Why is my child falling down so much?

An approach on how to manage children who present with poor coordination: A literature review and a study of three cases

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Abstract

While ataxia is a relatively common presenting symptom in pediatric patients, it represents only one possible cause of uncoordinated movements. Other possible causes of uncoordinated movements include ingestion of toxic substances, musculoskeletal diseases, psychogenic disorders, and epilepsy. Therefore, primary health care providers must recognize and eliminate other aetiologies of uncoordinated movements before attaching the label ‘ataxia’ to any patient presenting with poor coordination. Once the presence of ataxia is confirmed, the cause should be investigated. Furthermore, as ataxia may be vestibular, sensory, or cerebellar in origin, practitioners must evaluate the diverse symptoms and signs to effectively differentiate the various subtypes of ataxia. Three case studies will be presented to illustrate the complexity associated with the assessment of ataxia. Each case will introduce a pediatric patient who displays cerebellar ataxia as a concurrent feature of a gene-specific epileptic encephalopathy. These cases will provide an example of how ataxia may be differentiated from other causes of uncoordinated movements related to epilepsy and anti-seizure treatment, namely: nonconvulsive seizures, postictal state, and medication side effects or toxicity. The assessment of poor balance can be challenging at times; however, with an appropriate clinical assessment, the evaluation of incoordination does not need to be intimidating for general practitioners. With knowledge of the differential diagnosis of poor balance, medical practitioners will be able to confidently determine the presence of true ataxia from various ataxia mimickers, thereby allowing for timely and accurate diagnosis and appropriate management.

Introduction

Poor coordination is a relatively common presenting symptom and is, therefore, one with which general practitioners should be familiar. As it carries a broad differential diagnosis, health care providers must differentiate the various possible aetiologies to determine management, prognosis, and whether a referral for further investigations is necessary (1).

The differential diagnosis for poor coordination includes extrapyramidal movement disorders, ingestion of toxic substances, subtle seizures, postictal state, spasticity, weakness, psychogenic disorders, and ataxia (1). While these various causes will be outlined in this paper, a specific emphasis will be placed on further understanding and recognizing ataxia. Poor coordination is often thought to be synonymous with ataxia; however, pure ataxia is only one cause of uncoordinated movements. Therefore, mimickers of ataxia must be excluded when making an appropriate diagnosis. Further, once ataxia is confirmed, the specific system involved must be determined, for example, whether the ataxia is vestibular, sensory, or cerebellar in origin (2). This paper will focus mainly on the presentation of cerebellar ataxia, but both vestibular and sensory ataxia will be briefly discussed.

Ataxia may also present as a concurrent feature of neurological disorders such as epileptic encephalopathies (EE) (3). Epileptic encephalopathies represent a group of neurodevelopmental disorders in which epileptic activity adversely impacts brain function, contributing to cognitive, behavioural, and motor deficits (4). There are several possible causes of uncoordinated movements in patients with EE, such as nonconvulsive seizures, postictal state, and medication side effects or toxicity (1,5–9). These potential causes must be ruled out before ataxia is considered a concurrent feature of the disorder.

The purpose of this paper is to illustrate the complexities encountered when assessing ataxia. First, this paper will highlight the differential diagnosis of uncoordinated movements with a specific emphasis on cerebellar ataxia. Then, three case studies will be presented to demonstrate further the intricacies associated with assessing ataxia. Specifically, the case studies will highlight how ataxia may be distinguished from other possible causes of poor coordination related to epilepsy and antiseizure treatment. The case studies will introduce three patients from Manitoba who have been diagnosed with various gene-specific EEs. All three patients have ataxia as a concurrent clinical feature.

Differential diagnosis of poor coordination

1. Extrapyramidal movement disorders

Sydenham's chorea is a neurological disorder most commonly seen as a manifestation of rheumatic fever (10). This disorder is characterized by involuntary choreiform movements, hypotonia, muscle weakness, and gait disturbance. These movements typically worsen with stress and resolve with sleep. In this disorder, antibodies against Group A Streptococcus cross-react with neurons in the basal ganglia, causing an increased release of dopamine, and as a result, uncontrollable movements (10). These involuntary movements may be easily mistaken for ataxia and must be included in the differential diagnosis.

