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REVIEW

Childhood restless legs syndrome

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BACKGROUND: The last 20 years witnessed increased medical awareness regarding restless legs syndrome (Willis-Ekbom disease) among adults and children. However, it remains underdiagnosed and undertreated. Diagnosis relies exclusively on the history described by patients in their own words. Children who cannot adequately describe their symptoms represent a difficulty. To circumvent this, *probable* and *possible* restless legs syndrome have been instituted as diagnostic alternatives.

OBJECTIVE: This review aims to emphasize to general Pediatricians that among children restless legs syndrome is not only common, but also has the potential to impair the quality of life of affected patients and their caregivers.

METHODS: We performed a search in the database of Medline-PubMed for articles dated from January 1, 2008 to December 31, 2013. Many relevant articles before 2008 were also studied. Key words used were: restless legs syndrome and/or restless legs syndrome children. The Google Scholar database and pages in Portuguese were also investigated. We also searched for the theme in various relevant textbooks. We have added our personal experience to published literature.

CONCLUSION: We observed that restless legs syndrome is common in children, and its diagnosis requires knowledge and intuition on the part of the Pediatrician.

KEYWORDS: Restless legs syndrome; Willis-Ekbom disease; Restless legs syndrome in children.

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INTRODUCTION

Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a common neurological disorder[1-3]. In accordance with the International Restless Legs Syndrome Study Group (IRLSSG)[2,3], RLS may be diagnosed with the following criteria: (1) symptoms of the disease occur when the patient is at rest; (2) patient feels an impetus to move the legs, which is most frequently accompanied by unpleasant paresthesias; (3) patient feels relief during movement; (4) condition occurs only at night or is worse at night[2,3].

The prevalence of RLS in Brazilian adults is 6.4%[4], but data for the Brazilian pediatric population are lacking. In population-based studies in the United Kingdom, the United States, and Turkey, prevalence in children and adolescents is 2–4%. Moderate-to-severe RLS is believed to range from 0.5–1% of the pediatric population[5-7]. Females predominate among adults, but in childhood boys and girls are equally affected[5-7]. Onset of symptoms prior to age 20 years is reported in approximately 40% of adults with RLS[5-7]. A positive family history is estimated to occur in more than 60% of adult patients[3]. Consequently, the presence of a first degree relative of a child suspected to suffer from RLS is extremely useful for diagnosis. A genetic link for RLS is commonly found and several genetic loci have been identified; however, a true "responsible gene" remains undiscovered[8,9]. The genetic presentation of RLS is believed to be autosomal dominant with variable penetrance. RLS is a common, complex, and treatable neurological condition that may severely disturb sleep and impact quality of life of the affected subjects. Significant variability in RLS severity is common, and active disease may be interspersed with remissions of variable duration[1-3]. The majority of RLS patients do not suffer from the disease in a severity that requires pharmacologic treatment[3].

RLS has been described as a sensorimotor disorder[2,3]. Regarding its motor component, some controversy exists: would the impetus to move characterize a motor disorder in itself or would this simply be a response to unpleasant leg sensations?[10]. Regarding the sensory part of RLS, a question must be addressed: Are RLS symptoms generated centrally or peripherally in the nervous system?[11]. A majority believe that the annoying RLS symptoms are generated inside the blood brain barrier. However, some claim that they are generated in somatosensory receptors deep inside the legs[12-19]. Some aspects of RLS pathophysiology still remain elusive[20-22]. Interestingly, elevated thyroid hormones levels (e.g., Grave's disease) remarkably increase the incidence of RLS symptoms[23-26]. Accordingly, it has been suggested

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that RLS symptoms are generated in prone subjects when thyroid hormone secretion is not sufficiently modulated by dopamine[27-30], a hypothesis termed "imbalance between thyroid hormone and dopaminergic system RLS pathophysiology"[31-38]. Adding uncertainty to the real causes of RLS, another well-founded theory points to an impairment of the diencephalon-spinal dopamine system as the derangement underpinning RLS pathophysiology[39-41]. RLS is more common or symptoms are more severe in iron deficient patients, and symptoms ameliorate when iron treatment is administered[2,3,10]. These facts imply that iron deficiency also plays a role in RLS pathophysiology[42-44].

