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Clinical approach to tremor in children☆

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ABSTRACT

Pediatric Movement Disorders encompass a very large and complex group of diseases, among which Tremor is one of the least studied. Evaluation of tremors in kids carries significant challenges, in particular the fact that many tremor etiologies have other associated movement disorders that make tremor identification more difficult. Also, it is sometimes difficult to differentiate tremors from other shaking disorders. Yet, the correct identification of tremor leads to appropriate treatments and sometimes practical cures. Thus, in this paper we have strived to provide a succinct, clinically useful and practical review of pediatric tremors. The most useful classification of tremors in based on their predominance during rest or activity. By far, the most common tremor in children is during action. We provide a clinical algorithm on how to assess pediatric tremors at the bedside, as well as multiple useful tables. We also review common tremor etiologies.

1. Introduction

Shaking is common in the general population, and an important source of worry and disability. Based on the consensus of the Taskforce on Childhood Movement Disorders, tremor is defined as a rhythmic, relatively symmetric, back-and-forth or oscillating involuntary movement about a joint axis [1]. One of the biggest challenges to the practitioner is that not every shaking is due to tremor.

Tremors are usually central in origin and have been linked to the presence of oscillators both within the cortico-lenticular-thalamic-cortical and the cortico-cerebellar-thalamic pathways. There are some peripheral nervous system disorders where tremor is common, but still central oscillators are thought to be implicated.

Among the pediatric movement disorders, tremors have been significantly under-investigated. Long term natural history studies, therapeutic clinical trials and pathophysiological studies are all lacking. This poses significant difficulties to the pediatrician, as most medical decisions on tremor are guided by expert opinion, adult data, or previous clinical experience. For this and other reasons the evaluation of pediatric patients with can be challenging (Table 1).

In this review we intend to provide the busy clinician a practical, simplified approach to diagnosing tremors in the pediatric population.

2. Tremor mimics

Not everything that shakes is a tremor, and this is particularly true in the pediatric population. Since treatment and prognosis depends on making the correct diagnosis, it is critical to differentiate tremor from other causes of shaking, particularly in the pediatric setting. Within Table 2, we have a list of tremor mimickers, and we offer clues to help the clinician differentiate the phenomenology better.

Although most tremor mimickers are episodic in nature (Table 2), it is important to remember that dystonic and ataxic tremors can present intermittently as well. A number of conditions could present with intermittent tremors, including pyruvate dehydrogenase or carboxylase deficiency, Leigh's syndrome, Fatty acid oxidation disorders, partial urea cycle defects, organic- and aminoacidopathies, biotinidase deficiency, migraines, and the dominant episodic ataxias.

Part of the challenge of differentiating tremor from its mimickers is that often times they coexist in the same patient [1,2]. Angelman Syndrome is a good example of how complex the phenomenology identification can be. A sporadic disorder characterized by chronic encephalopathy and seizures, Angelman syndrome presents with several associated movement disorders including action tremor, intention tremor, dystonic tremor, stereotypic movements and cortical myoclonus [3,4]. And therefore in these patients, the presence of episodic shaking could be due to seizures, myoclonus or tremors. Other examples include Ataxia Telangiectasia (presents often with shaking, which can be attributed to either action tremor, intention tremor, dystonic tremors or chorea) and Leigh Syndrome (shaking could be due to clonus, action and intention tremors or even seizures). These examples are far from unique, and just are mentioned here to illustrate the issue, as most tremor metabolic and genetic disorders share the same difficulties.

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Table 1
Special challenges on pediatric tremor evaluation.