2. Ingestion of toxic substances

The ingestion of alcohol and drugs, exposure to heavy metals, and toxic doses of medications may also cause uncoordinated movements (5,6). Several classes of drugs that may cause poor coordination include benzodiazepines, antineoplastic, and antiepileptic medications. In

general, uncoordinated movements tend to occur within days to weeks of introducing a new drug or increasing the dose; however, the development of poor coordination with chronic use has also been reported (6). There are several signs that, if present, suggest toxic ingestion: altered mental status, reduced level or loss of consciousness (LOC), seizures, vomiting, and abnormal pupillary size and reactivity (5,6).

3. Epilepsy

Poor coordination may present as a result of nonconvulsive seizure activity, otherwise known as pseudoataxia or epileptic ataxia (5). Acute, fluctuating and more prolonged imbalance may also be a prominent feature in nonconvulsive status epilepticus (9). This presentation is not true ataxia; instead, decreased level of awareness, myoclonic jerks, and atonic seizures interrupt smooth movements of the limbs, thereby producing pseudoataxia. Often, the patient will appear inattentive or confused (8).

In addition to pseudoataxia, uncoordinated movements may occur as a manifestation of the postictal state (5,7). The postictal state occurs immediately after seizure termination and ends with the patient's return to baseline (7). This state is characterized by sensory, cognitive, and motor deficits, including altered LOC, confusion, autonomic dysregulation, and postictal paresis and weakness. The associated confusion or weakness seen in the postictal state may be mistaken for ataxia (5,7). Therefore, uncoordinated movements as a manifestation of the postictal state must be considered in the differential.

Finally, antiepileptic medications may also cause uncoordinated movements, either as a general side effect or as a result of toxic levels (5,6). Therefore, in patients with epilepsy,

healthcare providers must also consider the side effects or toxicity associated with antiseizure medications.

4. Weakness, spasticity, and clumsiness

Motor weakness may occur due to lesions in the cerebral cortex, brainstem, spinal cord, peripheral nerves, neuromuscular junction, and muscle (11). Muscle weakness can be easily assessed on clinical exam by looking for decreased resistance to active movement, pronator drift, or other asymmetries in arm or leg use (12). Motor weakness may present as poor coordination and can, therefore, be mistaken for ataxia. Spasticity, in which muscles are abnormally stiff from damage to upper motor neurons that leads to the inhibition of fluid movement, may cause poor coordination (1). Finally, unsteady gait may represent clumsiness due to a developmental coordination disorder or result from instability related to a patient learning to walk.

5. Musculoskeletal disorders

Specific musculoskeletal disorders, such as irritable hip, may also cause gait disturbance (1). Further, injury, deformity, or any process causing pain to the lower extremities or back may cause impaired balance or gait abnormality that can be mistaken for true ataxia (12). Typically, a gait disturbance due to pain is termed an antalgic gait.

6. Psychogenic disorder

Gait disturbance is a common feature of psychogenic or functional movement disorders (9). With this disorder, the gait disturbance can be differentiated from true ataxia by two main observations. First, the patient will lack any adaptation, such as a wide-based gait, to improve

balance. Second, the patient is unlikely to fall, as seen with true ataxia. Furthermore, tremor is the most common presenting feature of psychogenic movement disorder. This tremor may be postural and present both at rest and during action, making it distinguishable from a true cerebellar tremor, which typically occurs during a posture or on action. In addition, the tremor associated with psychogenic disorder will worsen during clinical examination and improve when the patient is distracted (9).

7. Ataxia

Finally, one significant cause of uncoordinated movements is ataxia. Ataxia is characterized by impaired coordination of movement and balance associated with a lack of muscle control during voluntary activity (13). In Manitoba, ataxia is a common presenting symptom in pediatric patients with a mean age of onset of three years (14). The prevalence rate of chronic ataxia was 6.59 in 10,000 individuals, while the incidence rate was 3.2 in 100,000 individuals less than 17 years of age over an 18-year study period. Numerous causes of chronic ataxia have been found in Manitoba, including Angelman syndrome, ataxia-telangiectasia, posterior fossa stroke, mitochondrial diseases, and syndromic EEs (14).