One interesting aspect of RLS is that many drugs may worsen, or even initiate RLS symptoms, a fairly uncommon feature[45-48].

■ PERIODIC LIMB MOVEMENTS IN SLEEP AND CORRELATES OF RESTLESS LEGS SYNDROME

Periodic Limb Movements in Sleep (PLMS) consist of stereotypical, intermittent, and repetitive movements of the limbs that occur during sleep[49]. Up to 90% of the sufferers of RLS have such movements[49], which are considered to be a supportive criterion for diagnosis[2]. The concomitance between RLS and periodic limb movements in sleep is so great that it suggests a causal link between the two conditions, and our assumption is that both are engendered by the same mechanism: increased esthesia of the superficial and deep somatosensory receptors in the legs[10].

It is noteworthy that not only do many drugs worsen the severity of RLS, but also many clinical conditions increase the severity of existing RLS, or even trigger new RLS episodes. There are many medical conditions in this category, such as pregnancy, hyperthyroidism, diabetes, kidney failure, rheumatoid arthritis and some neuropathies[23,50-53].

■ RESTLESS LEGS SYNDROME DIAGNOSIS IN ADULTS

The diagnosis of RLS is entirely clinical. The criteria for the diagnosis of RLS was proposed by the IRLSG in 2003, and then modified in 2012[54,55]. Briefly, the five diagnostic criteria for diagnosing RLS in adults, or children that are able to express their symptoms confidently, are[54-57]:

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. The urge to move may present without uncomfortable sensations, and sometimes arms or other body parts are also involved.
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move or unpleasant sensations are worse or only occur in the evening or night. When symptoms are present during the day and worsen at night the condition is classified as severe.
5. Symptoms are not solely accounted for by another medical or behavioral condition.

The 2012 update arbitrarily defined "simplified and updated research criteria for **probable** and **possible** pediatric RLS"[58]. For **Probable-RLS**, the child meets all five essential criteria for RLS, except criterion 4. For **Possible-RLS**, the child is observed to have behavior manifestations of lower extremity discomfort when sitting or lying, accompanied by motor movement of the affected limbs. The discomfort is characterized by RLS criteria 2–5.

Some clinical findings frequently present are **supportive criteria** for the diagnosis of RLS[54]: A) a family history of RLS; B) a positive response to dopaminergic drugs; C) periodic limb movements during wakefulness or sleep as assessed with polysomnography or leg activity devices (actigraphy). In our experience, a positive response to dopaminergic drugs is the most practical and useful supportive finding to establish a RLS diagnosis.

The severity of RLS varies greatly, from very mild to very severe, from patients that notice the disease as a curiosity to subjects that have their quality of life seriously impaired. If a patient describes symptoms occurring at least twice a week, this is considered a severe condition[3]. RLS severity is often quantified using the international RLS severity rating scale, a validated instrument that has also been used as a therapeutic outcome measure[3]. Details are available in Allen[3]. This scale has been translated and validated into Brazilian Portuguese by Masuko et al[56].

Polysomnography is not necessary except to rule out another condition of poor sleep such as sleep apnea. However, for the differential diagnosis of periodic limb movement in sleep, a whole night polysomnography in a sleep laboratory is mandatory[2,17]. These periodic limb movements are sudden jerking leg movements that commonly accompany RLS. These are repetitive, highly stereotyped movements that typically involve extension of the big toe with partial flexion of the ankle, knee, and sometimes the hip[58]. Each movement lasts approximately 0.5 to 10 seconds and is repeated every 20 to 40 seconds, with a range of 5 to 90 seconds[57]. The movements typically occur in clusters lasting several minutes to an hour. The patient is usually unaware of these movements but they may be elicited from a bed partner. The prevalence of PLMS increases with age, and in the vast majority of patients it is identified with RLS during sleep laboratory evaluations. For those patients who are diagnosed with these periodic limb movements, but do not fulfill RLS criteria, or do not present other sleep disturbances, the diagnosis of PLM disorder (PLMD) can be made. However, if RLS symptoms are present, RLS diagnosis supersedes that of PLMD.