Pediatric Tremor epidemiology and pathophysiology under-investigated
Tremor produces significant stress on parents.
The differential diagnosis is large and complex
Multiple movement phenomenologies tend to co-exist together in kids, making tremor recognition harder
It is difficult to obtain subjective historical details from young patients.
Differential diagnosis of action tremors is much more ample in the pediatric population.
Tremor frequency for each disease is different than in the adult population

3. Pediatric tremor classification

Historically, tremors have been classified in many different ways, but the most common classifications are based on anatomical location, etiology, frequency and activating maneuvers. The main goal of these classifications from the clinician stand point is to allow for a systematic organization of the tremor differential and to guide treatment. Recently, the Task Force on Tremor of the International Parkinson and Movement Disorder Society published a consensus statement on the classification of tremors [5]. Although any such efforts will have some limitations until more data is available, this classification will certainly help advance our understanding of tremor syndromes through standardization and consistency of the diagnostic process. Tremor was classified along two axes: Axis 1 – Clinical characteristics, and Axis 2 – Etiology. Although most of the data used to device this consensus came from the adult tremor population, it is important to note their classification based on age of onset. The authors suggested a rough categorization into the following age groups; infancy (birth to 2 years), childhood (3–12 years) adolescence (13–20 years), early adulthood (21–45 years), middle adulthood (46–60 years) and late adulthood (> 60 years) [5].

3.1. Frequency classification

In general, the frequency of a tremor is patient- and disease-specific. Tremor diseases tend to have their own tremor frequency band. Therefore, recognizing within a patient a particular tremor frequency could help determine the etiology of the condition. However, an important limitation to the use of tremor frequency to determine its etiology is the fact that most pathological tremors frequency spans between 4 and 8 Hz [5].

Tremor frequency can be grossly separated as low, moderate and high. Low frequency (4–8 Hz) is usually seen in action and dystonic tremors [5]. Moderate frequencies (7–11 Hz) are usually seen in action and physiologic tremors. Orthostatic Tremor is the most important high frequency (> 12 Hz) tremor, but it is rare in the pediatric population [6]. Although tremor frequency can help determine the diagnosis, its accurate measurement usually requires the use of advanced diagnostics. In fact, historically, electromyography or accelerometers have been rarely used in the general clinical setting. In more recent years, the advancement of technology is making the use of smartphone-based accelerometry more reachable and acceptable in the clinic, sometimes with significant accuracy [7].

3.2. Tremor etiological classification

The etiological classification of pediatric tremor can be divided into primary (or idiopathic) and secondary (or symptomatic) [8]. In most idiopathic tremors the most significant movement disorder is the tremor, and the rest of the examination is usually benign. On the other hand, when there is a known cause for a tremor, they are usually classified as secondary. Tremors with onset before age 5–7 are often concerning for static or metabolic encephalopathies, while tremors that start during adolescence are more commonly associated with enhanced physiologic tremor, functional tremors, substance-induced and Essential Tremor (ET) [9,10]. Diseases where tremor is not the chief phenomenology are not generally considered within tremor classification schemes.

3.3. Classification based on activating maneuvers

By far, the most useful classification of tremor for the clinician is based on its predominance during action or rest (Table 3).

Resting tremors are usually thought as tremors that occur while the limb is at rest. There are however some shortcomings to this definition for the practicing clinician. We would submit that resting tremors might be best described as those which disappear (or their amplitude is reduced) upon the volitional activation of the muscle that is shaking. This characteristic helps identify even the resting tremor re-emergence that can be seen during limb posture holding (postural tremor) from other action tremors.

While resting tremors are associated with significant morbidity in kids, action tremors are a lot more common. Action tremors are further classified as kinetic (simple or intention), isometric, task-specific and postural [5]. The use of the term postural tremor is not as satisfying clinically, as these tremors that occur while holding a body part against gravity could be etiologically related to either resting or action tremors. Most of the action tremors that are seeing in the clinic are kinetic in nature. There might be tremor at the beginning (initial kinetic tremor), during the movement (dynamic kinetic tremor) and while reaching the final target (terminal or intention tremor). To be able to differentiate between a postural and an intention tremor it is useful to notice that most intention tremors have a larger amplitude when approaching the target, in comparison with just holding the limb on the same position.