Ataxia

Causes of ataxia

Ataxia itself is a presenting symptom, not a disease; therefore, the underlying etiology must be elucidated (2). Ataxia carries a large number of causes and a complex classification scheme. An initial step in evaluating ataxia in pediatric patients is determining the timing of onset (2). Acute onset, typically described as less than 72 hours, suggests toxic, vascular or traumatic

aetiologies (1). Subacute onset is more likely to be caused by an infectious or inflammatory, or paraneoplastic disorder, whereas chronic ataxia is more likely due to genetic or neurodegenerative disorders.

1. Acute causes of ataxia. When evaluating an acute presentation of ataxia, practitioners must rule out three leading causes: stroke, toxicity, and trauma (7,11). Rarely, acute ischemic stroke, particularly within the posterior circulation, may result in acute ataxia (9). The ingestion of toxic substances is also a common cause of ataxia, as outlined above (5,6). Traumatic injury may also cause ataxia (12). However, it is unlikely for trauma to cause an isolated presentation. Finally, neoplasms, such as tumours originating in the cerebellum or spinal cord, may also be responsible if they suddenly enlarge or bleed (11).

2. Subacute causes of ataxia. Several subacute causes of ataxia should also be considered, including infection, inflammation, and metabolic disorders (12). Some common infectious causes of ataxia include the coxsackie and varicella viruses, which can cause cerebellitis. Inflammatory conditions, such as multiple sclerosis or acute disseminated encephalomyelitis, may also present with ataxia as a clinical feature. Finally, there is a wide range of genetic and metabolic disorders, such as biotinidase deficiency, Hartnup disease, and abetalipoproteinemia, which may also cause ataxia (12).

3. Chronic and progressive causes of ataxia. Typically, chronic ataxia is due to various genetic or neurodegenerative disorders (1). The genetic causes of chronic ataxia are extensive, and numerous aetiologies have been reported in Manitoba (14). The most common diagnoses include,

but are not limited to, Angelman syndrome, ataxia-telangiectasia, various mitochondrial disorders, ataxia presenting as part of a syndromic EE, and Rett syndrome.

Types of ataxia

There are several types of ataxia, including cerebellar, proprioceptive, and vestibular ataxia (2). These subtypes may be distinguished based on the structure from which the dysfunction originates and the associated signs and symptoms. While this paper will focus on cerebellar ataxia, it is important to recognize that these other two subtypes exist.

1. Vestibular ataxia. Vestibular ataxia may arise due to damage or dysfunction of the vestibular apparatus or impaired input from these structures to the cerebellum (2,11). Labyrinthitis and vestibular mononeuritis represent two examples of vestibular pathology that may result in vestibular ataxia (2,11,12). Vestibular ataxia will often be associated with nausea, vomiting, hearing loss, vertigo, and nystagmus with the fast phase directed towards the unaffected side (2,11). A lurching gait, or the tendency of an individual to fall to one side while ambulating, may also be seen (2,12). Typically, the patient will lean towards the ipsilateral side of the lesion (2).

2. Sensory ataxia. Sensory ataxia, also known as proprioceptive ataxia, results from impaired proprioceptive input from the peripheral nerves and spinocerebellar tracts to the cerebellum (2). The impaired transmission of proprioceptive information leads to sensory loss seen when testing vibration and joint position sense in the toes and fingers. Sensory ataxia may also manifest as the inability to stand with feet together and eyes closed, known as Romberg's sign, or as a high-stepping gait. Typically, proprioceptive ataxia is worsened when visual cues are removed.

Inflammatory disorders, such as Guillain-Barre Syndrome, are one potential cause of sensory ataxia (2).