Criteria for the diagnosis of RLS in children were further developed in 2012 by a pediatric RLS expert panel in collaboration with the International Restless Legs Syndrome Study Group[58]. When a patient of any age is able to inform in his/her own words the above mentioned criteria, a diagnosis of *definite*[58] RLS is established. For those who are not able to express the typical RLS symptoms in their own words (small children or cognitively impaired adults), but do present a clinical condition resembling RLS the diagnoses of *probable*, and *possible* RLS have been instituted. Probable-RLS is somehow more likely to be present than possible-RLS[58]. Probable and possible, rather than definite RLS are more frequently diagnosed by pediatricians. Both for adults and children, the "supportive clinical conditions" are very important, and we maintain that a family history of definite-RLS is the most important of them. In our

experience, when (i) a child has a sleep disturbance, (ii) a parent with definite-RLS, and (iii) no other disturbance that can explain the child's poor sleep, possible-RLS should be diagnosed in the very least. If RLS cannot be found in a child's parent, a childhood RLS diagnosis is more difficult. The diagnosis of periodic leg movement in sleep for children follows the same criteria as for adults. For details, see Deak and Winkelman[59]. When the patient has a sleep disturbance and periodic leg movement without a history of RLS or any other sleep disturbance, PLMD should be diagnosed. In our experience, this is a very rare condition in children. Moreover, it should be noted that the treatment for PLMD and RLS are the same[59].

Some specifiers for the determination of the clinical significance of RLS in adults should be addressed as recommended by the IRLSSG[55] such as significant distress or impairment in social, occupational, educational, or other important areas of functioning by the impact on sleep, energy/vitality, daily activities, behavior, cognition, or mood.

CHILDHOOD RESTLESS LEGS SYNDROME

Some children (mainly pre and adolescents, boys or girls) are able to describe their symptoms in their own words so that definite-RLS can be diagnosed. However, the majority of children are unable to adequately express themselves, leading to probable and possible-RLS diagnoses. The advantage of this classification is that we can justify to parents the use of practical measures, (**not** necessarily pharmacological treatment) that relieve RLS symptoms and improve the sleep of the affected child. Such measures applied to probable or possible-RLS apply exclusively to the presence of sleep disturbance.

SPECIFIERS FOR CLINICAL SIGNIFICANCE OF THE CHILDHOOD OR ADULT RLS

As in adults, a significant impact on sleep, mood, cognition, and function is frequently found. However, impairment is manifest more often in behavioral and educational domains[58]. Some important considerations by experts in childhood RLS from IRLSSG have been made[59] regarding diagnosing definite-RLS in children.

COMMON PRESENTATION OF RESTLESS LEGS SYNDROME PEDIATRIC PATIENTS

The great majority of pediatric RLS patients present to the interview with a history of poor, restless sleep. Small children, infants, and pre-scholars may have difficulty initiating sleep, awaken frequently, and demand the presence of caregivers to initiate or to return to sleep. Parasomnias, as terror in sleep, sleep talking, and bruxism are frequent, but sleep walking is not so common under the age of three. Almost inconsolable crying is very common, and children are then frequently brought to sleep for the rest of the night with their parents. Parents then note extreme stirring, with such frequent kicking and position changing that the parents' sleep is greatly disturbed. In their cot, children frequently move their legs beating them against the grill with a loud noise. In a very typical movement, infants may raise both legs and beat strongly against the mattress, or continuously rub legs one against the other. Behavioral insomnia is frequent, and so are awakenings, which further complicate the parents' own sleep. These are frequently present with the typical symptoms of chronic sleep deprivation. It is our assumption that all patients diagnosed with childhood behavioral insomnia deserve a screening for RLS, and this comorbidity must also be correctly addressed by the health professional. It is interesting to note that the last fifth of the usual period of sleep of an RLS patient (children or adults) is very sound and has been termed "the grace hour"[60].

As a consequence of their poor sleep, children do not have an entirely normal day. Small children become agitated and sometimes even turbulent, and tantrum spells are frequent. Small children do not appear fatigued. Instead, they behave restlessly. Older children are difficult to wake up in the morning, and manifest long periods of sleep inertia. Fatigue is commonly stated by older RLS patients, mainly in the afternoon, and schooling frequently is mediocre. At all ages, inattention is common, and children may be mistaken as attention deficit and hyperactivity disorder sufferers, which is indeed more common in RLS patients than in normal children. We have observed that due to their sleep onset difficulty, children are prone to present with delayed sleep phase disorder as a comorbidity. Conflicts among parents and children are common, as parents believe that their children are lazy, mainly in their relation to school duties. Frequently, pediatricians are required to address abnormal day functioning of their patients because such sleep disturbances must be ascertained. If any of the possible three diagnoses of RLS is attained, the condition must be addressed, and outcomes of this measure are frequently very positive.

