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Module IV Assignment

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**Spinocerebellar Ataxia Type 3**

**Epidemiology, Pathology, and Pathophysiology**:

Spinocerebellar ataxias (SCAs) are considered autosomal dominant inherited ataxias.1-5 According to the literature, there are over 30 identified types of spinocerebellar ataxias, with prevalence estimates ranging from 0.3 to 3.0 per 100,000.2,3 Of the spinocerebellar ataxias, Spinocerebellar Ataxia Type 3 (SCA3) is often considered the “most prevalent” worldwide.3-6 Other names for SCA3 included Azorean ataxia/disease and Machado-Joseph disease (MJD).1,2,5While signs/symptoms are normally evident around mid-adulthood, the literature suggests that childhood and late adult onset are also possible.1,5,6 Considering the degenerative nature of this disease, patients may survive 10-30 years after initial diagnosis.1,5,6

As an autosomal dominant inherited ataxia, a single copy of an altered gene can lead to this disorder.1 SCA3 is classified as a “polyglutamine” ataxia, and is caused by mutations in the ATXN3 gene.1,2,6 Within the ATXN3 gene, a DNA segment referred to as a “trinucleotide CAG” is repeated over 50 times.2 In normal genes, this segment is typically repeated 12-43 times.2 As a result of the increased length of the CAG repeat, the enzyme ataxin-3 is unable to fold into the appropriate shape.2 Normally, ataxin-3 is found throughout the body and is in part responsible for removing ubiquitin from soon-to-be degraded proteins to be used later in other processes.2 Furthermore, ataxin-3 may also play a role in the initial stages of transcription.2 At any rate, when ataxin-3 cannot form correctly, it becomes nonfunctional. As a result, “unwanted” proteins and ataxin-3 aggregate within the nucleus of cells.2 It is currently unclear how these aggregates affect cell function; however, some studies suggest the increased polyglutamine tract in ataxin-3 may result in neurotoxicity.2 Neurons and other brain cells are most affected by mutations in the ATXN3 gene.1,2 SCA3 has been associated with cell death in the brainstem, cerebellum, and spinal cord, leading to the characteristic signs and symptoms of SCA3.1

Pathological lesions are typically recognized in the spinocerebellar system as well as in the dentate nucleus of the cerebellum.2 Neurological testing often reveals if signs/symptoms are consistent with SCA3.1,6 Ultimately, DNA-based testing, specifically analyzing the mutation of the ATXN3 gene, can confirm the SCA3 diagnosis.1,2,6

The variability in age at diagnosis has to do with the extent of the CAG repeat mutation.7 Because of this, subtypes have been developed. Subtype I represents 13% of individuals with SCA3, and is characterized by early onset with “prominent spasticity, rigidity, and bradykinesia, often with little ataxia.”7 This subtype is also associated with a longer CAG repeat segment.7 Subtype II is considered the most common, with 57% of individuals demonstrating ataxia and upper motor neuron involvement around middle age.7 Subtype III manifests in 30% of individuals with SCA3 at a later age, typically with signs of ataxia and peripheral neuropathy and shorter repeat CAG segments.7 Despite the development of these subtypes, researchers admit that there is little clinical value to placing individuals into a specific subtype; there is often overlap of signs/symptoms, and one subtype may “evolve” into a different type as the disease progresses.7

**Bodily Systems Affected by Disease Progression:**

Multiple bodily systems may be affected directly or indirectly among patients with a diagnosis of Spinocerebellar Ataxia Type 3. However, not all patients demonstrate the following impairments as disease progression and symptom presentation can vary depending on subtype and length of CAG repeats.7,8 Additionally, other inherited and environmental factors may also contribute to observed impairments.8   
*Note: While there is currently no treatment to slow or stop the progression of SCA3, pharmaceutical interventions to treat associated symptoms (i.e. spasticity, rigidity, etc) are available. Some drugs may produce undesirable side effects that can negatively impact various systems as well.9-12* *For instance, severe side effects associated with the drugs Chantix (ataxia) and Sulfamethoxazole/Trimethoprim (spasticity) may cause changes in heart rate, chest pain, or trouble breathing.9-12*