3. Cerebellar ataxia. Cerebellar ataxia results from dysfunction within the cerebellum itself or its incoming and outgoing tracts (1). The cerebellum has been shown to have several roles, including ocular and limb motor control, speech control, and behaviour control. As such, patients with cerebellar ataxia may present with motor and non-motor symptoms and signs.

Clinical manifestations of cerebellar ataxia.

The following symptoms and signs help differentiate cerebellar ataxia from vestibular and sensory ataxia, as well as some of the other causes and presentations of uncoordinated movements as outlined above.

1. Gait. One of the most common presentations associated with cerebellar dysfunction is an unsteady and wide-based gait (1,12). An impaired stance, characterized by an increased width between the feet and the inability to stand with feet together for more than thirty seconds, suggests cerebellar ataxia (2). Truncal instability, which manifests as the oscillation of the body when sitting or standing, may also be present (1,2,12).

2. Voluntary movements. Dysmetria is one possible presentation of cerebellar ataxia, which refers to when the patient either over-or undershoots their intended target, as seen with the finger-to-nose or heel-to-shin tests (1,2,12). Dysdiadochokinesis, or nonrhythmic and impaired rapid alternating movements, is often seen in cases of cerebellar ataxia. Further, dyssynergia, or the

decomposition of movement into sequential tasks, may be seen (12). Intention tremor is another common clinical presentation associated with cerebellar dysfunction and is characterized by the increasing amplitude of oscillation at the end of voluntary movement (1, 2). Once again, this may be seen when completing the finger-to-nose test. Finally, titubation, which refers to involuntary, rhythmic oscillations of a body part, and hypotonia, which refers to decreased resistance to passive stretch, are also possible signs (1,2).

3. Ocular motor signs. The cerebellum plays an important role in ocular motor control (1). Several types of nystagmus, including downbeat and upbeat nystagmus, represent signs of cerebellar dysfunction. Saccadic, or jerky, ocular pursuit and saccadic dysmetria, in which inaccurate and fast eye movements cause a visual target to be missed, may also be present (1).

4. Speech control. Speech production requires the coordination of numerous muscles located in the tongue and orofacial area (1). Dysarthria, otherwise known as scanning speech, is one common sign of cerebellar disease.

Epileptic encephalopathy

In epileptic encephalopathy, frequent epileptic activity adversely impacts brain function, contributing to cognitive, behavioural, and motor plateauing or regression (4). It represents one group of neurodevelopmental disorders in which chronic ataxia may present. Of the 184 children with chronic ataxia in Manitoba, five patients had ataxia as part of a syndromic EE, with a crude prevalence rate of 1.48 per 100,000 children (14).

Clinical presentation

The clinical manifestations of EE are challenging to separate, as there is no clear genotype-phenotype correlation (3,4). Instead, EE tends to be associated with a broad spectrum of clinical features due to a phenomenon known as phenotypic heterogeneity or pleiotropy, in which mutations in a single gene lead to multiple phenotypes (3). While the clinical presentations associated with EE differ among patients and underlying genetic causes, several features are commonly found, including developmental delay and severe epilepsy that is usually drug-resistant. Ataxia is another neurological symptom that may present in patients with EE (3).

Methods

Three case studies are presented to illustrate the difficulties encountered in distinguishing the cause of incoordination in patients with EE. Each case study highlights one pediatric patient with EE, associated with a different genetic cause, that has cerebellar ataxia. The patients range in age from 6 to 16 years old, and all live in Manitoba.

Case studies

Patient A

Background information. Patient A is a six-year-old male with a history of developmental delay, hypotonia, relative macrocephaly, epilepsy, and ataxia. He presented initially at the age of three years and four months with a seizure after a fall in which he hit his head. The initial seizure consisted of right gaze deviation, nystagmus, and clonic movements in his right upper limb. The duration of the first seizure was unknown. He had two more seizures lasting 20 minutes and 45

seconds, respectively. It was thought that the seizures were due to the fall rather than the patient falling as a result of the seizures.

Over the next two years, the patient experienced nine breakthrough seizures. He was initially started on valproic acid, which required dose optimization to gain better seizure control. Additionally, at four years and two months of age, clobazam was introduced to enhance his seizure control. His final seizure occurred around five and a half years of age. He has since remained seizure-free.

