

Accepted Manuscript

Review Article

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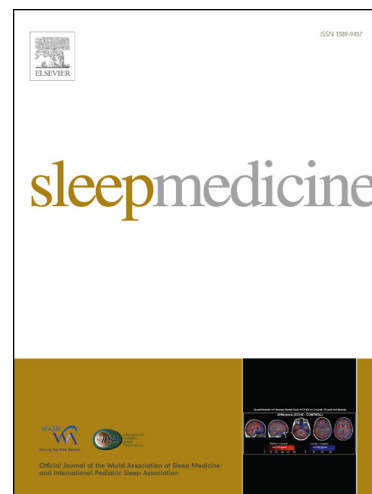
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PII: S1389-9457(13)01108-8

DOI: <http://dx.doi.org/10.1016/j.sleep.2013.07.013>

Reference: SLEEP 2253

To appear in: *Sleep Medicine*



Please cite this article as: Walters, A.S., Gabelia, D., Frauscher, B., Restless legs syndrome (Willis-Ekbom disease) and growing pains: are they the same thing? A side-by-side comparison of the diagnostic criteria for both and recommendations for future research, *Sleep Medicine* (2013), doi: <http://dx.doi.org/10.1016/j.sleep.2013.07.013>

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Review Article

Restless legs syndrome (Willis-Ekbom disease) and growing pains: are they the same thing? A side-by-side comparison of the diagnostic criteria for both and recommendations for future research

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Keywords: Growing pains, Restless legs syndrome, genetics, dopamine, anticonvulsants, Vitamin D, Pediatrics, childhood, adolescence

Abstract

There has been no previous side-by-side comparison of the diagnostic criteria for restless legs syndrome (RLS)(Willis-Ekbom disease) and growing pains. In our review, we explore this comparison emphasizing overlaps and disconnects, summarize recent literature exploring the relationship between the 2 entities, and make suggestions for future research.

There is considerable overlap in the diagnostic criteria for childhood RLS and growing pains. The literature also indicates that RLS and growing pains more commonly occur together than one would expect based on chance alone, and the family histories of RLS and growing pains often are overlapping. Leg rubbing to obtain relief from leg discomfort is common to both disorders, though walking to obtain relief seems unique to RLS. Childhood RLS also has been reported to be painful in up to 45% of cases.

The development of standard diagnostic criteria is necessary to move forward in the field of growing pains research. A quantitative and validated rating scale for growing pains severity already exists. Because of the clinical and genetic similarity between RLS and growing pains, studies that parallel those previously performed in RLS patients are recommended for growing pains patients. For example, a genome wide association study in growing pains patients of all possible genes with particular attention to those identified as related to RLS and a therapeutic trial of medications known to be effective in RLS would be welcome. Abnormalities in vitamin D metabolism also may be common to both disorders.

1. Introduction

To our knowledge, a side-by-side comparison of the diagnostic features of restless legs syndrome (RLS)(Willis-Ekbom Disease) and growing pains has not been previously performed.

The primary goal of our review was to perform such a comparison, emphasize overlaps and disconnects, summarize recent literature suggesting an overlap between the 2 disorders, and make recommendations for future research. We have reviewed the relationship between RLS and growing pains in the past [1]. In the intervening 10 years much new information has been obtained, which will be summarized in our review. Except in select circumstances relevant to our goal, older literature will not be included and we will refer to our previous review [1].

2. Literature search

A literature search on PubMed was performed for articles that defined the clinical characteristics of growing pains alone, RLS alone, and those that explored the relationship between the 2 entities. A variety of terms were arbitrarily selected and employed for the search, but the terms *growing pains in children*, *growing pains in children*, AND *diagnostic criteria* as well as *growing pains* AND *restless legs syndrome* uncovered more articles relevant to achieving the a priori goals of determining the present status of diagnostic criteria for growing pains and evaluating the current literature exploring the relationship between growing pains and RLS. A search was done using the term *growing pains in children* for all articles from January 2001 to March 2013, and the titles of 360 references were reviewed. Sixteen of these articles were considered to be of possible relevance to the stated a priori goals, and therefore the articles were further reviewed. An additional search also was done for literature subsequent to 2001 combining the terms *growing pains in children* AND *diagnostic criteria*. We found 27 articles, and 11 of which were reviewed for further relevance in accord with our primary goals. In addition, a search was done for literature subsequent to 2001 combining the terms *growing pains*