*Cardiovascular/Pulmonary:* While Spinocerebellar Ataxia Type 3 does not structurally impact the cardiovascular and/or pulmonary systems, patients are at an increased risk of deconditioning secondary to reduced physical activity, particularly at later stages of the disease when ataxic symptoms have progressed and ambulation becomes more difficult.13 Reduced activity and endurance can lead to the development of secondary health disorders, including obesity, diabetes, hypertension, or heart disease, which may further impact at patient’s quality of life and functional abilities.14 Additionally, patients who demonstrate dysphagia may also have a higher risk of aspiration, which may lead to pneumonia.8 Frequently, patients who die “early” from this disease often do so as a result of aspiration pneumonia.6 As the disease progresses, patients may demonstrate reduced ability to cough and clear secretions.7

*Digestive/Gastrointestinal:*  Patients with Spinocerebellar Ataxia Type 3 frequently demonstrate decreased body mass and BMI compared to the normal population.16 As the disease progresses, patients often lose weight, which some researchers suggest is related to a longer CAG repeat segment.16 Additionally, Saute et al identified increased peripheral insulin sensitivity among patients with SCA3.21 However, it is currently unclear whether the disease mutation or the overall neurological burden of SCA3 is responsible for weight loss demonstrated by this population.16,18 Nutritional management including referral to a dietician and/or nutritionist would be important for patients with SCA3 to ensure adequate nourishment. Some resources suggest that cachexia, which involves the loss of skeletal muscle mass that cannot be nutritionally reversed, also contribute to patient mortality at later stages of this disease.7,22

*Integumentary:* Patients with Spinocerebellar Ataxia Type 3 may demonstrate decreased sensation secondary to peripheral neuropathy, putting them at risk for neuropathic wounds.7,15 Skin breakdown is also possible among patients who require orthotics for spasticity management, making it necessary for therapists and caregivers to frequently monitor skin integrity.16 Additionally, patients with Spinocerebellar Ataxia Type 3 are at a higher risk of falls, thereby placing them at a greater risk for fall-related skin injury.17 Wheelchair use and immobility at later stages of disease progression may also make patients more susceptible to skin breakdown and pressure ulcers.7

*Musculoskeletal:* Musculoskeletal complications as a result of neuromuscular dysfunction are possible among patients with Spinocerebellar Ataxia Type 3. Peripheral neuropathies, or polyneuropathies, may contribute to muscle weakness and decreased sensation.7,15,16 Studies have shown that patients with later disease onset and small CAG expansions normally demonstrate peripheral neuropathy; however, some research suggest duration of disease and not CAG expansion length may be the main determinant of peripheral neuropathy among this population.15 Pain, numbness, and/or tingling associated with neuropathy may also occur.6,7,16 Muscle atrophy as a result of immobility and/or decreased input from the central nervous system at later stages of the disease is also possible.16 Muscle cramps in the lower limbs, arms, trunk, and face are often reported as a frequent and disabling symptom of SCA3.15 Interestingly, studies have not been able to find “clinical or neurophysiological differences” between patients with or without cramps.15 An increased fall risk puts patients with this disorder at a higher risk for fall-related injuries, including bone fracture.17 Additionally, spasticity can negatively impact muscles and joints, restricting overall joint motion and limiting a patient’s mobility.20 Asymmetrical pull of spastic musculature, muscle rigidity, or dystonia may result in altered posture and/or deformity, such as joint contracture.16,20

*Nervous:* Spinocerebellar Ataxia Type 3 primarily affects the central nervous system. As the name suggests, lesions of the cerebellum result in limb and gait ataxia, causing varying degrees of gait disturbance, incoordination, and balance dysfunction.1-8,15-18 Gait among this population is described as “lurching” or “jerky” secondary to associated symptoms of spasticity, which distinguishes SCA3 gait from purely cerebellar ataxic gait.18 In addition to ataxia associated with cerebellar dysfunction, other signs and symptoms related to dysfunction of the brainstem, oculomotor system, pyramidal and extrapyramidal systems, and peripheral nervous system are also demonstrated.7,16 While upper motor neuron signs including hyperreflexia are more frequently reported (25-100% of cases), lower motor neuron signs are also possible (11-67% of cases) and may be demonstrated more often at later stages of disease progression. 7,16 Early presentation of the disorder may also reflect difficulties with speech (dysarthria), diplopia, nystagmus, and spasticity.7,16