Comorbidities such as attention deficit hyperactivity disorder, depression, and anxiety occur more frequently in children and adults with RLS than in the general population. About one-quarter of individuals with RLS meet the criteria for attention deficit hyperactivity disorder[5,61]. Children with chronic kidney disease have an increased prevalence of RLS as compared with healthy children[62], similar to the findings in adults with chronic kidney disease[63]. In addition, children with sickle cell disease have an increased prevalence of symptoms of RLS, sleep disruption, and frequent periodic limb movements in sleep[64]. There is also evidence for an increased prevalence of periodic limb movement distress (PLMD) in children with migraine[65].

ANCILLARY STUDIES

Polysomnography has been previously discussed and should be performed if possible. Accelerometry (actigraphy) may be of value to reaffirm the presence of periodic limb movement[66].

Among the laboratory tests, studies of the iron status of subjects suspected of suffering from RLS is mandatory[59,60]. A hemoglobin evaluation and serum ferritin are extremely important. When red cell and hemoglobin studies do not demonstrate iron deficiency anemia, the patient may still have poor iron deposits that may represent an important etiological factor triggering the patient's RLS. When treated with iron, improvement or even cure of RLS is a possible outcome[2,3].

DIFFERENTIAL DIAGNOSIS

Several ailments may resemble childhood RLS, and are known as RLS mimics. The most common are positional discomfort, ligament sprain/tendon strain, positional ischemia (numbness), dermatitis, bruises, and growing pains. Less common mimics are leg cramps, arthritis, other orthopedic disorders, peripheral neuropathy, radiculopathy, myelopathy, myopathy, fibromyalgia, complex regional pain syndrome, drug-induced akathisia, and sickle cell disease. Having some cognizance of these medical conditions, it is not difficult to rule them out when a possible RLS is being studied, and when a face-to-face interview is undertaken. In epidemiological surveys, perhaps, these medical conditions may be confused with RLS. However a proper history and physical examination will solve doubts in relation to the correct diagnosis.

In our practice of almost ten years with emphasis on Sleep Medicine, we have learned that some medical conditions deserve comprehensive clinical studies when any of the three diagnoses of RLS is contemplated: infantile colic, childhood behavioral insomnia, childhood sleep apnea, attention deficit hyperactive disorder, epilepsy in sleep, Rolandic epilepsy, neuropathy, and occult gastro-esophageal reflux[58,60,61,69,70].

Curiously, in southern Brazil, gastro-esophageal reflux has often been mistakenly diagnosed as RLS. Not infrequently, due to their restless behavior, mainly during the night, small infants are thought to have occult gastro esophageal reflux. Infants cry during the night, and this is thought to be caused by acid reflux and consequently retro external pain. This is a generalized belief among many of the Brazilian pediatricians, although no evidence has been presented to support it. Furthermore, typical treatment for gastro esophageal reflux will not bring relief to the patient. On the contrary, the antiemetic drugs used frequently worsen RLS symptoms It is interesting to note that *occult* gastro esophageal reflux is extremely rare in children less than 2 years of age[71].

TREATMENT

Treatment for adult RLS patients is well standardized, but for children treatment is not quite so straightforward. However, for all patients some non-pharmacologic interventions are a *sine qua non* condition for achieving a good outcome: (i) Adequate sleeping habits, mainly going to bed in accordance with the patient's age and trying to get all the sleep the patient's age requires. (ii) Removal of television set, computers, smart phones, etc from the child's room is essential; these are detrimental for and may severely hamper good sleep hygiene. (iii) Avoiding excessive luminosity inside the house is important because intense indoor lights block liberation of melatonin by the pineal gland. Adolescents are particularly resistant to following healthy sleep habits, and are prone to have inconsistent bedtime hours on weekdays and weekends, an erroneous behavior impacting RLS[67]. (iv) Physical exercise should be encouraged: It has been shown to increase deep sleep in children, to improve RLS symptoms, and to be of benefit for mental health, especially depression[72-74]. (v) Caffeine is very harmful for the RLS patient and should be avoided[2]. (vi) Some medications, including sedating antihistamines, serotonergic antidepressants, and dopamine blockers (e.g. domperidone) can aggravate RLS[27]. Whenever possible these drugs should be avoided.