Sometimes patients can have tremor both during rest and action. Holmes tremor, also known as midbrain or Dentato-Rubral tremor, is a large amplitude, slow frequency tremor present at rest that worsens (through increased amplitude) during action or posture-holding. This localizes usually to the dorsal brain stem, and tend to be due to a focal lesion.

4. Clinical approach to pediatric tremor

4.1. First – is it really a tremor?

The first step in the evaluation is to recognize that not all that shakes is a tremor and to ensure that the phenomenology is consistent with a tremor (Table 2).

4.2. Second – is it a resting or an action tremor?

In the clinic, the main initial challenge is to differentiate between resting and action tremors (Fig. 1). If it is a resting tremor, assess for presence of parkinsonism, and proceed early on with a levodopa trial. If it is an action tremor, ensure that examination does not reveal any other focal findings. If there are other abnormalities, or the tremor is unilateral, proceed with appropriate imaging and lab testing. If tremor is the only finding, follow the patient over time. Lastly, consider treatment options based on specific etiology [1].

4.3. Third – ascertain additional historical and examination features

The clinician seeing a pediatric tremor needs to ascertain a number of historical and examination features including tremor time course, presence of distractibility, ability to be induced or amplified by other movements, family history and response to alcohol and medications. Presence of dystonia or parkinsonism on examination is of great importance. In the absence of such additional features, the diagnosis would most likely lie within the isolated tremor syndromes.

In the presence of tremor in a dystonic body part, the clinician must

Table 2
Pediatric tremor mimickers and how to differentiate them.

Movement phenomenology	Reasons why it looks like a tremor	Clues that differentiate from tremor
Seizure	Convulsions can produce oscillatory activation of agonist and antagonist muscles, causing shaking	Comes in spells. Duration is short. Frequency and amplitude tends to change during spell. Consciousness/following commands could be impaired. It's not altered by passive/active movements or changes of posture
Myoclonus (particularly cortical or poly-micro-myoclonus) [1]	Involves muscles across a joint, can flex or extend fingers repetitively, continual	There is lack of symmetric velocity on both directions. Due to myoclonus causing simple movements (jerk-release), there is absence of a midpoint for the oscillation. Movements are faster and less predictable.
Shivering	Involuntary shaking	Usually episodic. Amplitude fluctuates over time and within a single spell. Usually involves trunk muscles which is unusual on tremors
Myokymia	There is skin quivering, repetitive, continual.	Movements are usually irregular or arrhythmic.
Shuddering	Shaking	Episodic. Usually in infants.
Tics	Some tics can involve oscillations	Episodic, usually accompanied by other tics, fast frequency. Presence of premonitory feelings, ability to hold the tic.
Akathisia	Often akathisia involves oscillatory movements	Irregular movement, episodic, can be suppressed by patient.
Stereotypic movements	Often involves oscillatory movements. For example Infantile gratification tends to produce repetitive movements	Episodic. Most commonly while concentrated on a task. Movements are usually distractible.
Benign neonatal sleep myoclonus [19]	Repetitive jerks. Typically from birth to 6 months.	Movements occur only during sleep, and stop consistently upon arousal.

Table 3
Tremor classification based on activation maneuvers.

Type of tremor	Activation maneuver	Examples
Rest	Volitional activation of the muscle with tremor would stop the tremor or decrease its amplitude	Hypokinetic disorders Medication-induced Functional
Action (further subdivided into kinetic, postural, isometric and task-specific)	The tremor is induced or its amplitude increases by the volitional contraction of the shaking muscle.	
Postural	Tremor appears while holding body part in a position against gravity.	Less specific etiologically speaking.
Simple Kinetic	Usually during a multi-joint movement, tremor occurs.	Essential Tremor Medication-induced Functional
Intention	This is an action tremor which amplitude increases as the body part is reaching a specific visual target.	Characteristic of cerebellum and cerebellar pathways dysfunction.
Isometric	A tremor that occurs during isometric contraction of the muscle (no shortening of the muscle)	Often shares etiologies with enhanced physiologic tremors.
Posture-specific	Tremor only occurs when body is in a particular posture. Could be associated with dystonic tremor	Orthostatic Tremor occurs while standing and is rare in the pediatric population.
Task-specific	Occurs while performing skilled tasks. This could become a form of Task-Specific Dystonia [20]	Primary writing tremor Task-specific tremor of musicians

consider the possibility of dystonic tremor [11]. This poses a challenge to the pediatrician, as dystonia is a common co-existing phenomenology in kids with movement disorders. Dystonic tremors are usually irregular, jerky, asymmetric, with a characteristic null point.