This patient also has a developmental delay. However, slow improvement in his development has been seen over the past two years, though he is still behind. At three years and eight months of age, the patient had a total of ten words but could not put two words together. Over the next two years, he slowly added new words, and by five years and ten months of age, he used 50 single words in total but could still not put two words together.

The patient was born in the Philippines and immigrated to Canada at three years of age. The patient was born to a G1P0 mother, who had spotting at six weeks gestation. He was born at 39 weeks via caesarean section due to failure to progress. There is no relevant family history of seizure or developmental delay.

Physical examination. At three years and eight months of age, the patient displayed relative macrocephaly with a head circumference of 53cm (98th percentile). His weight was 15.3kg (42nd percentile), while his height was 99.1cm (32nd percentile). His cardiovascular, respiratory, and abdominal exam was unremarkable. He had no neurocutaneous stigmata or dysmorphic features. He had full extraocular eye movements, normal pupillary reaction to light, and normal facial movements. The patient also displayed pseudo-esotropia because he had epicanthic folds. He had

normal strength and reflexes but was hypotonic. He walked with an ataxic wide-based gait and required assistance to prevent him from falling. At three years and ten months of age, he displayed an intention tremor in his upper limbs bilaterally. Since then, his physical exam has remained unchanged.

Investigations. At the age of three years and ten months, the patient's EEG showed frequent epileptiform activity over the left temporal-central region. A brain MRI completed at the same age showed left mesial temporal sclerosis but did not show any other abnormalities that could explain his ataxia. The patient also underwent extensive routine, metabolic, and genetic testing (including a microarray CGH) were all unremarkable. Finally, at six years of age, the patient had whole-exome sequencing, which ultimately provided a diagnosis of CACNA1A-related EE following the discovery of a genetic mutation in the calcium channel gene (CACNA1A).

Current status. The patient continues to display intention tremor bilaterally and has an ataxic wide-based gait. The patient's EE is associated with chronic ataxia. His ataxia does not wax and wane and is present independent of when his seizures were not controlled or when his antiseizure medication doses were changed. He continues to be followed up regularly in the pediatric neurology clinic.

Patient B

Background information. Patient B is a seven-year-old male with a history of epilepsy, developmental delay, hyperactivity, and ataxia. The patient was referred for investigation of apneic spells associated with stiffness. These spells consisted of the patient becoming stiff, not breathing,

rolling back of his eyes, then waking up and vomiting. These episodes occurred daily, beginning at around five months of age. At ten months of age, the patient presented to the hospital after experiencing three sequential episodes, each lasting three seconds. Epilepsy was diagnosed, and as a result, the patient was started on phenobarbital following his initial hospital presentation. After one dose increase, his seizures were controlled. He remained seizure-free for almost a year, at which point the decision was made to switch his medication to levetiracetam as his development was slow (developmental delay may be a side effect of phenobarbital). Levetiracetam was also successful in controlling his seizures. After being seizure-free for two years, he was weaned off the levetiracetam. However, the seizures recurred at four years of age, and as a result, levetiracetam was restarted. Despite optimizing the dose, he continued to have breakthrough seizures, so clobazam was added, and the dose was titrated up several times until an effective dose was achieved. The patient's current treatment regimen has successfully controlled his seizures over the last 20 months.

There were no concerns regarding the patient's development during his initial visit to the pediatric neurology clinic at 13 months of age. He appeared to be reaching all of the appropriate milestones. However, the patient soon began to display developmental delay, particularly with language. He was only able to use one word and two signs to communicate at two years of age. Over the years, the patient gained more words, reaching a documented maximum of 20 words at three years of age. However, his speech regressed and became subsequently incoherent. For the past two years, the patient has been averbal. Further, the patient has hyperactivity. His hyperactivity is currently well controlled on lisdexamphetamine.