Massage applied onto the legs is very appreciated by many adult RLS patients. A specific type of massage for young patients developed by us has proven to be a valuable tool for calming down restless, crying babies diagnosed as possible-RLS, during the night. By a gentle gripping, at first the child's feet are gently kneaded three times. Immediately following this, the operator's hands move onto the child's legs, now positioning the grip in a manner that the palms of the hand are applied onto the calves of the baby and thumbs onto their tibias, and, again, gentle kneading should be applied three times. If the child's legs are long, this massage should be repeated onto the superior part of the legs. This same massage should be next applied to the infant's thigh; the operator should then return to the feet and repeat this procedure in the same sequence for some minutes. Most of the time infants respond favorably and calm down. If after at least three or four complete maneuvers the baby does not react favorably, this should be stopped. Effectiveness of this massage is one more evidence that RLS symptoms are generated in somatosensory receptors deep inside the legs because massage acts as a counter stimulus, in a way similar to the way moving the legs act when muscles compress somatosensory receptors.

PHARMACOLOGICAL TREATMENT

Iron therapy is indicated for every child whose ferritin levels are under 50–100 mcg/L if diagnosed with restless legs syndrome or PLMD, at least as a trial[67,75]. As mentioned above, iron is a cofactor for tyrosine hydroxylase enzyme, an enzyme participating in the limiting velocity reaction in the chain of reactions that start with tyrosine and conclude with dopamine production[10]. Although iron is widely used, some authors claim that there is no clear evidence supporting its use in RLS patients[76,77]. Nevertheless, treating many children with iron, we frequently notice improvement in RLS symptoms of the patient. Therapeutical iron dosing for iron anemia deficiency ranges from 3 to 6 mg/kg/daily to a maximum 150 mg daily of oral iron[78], usually twice a day. The most useful salt iron is ferrous sulfate[67]. Our preferred dosing is 4 mg/kg/twice a day. Greater dosing presents more gastro intestinal side effects. It should be used for 6 months and then ferritin levels should be re-evaluated. The pediatrician must be aware of the uncommon, however serious medical condition hemochromatosis[67]. It is interesting to prescribe the iron drops added to orange juice, or vitamin C, because it increases iron absorption[67].

Gabapentin is suggested as a first-line medication for children six years and older with RLS who require pharmacotherapy[67]. It has been shown to improve sleep quality and to reduce the sensory symptoms of RLS, and it is most useful when pain is also a complaint[67]. It is approved by the FDA as an anticonvulsant for children as young as three years. Many prefer gabapentin to dopamine agonists because of concerns about impulse-control issues with dopamine agonists (read below). One inconvenience with gabapentin that we have observed is residual sedation in the following day, a side effect that may be very troublesome. Because of this, we only use gabapentin when pain is a concern. Although uncommon, serious side effects with gabapentin do exist and the pediatrician must be aware of them[79]. Gabapentin, which is an analogue of GABA, inhibits

the excitability of the sensory neurons that convey messages to the cortex as do many other anticonvulsant drugs[10]. For children 6 to 12 years of age, begin gabapentin at 100 mg, one-half to one hour prior to bedtime, and increase after every one to two weeks by 100 mg, until symptoms are suppressed or to a maximum of 600 mg[67]. For children older than 12 years of age, begin gabapentin at 200 mg, one-half to one hour prior to bedtime, and increase after every one to two weeks by 100 mg, until symptoms are suppressed or to a maximum of 900 mg[67].