4.4. Fourth – is it a curable tremor etiology?

An important consideration is to never miss those tremor etiologies that are highly treatable, or curable, or those where prognosis would worsen by delaying the diagnosis (Table 4).

4.5. Fifth – determine likely etiology

Once the specific tremor syndrome has been determined, it would be important to then attempt to reach an etiology designation, making an effort to differentiate between acquired and genetic conditions.

5. Specific pediatric tremor disorders

5.1. Essential Tremor

Essential Tremor (ET) is a primary tremor disorder that usually occurs in the absence of other significant neurological deficits. The cerebello-thalamic pathways have been linked to ET, and in fact, mild ataxia can be seen in these patients. In adults, use of alcohol can relieve the symptoms, but this is not a useful clue in the pediatric population. Importantly, ET is a familial disease in the majority of patients, and therefore a comprehensive family history is a must.

The tremor is characteristically kinetic in nature, although intention tremor is often associated. Although tremor tends to worsen with fatigue and stress, it is present continuously. Location is in the hands symmetrically, although sometimes can be asymmetric [12]. Tremor in other areas are usually less severe than in the hands, but face, neck and laryngeal tremors are all common in ET. The tremor frequency in pediatric ET is higher than in adults and it slows down over time.

In terms of diagnostics, it is useful to see stability of the tremor and the continuous absence of other neurological deficits for at least a year. Evaluation of the patient's handwriting and drawing of spirals tends to be useful, and can help monitor the disease over time. The use of tremor severity scales as TETRAS can also be very helpful for monitoring of treatment benefit [13].

ET treatment is usually conservative in young patients, as the use of pharmacological agents is reserved for those with functional impairment and affectation of quality of life. There are no evidence-based guidelines for Pediatric ET treatment. Initial dose of propranolol is 1–2 mg/kg/day, and maintenance is up to 120 mg/kg/day, divided in 2 or 3 doses. Primidone initial dose is 12.5–25 mg per day, with slow incremental up to 250 mg per day. Topiramate might be another option. Deep Brain Stimulation surgery has been shown to be highly effective in adults with ET.