AND *restless legs syndrome*. We found 19 articles, and 14 of which were considered to be possibly relevant to our goals. Further articles were obtained in attempt to achieve the aforementioned goals from a complete review of the reference list of all of the articles obtained for relevance. Articles published before 2001 were not included in the review except when their historical importance was apparent, per the opinion of the first author (AW).

3. Diagnostic criteria

3.1. *Criteria for RLS*

Recently, the diagnostic criteria for childhood RLS have been merged with those of the adult criteria, so that the 2 entities are identical [2-4]. For a diagnosis of definite RLS the subject must be able to describe the symptoms of RLS in their own words. The criteria for childhood RLS include (1) an urge to move one or both legs usually but not always associated with leg discomfort that may or not be painful; (2) the symptoms are worse later in the day or night; (3) the symptoms are worse at rest (i.e., sitting, lying); and (4) there is at least partial and temporary relief by activity such as walking or moving around in bed; and (5) in addition, it has recently been appreciated that some subjects can superficially meet all of the previous criteria for RLS but have another disorder instead of RLS, such as leg cramps or positional discomfort. These disorders should be excluded by further patient questioning [2-4] (Table 1).

3.2. *Criteria for growing pains*

In contrast to RLS, there is no unified definition for growing pains. Two groups of authors have attempted to actually enumerate diagnostic criteria for growing pains [5-8] (Table 2). Both groups stated that their diagnostic criteria were adopted from that of Peterson [9,10]. However, the 2 groups come up with somewhat different diagnostic criteria (Table 2). Part of the reason for this difference is that Peterson did not actually provide diagnostic criteria with enumeration of inclusion and exclusion criteria, but instead he offered a general description of the disorder. Peterson actually said:

Through the years, *growing pain* has gradually been defined. It consists of intermittent, often annoying pain or ache, usually localized in the muscles of the legs and thighs. The pain or aching may be associated with a feeling of restlessness. The most common sites of pain are in the front of the thighs, in the calves and behind the knees. The groin is sometimes affected. The pains are deep and localized in areas outside the region of the joints. Pain in the joints requires detailed investigation to rule out rheumatoid or intra-articular conditions. The pain is typically bilateral, which is an important differentiation from serious causes of pain in the limbs, which are usually unilateral. The pains usually occur late in the day and in the evening, although they may have their onset at night and awaken the child from sleep. When the child awakens in the morning, the pain has disappeared. The pains typically occur in children and young adolescents, but they may commence in early infancy and disappear once the child reaches maturity. In older children, the pain may resemble what adults more accurately describe as cramps in the legs, creeping sensations, or restless legs. However, Ekbom makes sharp distinctions between growing pains and restless legs. Growing pains may be accentuated by increased running during the day. Pain from fatigue may occur with or without excessive physical activity in children. Its character resembles the condition designated growing pains, but in contrast to growing pains, the pain of fatigue disappears after rest. Growing pains are not associated with limping or limited mobility. The case history does not indicate local trauma or infection. The pain is not associated with local tenderness, erythema, or swelling. There is a lack of objective findings. Results of physical examination, laboratory studies, and roentgenograms are normal [9,10].