Clonazepam is the most used single benzodiazepine drug in children with RLS[67], and we have observed good results with it in small children (8 months to 2 years). For children older than 2 years, we have been using hypericum perforatum as our first choice for treatment (read below). Effective dosages range from 0.250–0.500 mg, daily, 1 or 2 hours before bedtime. Several pediatric case series have reported benefit with benzodiazepines for RLS and PLMD[67]. Although the possibility for next-morning "hangover" sedation should be monitored, we, as other authors[67], have found this to be uncommon in RLS/PLMD pediatric patients. Not so uncommonly, some patients present a paradoxical alerting reaction which is the most common adverse effect[67], precluding its use for these patients. It is believed that clonazepam is better suited for patients that present anxiety as comorbidity to RLS. We found clonazepam extremely useful for patients where "sleep is terror" is a prominent feature of the sleep disturbance of the affected RLS patient.

Clonidine, which is an alpha-2 adrenergic agonist, was developed for the treatment of hypertension, but was subsequently found to help attention deficit hyperactivity disorder and sleep onset in children. The beneficial effects of clonidine on RLS symptoms highlight the importance of the connection between the sympathetic system and the thyroid/hypothalamic axis. The sympathetic system has nerve projections to the thyroid gland and induces thyroid hypothalamic release[33]; when excessive, this may cause imbalance between thyroid hormones and the neurohormone DA. Clonidine targets the enhanced functioning of the SS, which makes it a useful drug for alleviating RLS symptoms that are occasionally generated in response to an exacerbation of the SS tonus[27]. It is the most commonly used prescription medication for sleep in children[67], and is particularly useful when there are severe sleep onset problems in pediatric RLS patients. However, because clonidine has a relatively short duration of effect, it may not be effective for problems with sleep maintenance[67]. Adverse effects include vivid dreams or nightmares, which are dose-related and which occur in about 5 percent of children treated with clonidine. Because of a risk for rebound hypertension, clonidine should not be stopped abruptly[67]. For children 6 to 12 years of age, an initial dose is 0.05 mg, one-half hour prior to bedtime. The dose can be sequentially increased every three to seven days in 0.05 mg/day increments, until sleep onset is improved or until a maximum of 0.3 mg per dose is reached[67]. For children older than 12 years of age, an initial dose is 0.1 mg, one-half hour prior to bedtime. The dose can be sequentially increased every three to seven days in 0.1 mg/day increments, until sleep onset is improved or until a maximum of 0.4 mg per dose is reached[67].

Dopamine agonists, pramipexole or ropinirole, are considered first-line medications for adults with RLS/PLMD, and multiple published studies have shown that they also are effective for pediatric RLS[2,3]. They are considered valid medications for children with definite, moderate-to-severe RLS who have failed to respond to other treatments[67]. However, in adults, dopamine agonists have been associated with augmentation (paradoxical worsening of RLS sensations)[2,3,79] and with problems with impulse control, such as pathologic gambling and hypersexuality[67]. Considering these severe potential side effects, we rarely use dopaminergics (our experience is only with pramipexole) When we do use them, we monitor the children carefully for augmentation and changes in behavior. With adolescents, pramipexole must be very carefully controlled. Pramipexole should be given two or three hours before the RLS symptoms start, which is usually in the evening. We initiate treatment with this drug at 0.125 mg once daily, and we never increase dosage. If 0.125 is not effective, we discard it altogether. Only, and rarely, for adults have we found reason to increase the pramipexole dose to 0.250 mg daily.