The patient was born at 40 weeks' gestation via caesarean section. There were no complications or exposure to teratogens during pregnancy. He is of Hutterite ethnicity and is the

fourth of five children. His parents and siblings are all healthy, except for one older brother with ADHD. A distant family history of seizures is present; however, further details are unknown.

Physical examination. At 13-months of age, the patient weighed 11.7 kg (85-97th percentile). His height was 76.5 cm (50th percentile), and his head circumference was 46.5 cm (50th percentile). His cardiovascular, respiratory, and abdominal exam was unremarkable. He did not display any neurocutaneous lesions, and his Wood's lamp dermatological exam was normal. He did not have any dysmorphic features. His pupils were equal and reactive, and he had full extraocular eye movements. There was no evidence of nystagmus. He did not display any facial asymmetry or abnormal tongue movements. Initially, his motor exam, including tone, strength, coordination, and reflexes, was unremarkable. However, at two years and five months of age, he began to display an ataxic wide-based gait with a tendency to fall, intention tremor bilaterally in his upper limbs, and decreased tone. At the age of four years and two months, he began to display dysmetria in his upper limbs. Over the next couple of months, his gait became steadier but was consistently ataxic and wide-based. There have been no further changes on subsequent physical exam.

Investigations. At one year of age, an EEG showed intermittent interictal epileptiform discharges and intermittent polymorphic slow wave activity over the left frontotemporal head region, which suggested an underlying dysfunctional brain. A brain MRI completed at 17 months of age was unremarkable. The patient had extensive routine, metabolic, and genetic testing (including a microarray CGH), which were all unremarkable. At seven years of age, whole-exome sequencing revealed a diagnosis of STXBP1- encephalopathy, following the discovery of a genetic mutation in the syntaxin binding protein 1 (STXBP1) gene.

Current status. The patient continues to display significant developmental delay, particularly with expressive language. He has an ataxic wide-based gait. He is hypotonic and has intention tremor with dysmetria in his upper limbs. He is followed up regularly in the pediatric neurology clinic.

Patient C

Background information. Patient C is a 16-year-old female with Rett syndrome and celiac disease. She has intellectual disability, epilepsy, ataxia, and behavioural difficulties. She had two hospital admissions for seizures occurring when she was three years old. Before the initial admission, she experienced four seizures over a five-hour period. During these episodes, her eyes rolled up, her arms jerked, and her legs flexed. The seizures lasted between 30 seconds and two minutes. A month later, she was admitted again due to another cluster of seizures, during which she experienced nine seizures, each lasting between five and 30 seconds, over a period of 24 hours. She was started on valproic acid.

Over the next several months, the patient continued to experience frequent clusters of seizures spread over a few hours. During that time, her valproic acid dose was optimized. When she was five years old, the seizure clusters were eliminated with the introduction of clobazam. Over the next several years, however, she continued to experience frequent breakthrough seizures, some associated with intercurrent illnesses. Both the valproic acid and clobazam doses were optimized. Eventually, at the age of nine years, a third medication, lamotrigine, was added to enhance seizure control. The lamotrigine improved her seizure control and ultimately allowed for the clobazam to be weaned. Despite the optimization of lamotrigine, she continued to experience breakthrough seizures.

At the age of 12 years, the patient experienced another seizure exacerbation, likely related to the onset of puberty. Since neither valproic acid nor lamotrigine doses could be further increased, another medication, levetiracetam, was added. Levetiracetam significantly improved her seizure control; however, she began to display behavioural issues, a recognized side effect of this medication, and, as a result, the dose was decreased. She continued to experience mild behavioural problems and was started on vitamin B6, which has been shown anecdotally to reduce levetiracetam-induced behavioural disturbances. The addition of vitamin B6 was successful in improving her behaviour. She continued to experience infrequent seizures between 13 and 14 years of age, so both levetiracetam and lamotrigine doses were optimized further. Currently, her seizures are well controlled with valproic acid, levetiracetam, and lamotrigine with rare breakthrough seizures.