Extra-pyramidal motor signs are more frequently observed among patients with SCA3 compared to the other subtypes of spinocerebellar ataxia.7,15 Dystonia and parkinsonian features, including resting tremor, bradykinesia, and rigidity, have been described among some patients with SCA3.7,15,19 Interestingly, movement disorders demonstrated by patients with SCA3 vary; the available literature suggests that hypokinetic disorders (i.e. parkinsonism) and hyperkinetic disorders (myoclonus, chorea, tremor, etc) are possible, thereby suggesting the presence of deterioration of other brain areas in addition to the cerebellum.15

Additional clinical features of the disease may include the following: vocal card paralysis; vestibular dysfunction; autonomic nervous system issues, including bladder and thermoregulation disturbances, impotence, and orthostatic hypotension; and sleep disturbances (rapid eye movement issues and/or restless leg syndrome).7,15,16 Some literature suggests pain in the lumbosacral region may precede ataxic symptoms.7 Furthermore, deficits involving executive and emotional functioning, verbal fluency, and memory have also been described among patients with SCA3.7,15 In later stages of disease progression, facial and/or temporal muscles may atrophy; tongue atrophy and fasiculations may occur; and perioral fasiculations may be present.16 Opthalmoparesis and slowing of eye saccades with limitations in upward gaze and disconjugate eye motion have also been reported.16 The literature also suggests that hyporeflexia or areflexia of previously hyperactive deep tendon reflexes is possible.16 While significant muscle atrophy and weakness are rare, patients may present with wasting of the limb musculature and muscle fasiculations.16

**APTA Guide Preferred Practice Patterns:23**

Currently, the ATPA no longer recommends the use of practice patterns for clinical decision-making, as they have not been systematically reviewed.23 However, preferred practice patterns may be useful for educational purposes.23 With this in mind, the following practice patterns are related to individuals with Spinocerebellar Ataxia Type 3:

4C: Impaired Muscle Performance

5A: Primary Prevention/Risk Reduction for Loss of Balance and Falling

5E: Impaired Motor Function and Sensory Integrity Associated with Progressive Disorders of the Central Nervous System

6B: Impaired Aerobic Capacity/Endurance Associated with Deconditioning

7A: Primary Prevention/Risk Reduction for Integumentary Disorders

**Activity/Participation Limitations and Quality of Life:**

Onset of Spinocerebellar Ataxia Type 3 is characterized by gait disturbances and slurring of speech.16 Patients may not initially need assistive devices for ambulation; however, with disease evolution, patients will be increasingly limited in their ability to independently ambulate without a device secondary to gait disturbances and balance dysfunction.7,16 Decreased dynamic and static balance are associated with an increased risk of falls, which has been shown to directly impact a patient’s ability to perform self care activities, transfers, and ambulation.17 Limb ataxia may also impair a patient’s ability to perform reaching or fine motor movements during functional activities.7,16,19 These impairments combined with decreased cardiovascular endurance may limit a patient’s abilities to keep up with their peers; participate in sporting and/or leisure-time activities that they may have enjoyed prior to diagnosis; and/or complete work-place related functions. Verbal communication issues secondary to dysarthria and swallowing difficulties due to dysphagia may also limit an individual’s ability or desire to participate in social situations.16 As the disease progresses, patients with SCA3 become increasingly more dependent on caregivers for assistance with activities of daily living, wheelchair mobility and transfers, and transportation.6-8,16