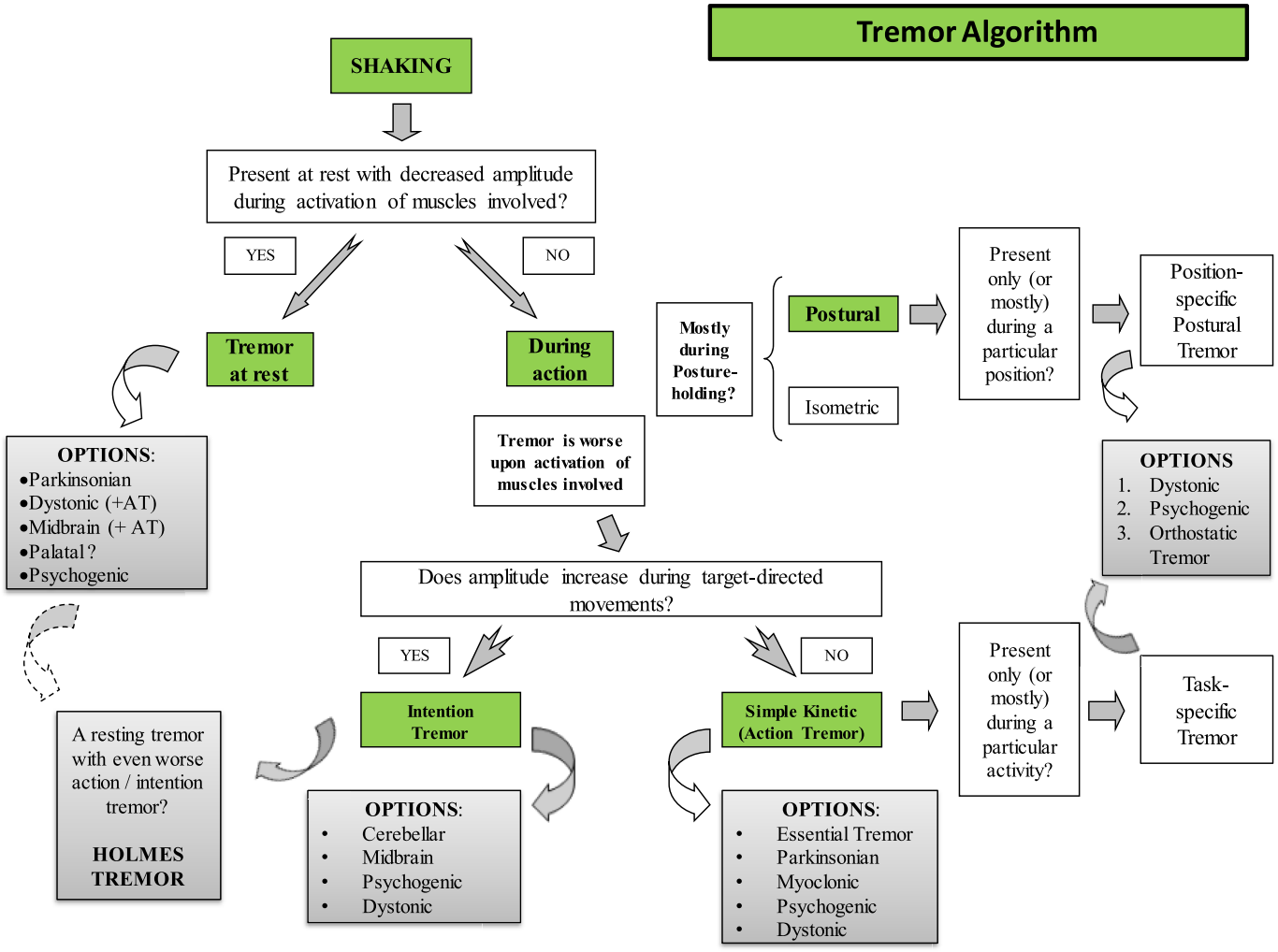

Fig. 1. Tremor clinical algorithm. (AT = Action Tremor).

5.2. Dystonic tremor

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures or both [11]. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation. The presence of tremor in a dystonic body part should alert the physician to the possibility of a dystonic tremors. Its differentiation from other action tremors is critical, as evaluation and treatment differs significantly. The newer classification of dystonia distributes them into Axis I –Clinical Characteristics-, and Axis II –Etiologies-, and allows for better recognition of specific dystonic syndromes [11]. Onset of dystonia during childhood is more likely to progress from focal to generalized, and therefore carries a differentiating prognostic factor from adult-onset dystonia [8].

Perhaps the most important feature in pediatric dystonia is the age of onset. Onset during infancy (birth to 2 years) can be associated with metabolic disorders, and therefore it is extremely important to perform a metabolic work-up. Among the tremor conditions that typical present during infancy, Tyrosine Hydroxylase deficiency is a very important one, as two of its forms (Dopamine responsive dystonia and infantile parkinsonism) can be treated with levodopa. In the United States and many other countries, the newborn screening includes a number of disorders that can produce dystonic tremor during infancy and early childhood, including Galactosemia and Glutaric Acidemia Type I.