Physical examination. At five years and seven months of age, the patient's height and weight were 118 cm (90^{th} percentile) and 25.7 kg (90-95^{th} percentile), respectively. Her head circumference measured 50 cm (25-50^{th} percentile). Her cardiovascular, respiratory, and abdominal exam was unremarkable. She did not display any dysmorphic features. Her pupils were equal and reactive to light, and her extraocular eye movements were full. She had normal smooth ocular pursuit and saccades and showed no evidence of nystagmus. Her facial movements were normal. She was hypotonic, but strength and reflexes were normal. She displayed head titubation and both intention tremor and dysmetria in her upper limbs. She also presented with an ataxic but not wide-based gait. At six years of age, she began to display truncal titubation. At seven years and six months of age, her speech became dysarthric, and her ataxia worsened with the development of a wide-based gait. Over the next several years, her clinical exam worsened, likely

due to the natural history of Rett syndrome. By the age of 11 years, her gait became more ataxic and wide-based, and both her intention tremor and head titubation worsened.

Investigations. The patient has undergone extensive routine, metabolic, and genetic workup (including karyotype and methylation studies for Angelman syndrome), which have all been unremarkable. An EEG completed when the patient was four years of age showed diffuse dysfunction with hemispheric epileptiform activity, mainly located over the left parietal region, with spread to the central and temporal regions. Her brain MRI was normal. Around seven years of age, a mutation in the methyl-CpG binding protein 2 (MECP2) gene was discovered, and the patient was diagnosed with Rett syndrome.

Current status. The patient's ataxia remains stable. She continues to display intention tremor and dysmetria in her upper limbs, truncal titubation, and an ataxic wide-based gait. She is followed regularly in the pediatric neurology clinic.

Discussion

When a patient presents with uncoordinated movements, the differential diagnosis can be complex and extensive (1). Therefore, the many disease categories associated with uncoordinated movements must be differentiated and ruled out when assessing such patients. Uncoordinated movements may be caused by extrapyramidal movement disorders, ingestion of toxic substances, medication side effects or toxicity, epilepsy, muscle weakness, musculoskeletal diseases, psychogenic disorders, spasticity, and ataxia (1). Differentiating ataxia from the other possible causes of poorly coordinated movement is essential for the health care provider.

Once the presentation has been determined to be ataxia, the next step is deciding which type of ataxia is present. There are three main types of ataxia: cerebellar, vestibular, and proprioceptive (2). The three subtypes of ataxia differ based on the structure from which the dysfunction originates: the cerebellum, the vestibular system, or the nerves, respectively. These subtypes of ataxia may be differentiated based on their unique symptoms and signs. Cerebellar ataxia may have a varied clinical presentation, including a wide-based gait, dysmetria, dysdiadochokinesia, intention tremor, rebound, dysarthria, pendular reflexes, hypotonia, jerky ocular tracking, dysmetric saccades, and downbeat, upbeat or gaze-evoked nystagmus (1,2,12). Cerebellar ataxia occurs due to dysfunction within the cerebellum or its afferent or efferent tracts (1). Vestibular ataxia occurs due to impaired function of the vestibular system (semicircular canals, saccules, utricles, vestibular nerves) and its tracts to the cerebellum (2). As a result, vestibular ataxia manifests as nausea, vomiting, vertigo, poor balance, and fast phases of nystagmus towards the contralateral side of the lesion (2,11). Patients may also veer towards the ipsilateral side when attempting to walk in a straight line (2,12). Proprioceptive, or sensory ataxia, arises from the loss of proprioceptive sensory input from the nerves and spinocerebellar tracts to the cerebellum (2). Therefore, patients will have difficulty assessing their joints' position in space and will be unable to touch their nose with their eyes closed. Further, individuals with sensory ataxia will show a high-stepping and feet-slapping gait (2). They will also have difficulty standing with their feet together and eyes closed, known as a positive Romberg sign (2,12).

When analyzing the three case studies, it is clear that all three patients are displaying cerebellar dysfunction with ataxia. Each of the three patients has intention tremor and an ataxic wide-based gait. Further, both patients B and C show evidence of dysmetria. These three manifestations are all examples of cerebellar dysfunction (1,2,12). The lack of signs associated

with vestibular and sensory ataxia, such as unilateral nystagmus and worsening of symptoms with closed eyes, further reinforces that the patients have cerebellar ataxia (2,11).