Physical therapists will be essential during these stages to recommend appropriate assistive devices and/or home modifications; prescribe or refer patients for appropriate orthotics needed to control spasticity; develop a plan of care focusing on maintenance of function, including cardiovascular/pulmonary performance; and provide patient and caregiver education. Assistive devices and gait/balance training may allow patients to be more independent with mobility for as long as possible as the disease progresses. Referrals to speech therapy to address dysarthria and/or dysphagia and ophthalmic intervention for vision impairments may also be needed.7,16

Depression and anxiety are often associated with this disease, potentially due to psychosocial factors or due to changes in brain structure and/or function.15,18,24 Impairments associated with this disease limit a person’s independence and reduce self-efficacy, thereby contributing to feelings of depression and reduced quality of life which are commonly reported among patients with SCA3.15,18,24 The literature suggests that depression is likely underreported within this population; consequently, a large proportion of patients with SCA3 are not receiving proper treatment.15

**Interventions:**

Current research involving Spinocerebellar Ataxia Type 3 physical therapy interventions are limited in that they often include other patients with differing forms of ataxia with generally low sample sizes and poor methodological rigor.25-30 This comes as no surprise considering the rare nature of spinocerebellar ataxias in general. In a systematic review involving various physical therapy interventions for improving function among patients with spinocerebellar ataxia, researchers observed that patients with less severe involvement retained the benefits of interventions, and recommended long term practice of exercises for maintaining improvements in function.25 One of the major challenges noted regarding functional improvement within this population is the degenerative nature of the disorder and its effect on “virtually all parts of the cerebellum.”25,26 Current evidence suggests that high-intensity training may be appropriate for improving motor performance among patients with degenerative ataxia.27

In one study by Ilg et al, researchers examined the effects of four weeks of intensive coordinative training on 16 patients with degenerative cerebellar disease.26 Training consisted of three, one hour sessions per week including the following exercise “categories”: static balance, dynamic balance, “whole body movements to train trunk-limb coordination,” protective stepping and fall strategies, and movements to counteract or treat contracture.26 The intervention period was followed up with an eight week home exercise period.26 The results of the study demonstrated “significant reduction of ataxia symptoms” as measured by the SARA (Scale for the Assessment and Rating of Ataxia) among all patients in the study post-intervention and at follow-up after the eight week home exercise period.26 Additionally, quantitative movement analysis showed “significant improvement” related to intralimb coordination and balance control during ambulation and balance tasks among patients with cerebellar ataxias.26 Goal attainment scores among the cerebellar group of patients in the study also were achieved.26 However, researchers do note that there was not a significant change in body sway during dynamic balance tasks on the treadmill, potentially due to a lack of training at home that would demand “whole body coordination” (due to safety reasons).26 Overall, I believe this study provides some evidence for coordination training to improve function among patients with cerebellar degeneration.

A follow-up study was performed by Ilg et al to assess the effects of the aforementioned four week intensive training program 12 months after the intervention period.27 During these 12 months, subjects were asked to continue their training at home for one hour per day. Exercises were individualized based on the individual’s abilities and level of functioning.27 Despite underlying disease progression, patients demonstrated significantly better SARA score at long-term follow-up compared to baseline by 3.1 points.27 Authors suggest that the retention of training effects is “equivalent to gaining back at least one or more years of natural disease progression.”27,28 Furthermore, researchers point out that training intensity of coordination exercises correlates significantly with reductions in SARA scores at 1 year, thereby suggesting the importance of continuous training for maintenance of functional improvements.27

