 17, 2015 [cited 2015 24 September]; Available from: <http://www.ninds.nih.gov/>.
5. *Diseases and Conditions: Ataxia*. 2014 March 29, 2014 [cited 2015 24 September]; Available from: <http://www.mayoclinic.org/>.
6. *Ataxia*. 2015 12 May 2015 [cited 2015 26 September]; Available from: <http://www.nhs.uk/>.
7. *Causes of Ataxia*. 2015 [cited 2015 8 November]; Available from: <http://ataxia.org/>.
8. Susan L. Perlman, M., *Evaluation and Management of Ataxic Disorders: An Overview for Physicians*. 2007, the United States of America: National Ataxia Foundation. 32.
9. Polly Swingle, P., *Four Components to an Effective Physical Therapy Program for Ataxia*. 2013. p. 32 - 38.
10. *What is FA?* 2015 [cited 2015 7 November]; Available from: <http://www.curefa.org/>.
11. *Friedreich's Ataxia*. 2015 2015 [cited 2015 18 October]; Available from: <http://www.mda.org/>.
12. *Friedreich's Ataxia*. 2014 [cited 2015 7 November]; Available from: <http://www.chop.edu/>.
13. *Friedreich's Ataxia*. 2015 [cited 2015 7 November]; Available from: <https://rarediseases.org/>.
14. *Friedreich's Ataxia*. 2015; Available from: <http://brainfoundation.org.au/>.
15. *Friedreich's Ataxia: Fact Sheet*. 2014 [cited 2015 7 November]; Available from: <http://www.ninds.nih.gov/>.
16. *Ataxia -Treatment*. 2015 12 May 2015 [cited 2015 4 December]; Available from: <http://www.nhs.uk/>.
17. *Ataxia Treatment*. 2013 2 July 2013 [cited 2015 5 December]; Available from: <http://www.news-medical.net/>.

18. *Coordinative Physiotherapy for Patients with Ataxia*. [cited 2015 6 December]; Available from: <http://www.ataxia.org/>.
19. Davenport, F. *New clinical trial reveals early promise for treatment for Friedreich's ataxia*. 2014 2 May [cited 2015 16 December]; Available from: <http://www3.imperial.ac.uk/>.
20. *Nicotinamide (Vitamin B3) in Friedreich's Ataxia*. Available from: <http://imperial.crf.nihr.ac.uk/>.
21. David R Lynch, K.H.F., *Nicotinamide in Friedreich's Ataxia: useful or not?* 2014: National Institute of Health.
22. *Effect of Nicotinamide in Friedreich's Ataxia*. 2012 9 September 2015 [cited 2015 16 September]; Available from: <https://clinicaltrials.gov/>.
23. Libri V, Y.C., Athanasopoulos S, loyse N, Natisvili T, Law PP, Chan PK, Mohammad T, Mauri M, Tam KT, Leiper J, Piper S, Ramesh A, Parkinson MH, Huson L, Giunti P, Festenstein R., *Epigenetic and neurological effects and safety of high-dose nicotinamide in patients with Friedreich's ataxia: an exploratory, open-label, dose-escalation study*. 2014.
24. *Vitamin B3 (Niacin)*. 2015 [cited 2015 19 December]; Available from: <https://umm.edu/>.
25. *Niacinamide*, T.H.A. Inc., Editor. 2012.



# Table of Figures

**Figure 1** Spinocerebellar Atrophy (MRI) **a.** Cerebellum and spine shrinkage **b.** Normal Cerebellum and spine ..... 4

**Figure 2** Spinocerebellar Atrophy (Anatomy) ..... 4

**Figure 3** Autosomal Dominant Inheritance ..... 6

**Figure 4** Autosomal Recessive Ataxia ..... 6

**Figure 5** CAG repeat expansion ..... 8

**Figure 6** Frataxin in the Mitochondria..... 9

**Figure 7** Rotation in Lying ..... 12

**Figure 8** Rolling on a Mat..... 12

**Figure 9** Quadruped Position (1) ..... 13

**Figure 10** Quadruped Position (2) ..... 13

**Figure 11** Shifting the Weight to the side ..... 13

**Figure 12** Shifting the Weight to the side (harder) ..... 13

**Figure 13** Standing Up ..... 13

**Figure 14** Sitting Down..... 13

**Figure 15** Kneeling Position..... 14

**Figure 16** Standing Up from the Ground Using Bear Stand ..... 14

**Figure 17** Standing Up from the Ground Using Bear Stand (2) ..... 14

**Figure 18** Side Steps..... 14

**Figure 19** Steps Forwards or Backwards ..... 14

**Figure 20** Cross-Step Front ..... 15

**Figure 21** Throwing and Catching a Ball..... 15

**Figure 22** Forearm Rotation..... 15

**Figure 23** Forearm Rotation..... 15

**Figure 24** Structure of Nicotinamide ..... 16

**Figure 25** Vitamin B3..... 16

# Tables

**Table 1** Genetic Aspects of SCA..... 8