3.3. Working group combined criteria for growing pains

Because there are no contradictions between the diagnostic criteria provided by Evans and Scutter [5-7] and those provided by Champion et al, they have both been combined in Table 2 [8]. However, Champion et al [8] lists any 3 of his first 4 criteria as being essential for the diagnosis of growing pains. In addition, they mention mention age of onset and duration of symptoms as part of their diagnostic criteria but Evans and do not [5-7]. On the other hand, Evans and Scutter mention the bodily distribution of the symptoms as part of their diagnostic criteria but Champion et al do not [8] (Table 2). A review of the other growing pains literature showed that other authors used incomplete forms of the much more detailed criteria for growing pains established by Evans and Scutter [5-7] and Champion et al [8]. It should be emphasized that our review was only an initial attempt at establishing a unified set of criteria for the diagnosis of growing pains and was strictly done for comparative purposes to RLS. The true establishment of universally agreed on criteria will depend on a consensus of growing pains researchers.

3.4. Overlap of the criteria for RLS and growing pains

All 10 of the criteria listed in Table 2 are typical of RLS with 2 exceptions. The first exception is that growing pains are thought to be strictly bilateral, whereas RLS can be seen bilaterally or unilaterally [11-20]. In addition growing pains are identified as being strictly painful, whereas a variety of different types of leg discomfort are seen in RLS including pain, which is not an uncommon presentation in RLS. Rajaram et al [12] reported a series of 10

children with true RLS who were originally misdiagnosed as having growing pains. The reason for this misdiagnosis was that the RLS was described as painful. In another series of 33 RLS children [21], 55% of patients reported their symptoms as nonpainful, but up to 45% of the children described their symptoms as painful. On the other hand, a nonpainful form of growing pains also has occasionally been identified [22], and Pavone et al [23] found that 20% of the growing pains subjects in their study sample actually had unilateral symptoms suggesting some form of overlap between growing pains and RLS.

With the exception of one report of which we are aware, the topography of the leg discomfort in RLS or growing pains has not been formally studied [24]. Although not formally studied, identities between RLS and growing pains from comparing clinical series reports are as follows (Fig. 1): (1) the age of onset of childhood RLS is similar to that of childhood growing pains; (2) the nighttime predominance of RLS is well-documented in the literature in RLS of the idiopathic or familial type and nighttime also is the predominant time for growing pains symptoms; (3) there is no limitation of activity or limping in either condition; (4) RLS and growing pains discomfort can commonly be found in the anterior thigh, calf, and posterior knee and many times are felt coming from deep inside the muscles; (5) symptoms frequently are intermittent with days or weeks without leg discomfort, especially when the symptoms first begin in both disorders; (6) the physical and neurologic examination in RLS reveals no abnormalities with the idiopathic or familial form of RLS, which is the most frequent type seen in childhood and the physical and neurologic examination in growing pains, also reveals no abnormalities; (7) there is no laboratory evidence of joint or orthopedic problems in either disorder; (8) symptoms often last more than 3 months in both disorders; and (9) there is no associated lack of well-being except for the RLS or growing pains itself [11-20,24] (Fig. 1).

On the other hand, the urge to move the legs and get up and walk around to relieve leg discomfort, which is the primary feature of RLS, is not observed in growing pains (Fig. 1). In addition, we also do not see relief by activity as a component of the diagnostic criteria for growing pains (Fig. 1). Growing pains pain patients typically rub their legs rather than walk around to provide relief of discomfort [5-8]. However, one could argue that the symptomatology of growing pains is not so discrete in this regard, as it is common for RLS patients to rub their legs or provide counter stimuli to relieve their leg discomfort in addition to walking [11-20]. In one study of children and adolescents with RLS, 42% of subjects reported walking, 33% reported rubbing their legs, 27% reported stretching their legs, 24% reported kicking their legs, and 12 % reported running or exercising to obtain relief of their RLS symptoms [21].

Although both disorders are said to be worse at night, it is not clear if growing pains symptoms are worse at night because the patients are lying down, thus fulfilling the RLS criteria of worsening at rest, or if they are worse at night because of a circadian factor, thus fulfilling the RLS criteria of worsening at night. In RLS, studies have suggested that both factors are operative, thus justifying the maintenance of the separation of the worsening at rest and worsening at criteria for RLS [25-27] (Fig. 1).