In a study investigating the use of exergames-training on 10 adolescents (age 15.4 +/- 3.4 years) with mild to moderate progressive spinocerebellar ataxia, researchers used commercially available Xbox Kinect videogames specifically selected to target “goal-directed limb movements, dynamic balance, and whole-body coordination” in an effort to improve ataxia and overall balance.28,29 The initial two weeks of the program involved training by a physical therapist for one hour per day, four days a week.29 After training, participants were instructed to continue to play the exercise-based games for six weeks at home and document the intensity of their playing “in a daily training protocol.”29 Subjects were assessed two weeks before the intervention, immediately before training, after two weeks of training, and after the six week home training phase.29 Following the intervention period, subjects demonstrated improved “game-specific behavior and scores” for all games played.29 Comparisons between SARA scores assessed at the beginning of the intervention and following the intervention revealed a reduction in overall score (2 point reduction on average), suggesting improvements in symptoms of ataxia.29 Additionally, Dynamic Gait Index (DGI) scores also decreased, suggesting an improvement in dynamic balance.29 Gait analysis revealed significantly reduced step variability and lateral sway and significantly decreased target error for both lower extremities.29 Researchers determined that improvements in ataxia were dependent upon the intensity of home training; subjects who trained more intensely at home demonstrated the greatest reductions in SARA scores.29 Authors concluded that the use of motivational, cost-effective intensive coordination training in the home environment may improve whole-body coordination and balance among children with degenerative ataxia.29 While there are multiple limitations to this study, including small sample sizes, younger age compared to average age of onset associated with SCA3 (mean age 30-38), and variable type of degenerative ataxia, this does provide promising preliminary findings for use of exergaming among patients with SCA3 to improve not only symptoms of ataxia, but fitness as well.16,28,29 However, it is worth noting that exergaming should be used to complement physical therapy based training programs as a way for patients to practice coordination skills, but should not be used to replace formal physical therapy.28

In a study by Miyai et al, researchers designed a relatively large randomized control trial with the aim of assessing the effectiveness of intensive rehabilitation among 42 patients with varying types of degenerative cerebellar diseases.30 Participants were randomized to an immediate or delayed-entry control group via blinded allocation. The subjects in the immediate group underwent four weeks of inpatient rehab, involving one hour of physical therapy and one hour of occupational therapy on weekdays, along with one hour of PT or OT on weekends.30 Postural balance and gait training were focused on during physical therapy sessions, with exercises provided to promote general conditioning, ROM, strengthening, static and dynamic balance, walking stability on various surfaces, and ascending/descending stairs.30 After discharge from the hospital, patients received 20-40 minutes of home PT per week, and were advised to continue the program after discharge.30 Patients were assessed at 12 and 24 weeks post-intervention. Subjects in the delayed-entry group were allowed to participate in the intervention following two baseline assessments at 0 and 4 weeks.30 This allowed the delayed-entry group to act as controls for assessing short-term effects of the first four weeks of the intervention for the immediate group.30 Results imply that participants in the immediate group demonstrated significantly greater improvements in SARA scores, Functional Independence Measure (FIM) total and motor scores, functional ambulation category (FAC) scores, and number of falls following the first four weeks of rehabilitation.30 Truncal ataxia scores improved more than limb ataxia scores.30 Furthermore, the immediate group also demonstrated significant improvements in gait speed.30 Long-term effects on SARA score, gait speed, and FAC scores were also significant for both groups at the 12 week follow up.30 Authors state that “normalized gait speed” remained improved even at 24 weeks following the intervention.30 While this study utilizes a larger sample size, none of the participants had Spinocerebellar Ataxia Type 3, therefore limiting the generalizability of this study’s findings to the population of interest. However, authors conclude that four week of intensive therapy may improve ataxia, ADL performance, and gait dysfunction among patients with degenerative cerebellar ataxias. Future studies that involve a similar protocol and include patients with Spinocerebellar Ataxia Type 3 are necessary to determine the overall impact such rehabilitation strategies may actually have on patients with SCA3.

Based on the current state of evidence, it appears that more studies are needed to determine the most appropriate type of exercise and suitable parameters (intensity, duration, frequency, etc) to use for training this patient population in order to improve motor performance. While all of these studies are not specific to patients with SCA3, the rarity of this disorder makes it necessary to extrapolate findings among research studies involving cerebellar dysfunction in order to develop reasonable exercise programs for patients with SCA3. At any rate, evidence suggests that longer duration, greater intensity, and continuity of exercise training may help improve and/or offset progressive ataxia.25-30

**Assessments/Outcome Measures:**

Objective *assessments* of the patient’s ability to perform functional tasks during the course of their care will be imperative for monitoring functional abilities and limitations. The following assessments would likely be appropriate to use for patients with SCA3 at initial evaluation and as the disease progresses:31