One area where differentiating ataxia from other causes of uncoordinated movements is challenging is in individuals with EE. There are several potential causes of uncoordinated movements occurring in individuals with epilepsy that can be mistaken for ataxia. Uncoordinated movements may result from nonconvulsive status epilepticus and are often associated with a decreased level of awareness, myoclonic jerks, and interrupted smooth movements of the limbs, leading to pseudoataxia (5,9). Motor deficits, confusion, sleepiness, and lethargy occurring in the postictal phase of an epileptic seizure may also be mistaken for ataxia (7).

Further, antiseizure medications may also cause uncoordinated movements via several mechanisms (5,6). These include poor coordination as a general side effect, due to the sedating effect of the medication, or due to toxic levels of antiepileptic medications (5,6). Therefore, in patients with epilepsy, the above three factors, nonconvulsive seizures, postictal state, and medication effects, must be ruled out before determining that a patient displays ataxia, especially when their 'ataxia' is fluctuating (1,5–9).

In each case, the three causes of poorly coordinated movements that may be seen in the setting of EE and antiseizure medications have been ruled out. The medication levels for each of the three patients have been monitored regularly since starting treatment to ensure that toxic levels are not present. Further, the ataxia has been present in all three patients despite numerous medication and dose changes, highlighting that the ataxia is not a result of a medications' side effect. Each of the patient's ataxic behaviour is present consistently and constantly. Therefore, it does not show an association with the postictal state or nonconvulsive seizures, especially during the time periods when their seizures were fully controlled.

While our understanding of EEs has expanded significantly over the past twenty years, they remain a complex group of neurodevelopmental disorders with variable presentations (4). Currently, several genetic abnormalities have been associated with infantile EEs (3). The above case studies highlight three of these genes: CACNA1A, STXBP1, and MECP2. Both CACNA1A and STXBP1 have been associated with infantile ataxias and early infantile EEs, thereby suggesting a common end result in both disorders (15). In addition, the use of whole-exome sequencing has facilitated the diagnosis of the first two cases underscoring the importance of genetic advances in the discovery of new disease-causing genetic mutations.

Currently, how these genes lead to the development of ataxia is not well understood. Thus far, several potential mechanisms of action have been suggested. For example, CACNA1A encodes calcium channels found in Purkinje cells in the cerebellum, and thus any alteration in their structure or function, caused by a genetic mutation, may cause ataxia (15). In comparison, STXBP1 has been found to impact the release of neurotransmitters from synaptic vesicles (15). In contrast, it has been suggested that MECP2 plays a role in transcription repression and mediating spontaneous neurotransmission and short-term synaptic plasticity (16). Further research is necessary to increase our understanding of the pathomechanism of ataxia as a concurrent feature in cases of EE to facilitate improved and targeted treatment and management strategies.

The above cases were discussed to illustrate the different aetiologies of poor coordination found in patients with different gene-associated EEs. This paper aimed not to be exhaustive or comprehensive but merely illustrative, highlighting one limitation of this paper.

Conclusion

Ataxia is a relatively common presenting symptom in childhood but represents only one possible cause of uncoordinated movements. Therefore, health care providers must recognize and rule out several other possible differential diagnoses and mimickers of ataxia to accurately determine the presence of ataxia and allow for timely management. Furthermore, health care providers must be aware of the various subtypes of ataxia (vestibular, sensory, cerebellar) and describe their clinical presentations in an informative and accurate manner. The case studies discussed highlight the complexity in recognizing ataxia as a concurrent feature of EE and provide an example of the approach healthcare providers must take when presented with a patient showing uncoordinated movements. While these case studies highlight specific examples of EE associated with ataxia, the underlying principles to differentiate the various causes of poor coordination may be applied to any clinical setting. Thus, with an appropriate clinical approach, the presence of uncoordinated movements does not need to be intimidating to health care providers.

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