Dystonic Cerebral Palsy has also an early age of onset, but clinicians have to be very careful before making this diagnosis, since many genetic disorders can present with early dystonia [14] DYT1 dystonia, an autosomal dominant disease with incomplete penetrance due to with a deletion on the *TOR1A* gene, has variable age of presentation. Although Dopamine-Responsive Dystonias caused by mutations in the gene *GCH1* tend to start between 2 and 6 years of age, late presentations are not uncommon, and therefore they need to be considered as part of the differential, chiefly due to its treatability (Table 4). Panthotenate Kinase-Associate Neurodegeneration can present with dystonic tremor and its age of onset is within the first decade in its classical form.

In contrast with many tremors, kids with dystonia usually need to undergo Brain MRI imaging. A levodopa trial should be tried in every patient with dystonia or parkinsonism. There are many genetic and other tests that are carried out in dystonia, but are not the focus of this review. Beyond levodopa, treatment of dystonias usually encompasses anti-cholinergic drugs, benzodiazepines, baclofen, chemodenervation and Deep Brain Stimulation surgery.

5.3. Resting tremor with parkinsonism

Parkinsonism is defined as the presence of bradykinesia/akinesia plus either resting tremor or rigidity. Most causes of parkinsonism in children come with multiple movement disorders [15]. Although in adult-onset Idiopathic Parkinson Disease tremor prevalence is high (about two thirds of the patients), resting tremor is rare in childhood parkinsonism. During the early ages, parkinsonism tends to be

Table 4
Never-miss disorders that can present with tremor.

Condition	Test to consider running	Comments
Thyroid disorders	TSH, T3, T4	Both hypo and hyperthyroidism have been linked to shaking.
Wilson Disease [21]	Ceruloplasmin, 24-hr urine copper	Any tremor type possible. In kids often the disease presents with liver dysfunction.
Dopamine-responsive Dystonia o Infantile parkinsonism due to Tyrosine Hydroxylase (TH) deficiency	Levodopa trial. Molecular genetic testing done to provide specific therapy	These two forms of TH deficiency respond to levodopa. Presentation is usually in infancy.
Dopamine-Responsive Dystonia due to *GCH1* mutation	Levodopa trial might serve as a screening test. Molecular genetic testing done to provide specific therapy	Usually resting or dystonic tremor, although postural and kinetic tremors possible.
Vitamin Deficiencies: Vit E	Vitamin E level, consider lipoprotein measurement	Can present with dystonia, ataxia, and/or action/ intention tremors
Vitamin Deficiencies: Vit B12	MMA and Homocysteine. Also B12 level.	Can present with ataxia, dystonia, neuropathy. Tremor is usually action or intention.
Zinc or Magnesium Deficiencies	Check levels	Mostly action and intention tremors
Structural lesions, including stroke, trauma, malformations and tumors	Imaging in the presence of any focal abnormality on exam (or by history), or if sudden onset, or suspect of trauma	Mostly action, midbrain, intention or dystonic tremors
Galactosemia [22]	Usually part of the newborn screening program (measuring Galactose-1-phosphate uridyltransferase activity in blood [23].	Ataxia, action and intention tremor.
Paraneoplastic Syndromes, including Cerebellar syndromes and anti-NMDA receptor Antibody syndrome	Paraneoplastic panel, imaging, spinal tap	Cerebellar syndromes present with large action and intention tremors. Anti-NMDA receptor has slow tremors usually.
Medications and street drugs (dopamine blockers, Valproic acid, SSRIs, anti-epileptics, stimulants, bronchodilators, anti-arrhythmics, etc) [24]	Urine drug screen, specific serum drug levels	Enhanced physiologic, action and intention tremors are most common. Dopamine blockers produce resting tremor and/or parkinsonism.
Infectious cerebellitis	CSF studies, usually VZV. Brain imaging. Consider in sudden onset.	Mostly action and intention tremor.
Pheochromocytoma	Serum and urine metabolic testing	Usually presents as enhanced physiologic tremor.
Glutaric Acidemia Type I	Usually part of the newborn screening program in most countries. Consider genetic testing	Treatment can prevent severe brain damage. Can present with macrocephaly.
Spinal Muscular Atrophy	SMA genetic testing	New treatments available. Hand tremors can be the presenting symptom.

associated more with dystonic and ataxic tremors, as it characteristically is seen in metabolic disorders and less likely in static encephalopathies. Also, DRD typically starts between 2 and 6 years of age (see above in *Dystonic Tremors*). DRD can be indistinguishable from Juvenile Parkinson Disease, and can include motor fluctuations and even dyskinesias [16].