Saint John's wort is an herbal inducer of the cytochrome P4503A4 isoform and is devoid of serious side effects[81]. It has been used as treatment for adult RLS or childhood RLS[27]. It is a standardized extract of hypericum perforatum used to treat mild to moderate depression in adults and children older than six years of age. The usual adult dosage is 300 mg three times daily. It is considered to be a fairly safe drug[80]. It is an inducer of the CYP3A4 isoform[81], and is also believed to be a mild reuptake inhibitor of the monoamines dopamine, norepinephrine, and serotonin[80]. Saint John's wort acts as a ligand for the nuclear pregnane X receptor to enhance the expression of CYP4503A4 and also stimulates the expression of P-glycoprotein (Pgp)[81], which may result in decreased uptake of many xenobiotics and compounds, including TH. It is known that CYP3A4 and Pgp are coexpressed in many tissues, mainly in the liver and intestinal wall[82]. In 2013, we published an open label pilot trial with SJW and treated 21 patients of whom 17 improved entirely from their RLS and also their poor sleep. Since then, we have been using it as our first choice for adults and children older than 1 year of age. The results have been good as more than 84% from already treated 36 adults and 11 children (unpublished data) responded positively to treatment. Those patients that did not respond were then effectively treated with pramipexole (adults), or clonazepam (children younger than 6 years of age). Thus far, only one adult patient presented with a side effect, sun photosensitivity, that indicated suspension of the drug. Saint John's wort diminishes the level of circulating thyroid hormones and is also a mild dopaminergic agent, this being the rationale behind its use. For adults, we prescribe it at a dose of 600 mg daily for five days, and thereafter 300 mg daily for another 5 days. Within these ten days of treatment, the patient decides whether he wishes to stop or continue using the drug, depending on how successful it appears to him/her. However, maintenance of treatment should be encouraged, that is, the patient is persuaded to take a few drug-holidays and to return to the treatment only if and when symptoms reappear. A lapse of time that has been varied from 2 to 8 days has been typical in our experience. The drug should be taken 2 or 3 hours before bedtime. For children, we prescribe Saint John's wort at a dose from 160 mg (initially) daily, and if the results are not good, the dose may be increased to the maximum of 240 mg daily. For children older than 6 year of age, we start with 300 mg daily and do not increase. If the child does not respond, clonazepam is the alternative, and if this drug fails, gabapentin or pramipexole should be tried.

Combination therapy: in refractory or severe cases of RLS, it is essential as a first step to assess for possible alternate diagnoses or comorbidities, as for instance, iron depletion, and for compliance with nonpharmacologic and pharmacologic therapies. If this reassessment does not lead to an alternate approach, it is worthwhile to a try a combination therapy of a dopamine agonist and a medication that will consolidate sleep, such as gabapentin. Gabapentin is also very effective in conditions where pain persists as a great problem. An alternative combination is clonidine (for sleep onset), with gabapentin and clonazepam (for sleep maintenance). If children with attention deficit and hyperactivity disorder are treated with stimulants, their effects will have worn off by bedtime and should not impair sleep by themselves[68]. Children with attention deficit and hyperactivity disorder *and* RLS may receive clonidine as a sleep onset aid together with other more specific treatment for RLS, as SJW or pramipexole. Children (mainly adolescents) with a depressed condition as a comorbidity with RLS may benefit from a greater Saint John's wort dose, 600 to 900 mg daily, twice or thrice a day. For a serious depressive syndrome, bupropion should be the drug chosen as it does not worsen RLS as SSRI does[67].

CONCLUSION

RLS is common in pediatric practice. In the great majority of cases, it is underdiagnosed and undertreated This is a great concern as it has the potential to seriously impact general health and the quality of life of the affected children, and also of their families. RLS may be simply diagnosed and treated by the general pediatrician, and only the most severe cases are to be referred to the specialist.

CONFLICT OF INTEREST

The authors declare no conflict of interest

RESUMO

TEMA: Os últimos 20 anos testemunharam maior conscientização médica sobre síndrome das pernas inquietas (doença de Willis-Ekbom) entre adultos e crianças. No entanto, permanece uma entidade mórbida subdiagnosticada e subtratada. O diagnóstico baseia-se exclusivamente sobre a história descrita pelos pacientes em suas próprias palavras. Crianças que não podem descrever adequadamente seus sintomas representam uma dificuldade. Para contornar isso, instituíram-se, como alternativas diagnósticas, síndrome das pernas inquietas provável e possível.

OBJETIVO: Esta revisão tem como objetivo enfatizar a pediatras gerais o conceito de que, entre as crianças, síndrome das pernas inquietas não é apenas comum, mas também tem o potencial de prejudicar a qualidade de vida dos pacientes afetados e de seus cuidadores.

MÉTODO: Foi realizada na base de dados do Medline-PubMed uma busca de artigos datados a partir de 1 de Janeiro de 2008 até 31 de dezembro de 2013. Artigos relevantes anteriores a 2008 também foram levantados. Palavras-chave utilizadas foram: "restless legs syndrome and/or restless legs syndrome children". O banco de dados e páginas em Português Google Scholar também foram investigados. Procuramos o tema também em vários livros de texto relevantes. Adicionamos nossa experiência pessoal à literatura publicada.

CONCLUSÃO: Observou-se que a síndrome das pernas inquietas é comum em crianças. e seu diagnóstico requer conhecimento e intuição por parte do pediatra.

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