* *Postural control*: Assess static and dynamic balance during stance, gait, and sitting.31
* *Control of limb movements*: Rapid alternating movements, finger-nose-finger, heel to shin, and handwriting can help assess coordination deficits.31
* *Control of eye movements*: Examination of ocular fixation, smooth pursuit, saccades, vestibuloocular reflex (VOR), and any demonstration of nystagmus can be useful for monitoring visual deficits.31
* *Control of speech*: Assess the patient’s ability to communicate and determine presence/absence of dysarthria.31 (Refer to speech therapy.)
* *Task complexity*: Some sources suggest that more complex task performance, such as standing with feet in tandem and arms outstretched at sides, often provides a more sensitive assessment for detecting mild ataxia.31
* *Task performance speed*: Patients often unconsciously compensate for dysmetria and/or dysdiadochokinesia by performing tasks more slowly.31 Faster attempts often reveal incoordination.
* *Severity of extra-cerebellar symptoms*: Symptoms of spasticity, dystonia, altered reflexes, or decreased sensation may be present.31 Therefore, it is important to assess and treat (if indicated) these components for effective disease management. Deep tendon reflex testing, assessment of tone/spasticity using the Modified Ashworth Scale, and sensation testing (light touch, sharp/dull, etc) should be performed.31,32
* *Gait*: Assessment of gait velocity/speed and cadence can be performed to monitor changes in gait over time.31

*Outcome measures* have been designed specifically for patients with Spinocerebellar Ataxias. Other more general outcome measures may also be appropriate to incorporate into a patient’s evaluation when assessing patients with SCA3.

* Scale for the Assessment and Rating of Ataxia (SARA): an 8-item rating scale used to assess ataxia severity, with gait, stance, sitting, speech, finger chase, nose-finger test, and rapid alternating movement components. 33-35 Scores range from 0-40, with “0” indicating no ataxia, and “40” indicating severe ataxia. 33-35
* International Cooperative Ataxia Rating Scale (ICARS): 100-point scale consisting of 19 items related to posture/gait disturbance, limb kinetic function, speech disorder, and oculomotor disorder.33 Higher scores represent worse performance. The SARA is often utilized in place of the ICARS, as it is less time consuming to administer.33
* Neurological Examination Score for Spinocerebellar Ataxia (NESSCA): This rating scale aims to assess neurological features of SCA3 in an 18-item format scored from 0-40, with higher scores indicating worse performance.33 Fourteen items of this questionnaire correspond to a standard neurological assessment, and four items rely on patient report of symptoms.33
* Inventory of Non-Ataxia Symptoms (INAS): a 30-item questionnaire used to assess the presence of non-ataxic signs and symptoms, including reflex abnormalities, spasticity, muscle atrophy, dystonia, impaired sensation, and vision issues.35,36 The presence of symptoms is recorded and converted into an INAS count, which ranges from 0 (no non-ataxia signs) to 16 (all systems affected).35,36
* Spinocerebellar Ataxia Functional Index (SCAFI): a short, 3-item functional assessment of gait, dexterity, and speech.35,37
* EQ-5D: Generic instrument used to measure health-related quality of life in five dimensions, including self-care, mobility, usual activities, pain/discomfort, and anxiety/depression. Scores for each dimension range from 1 (no problems) to 3 (extreme problems). Unfortunately, no specific health-related QOL tool has been developed for patients with SCA3; however, the EQ-5D has been used to date in studies involving patients with degenerative ataxias.38,39
* Functional Independence Measure (FIM): 18-item scale that is used to assess daily tasks involved in self-care, sphincter control, transfers, locomotion, communication, and social cognition. Scores range from 18-126, with higher scores indicating greater independence with ADLs. While this scale is not specific to SCA3, it has been used in multiple studies involving patients with spinocerebellar ataxias.17,25
* Tinetti Balance and Gait Assessment: If needed, a therapist may choose this measure to assess a patient’s risk of falls. The scale is made up of 17 items related to balance and gait, with scores lower than 19 indicating a high risk of falls.17

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