Importantly, the presence of resting tremor should alert the pediatrician to the possibility of Juvenile Parkinson Disease, and drug-induced parkinsonism. Drug-induced parkinsonism is associated with dopamine blockers prescribed for either gastro-intestinal or behavioral indications, and is a fully reversible cause of tremors that should be always kept in mind. Juvenile Parkinson Disease (JPD) is usually genetic in nature, and the most common cause is an autosomal recessive mutation in the *parkin* gene, called PARK2. Structural, infectious and a number of neurodegenerative (Huntington Disease, Rett syndrome, Panthotenate Kinase-Associated Neurodegeneration, Niemann-Pick type C) and metabolic disorders (Fahr disease) can produce tremor and parkinsonism [8].

Management of JPD mirrors the same medications and strategies used for the management of adult Parkinson Disease, particularly due to the lack of prospective studies in the younger population. Levodopa, anticholinergics, dopamine agonists and inhibitors of dopamine catabolism are all used. JPD tend to be commonly associated with motor fluctuations and medication-induced dyskinesias. Although JPD responds well to levodopa, secondary parkinsonisms have a variable response. Initial carbidopa/levodopa dose is 1 mg/kg/day (of levodopa) and can be increased up to 15 mg/kg/day. The use of Deep Brain Stimulation in pediatric patients with parkinsonism has not been properly investigated at this point.

5.4. Enhanced physiologic tremor

Physiologic tremor is present in normal individuals, but its amplitude increases in some patients and can be a cause of worry for the parents. There are several factors that can enhance physiologic tremor. In the pediatric population, the use of excessive caffeine (commonly through sodas), lack of sleep and medications (bronchodilators) are common etiologies. Hyperthyroidism is also a treatable cause and should be ruled out particularly in the presence of weight loss, fatigue and heat intolerance. In kids with tremor, hypertension or labile blood pressures, pheochromocytoma should be considered. Although most common age of presentation is between 20 and 50 years, pheochromocytomas can present earlier.

The presentation of enhanced physiologic tremor can often be episodic in nature, particularly during adolescence. In this case, a request of the parents to videotape multiple tremor spells can be very useful. Treatment is based on avoidance of causal substances, and the use of Occupational Therapy.

5.5. Functional tremor

Functional Tremors are common in the pediatric population. Onset is usually sudden, and tempo tends to be episodic in nature. If constant, there can be unexplainable periods of normality. Functional Tremor tend to be associated with other functional neurological disorders including give-away weakness and non-dermatomal hypoesthesia [17].

Phenomenology is characterized by variability (of rate, amplitude, muscle involved and direction). A very important feature is the presence of distractibility (tremor changes amplitude or stops while distracted) and entrainability (tremor assumes the frequency of other volitional movements).

Diagnosis requires making sure that other etiologies are not plausible, and the presence of the characteristic clinical features mentioned above. Functional tremors tend to respond to treatment. The main initial therapeutic intervention is to give a clear diagnosis to the patient and family, explain that the condition is common, and that the

physician will monitor treatment closely. There are many forms of Cognitive Behavioral Therapy, Motor Re-training and Habit Reversal Therapies that have been successfully used to control these movements [18]. In the adult population, long term success has been reported in up to two-thirds of the functional movement disorders patients that undergo therapy.

Conflicts of interest

Dr. Torres-Russotto has been a consultant or a speaker for AbbVie, Adamas, Allergan, GKC, Ipsen, Lundbeck, Revance, Sunovion and Teva.

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