4. Recent studies examining the relationships of RLS and growing pains

The results of the studies on the relationship between growing pains and RLS are summarized in Table 3. In our original case reports of childhood RLS in 2 pedigrees, we noted that some of the children had growing pains in addition to RLS [17]. This finding inspired us to do a historical review of the potential links between growing pains and RLS published in 2002

[1]. Since the publication of the 2002 review, there have been 9 additional studies exploring this relationship [8,11-15,18-20].

In a prospective study by Bassetti et al [15] of 55 consecutive RLS patients, a history of growing pains was more frequent in those with onset of RLS <20 years (27% [4/15]) as opposed to those with age of onset >20 years (3% [1/40]; $P=.005$) [15].

In a survey of 866 children from 2 community-based general pediatric clinics where children were screened for symptoms of attention-deficit/hyperactivity disorder (ADHD) and associated features, odds ratios (OR) for RLS and for growing pains were separately calculated. There was an identical 1.9 greater OR of having either disorder if ADHD symptoms were present. However, the OR for the association of growing pains with ADHD was statistically insignificant (OR, 1.9 [95% confidence interval {CI}, 0.9–3.6]), whereas the OR for the association of RLS with ADHD was statistically significant (OR, 1.9 [95% CI, 1.1–3.2]). The association between growing pains and RLS was not directly tested. Thus the experimental design and the results of this study did not indicate any relationship between growing pains and RLS [13].

In 2004 Rajaram et al [12] made the point that growing pains could be a misdiagnosis for RLS. In that study, we noted that 10 of 11 children with a diagnosis of growing pains actually met criteria for RLS. The fact that childhood RLS was much less appreciated by the medical community than growing pains may have accounted for this result.

In a study by Gamaldo et al [20] in which 973 relatives of RLS patients were screened for RLS and other associated factors, the OR for the association of a childhood history of growing pains with RLS was statistically insignificant in women (OR, 1.59 [95 % CI, 0.99–2.56]) and in men (OR, 0.75 [95% CI, 0.37–1.50]). Thus this large study also did not indicate any relationship

between growing pains and RLS. This study was a retrospective study of adults [20], but the authors did try to overcome this bias by also interviewing the mothers of the respondents about the symptoms of the respondents in childhood. However, the primary respondents were middle aged and the mothers were presumably at least 20 years older, making recall bias an inherent part of the experimental design [20].

In a large survey of 10,523 families in which parents were asked about the symptoms of RLS and other associated factors in their children, Picchietti et al [11] reported that growing pains were significantly more prevalent in children with RLS than in those without RLS (80.6% vs 63.2%; $P < .001$). The fact that the question on growing pains in this study merely asked if the children had ever had any symptoms of growing pains and did not ask if the symptoms were past or present, major or minor, bothersome or nonbothersome, or frequent or infrequent, may account for the high numbers in both groups.

In a survey of all patients in a pediatric practice with childhood RLS, Picchietti and Stevens [19] reported that 55.5% (10/18) patients had a history of growing pains. In this study, the presence of recurrent limb discomfort was added to the definition of growing pains to assure a more accurate diagnosis. However, the diagnosis was primarily parent dependent and most of the children could not retrospectively recall the growing pains in remarkable detail [19].

In a case control study of pregnant women, Balendran et al [14] reported that 22.5% of 211 women had RLS. A history of growing pains more frequently was reported by the pregnant women with RLS (17.02% [8/47]) than the pregnant women without RLS (6.71% [11/164]; $P = .042$). Similarly, a family history of growing pains and a family history of RLS were more common in pregnant women with RLS than in pregnant women without RLS ($P = .025$ and

$P=.018$, respectively). The authors concluded that “RLS in pregnancy is predicted by family history of RLS and growing pains and by childhood history of growing pains” [14].

In a prevalence study of RLS in Turkish children and adolescents, Turkdogan et al [18] conducted a cross-sectional population study of 4346 students in 3 primary and 4 high schools using random selection methods. A questionnaire was administered to the children, and those who were suspected to have definite RLS were then further screened in a subsequent personal interview with an expert. The families of those personally interviewed were then administered another questionnaire. Definite RLS was present in 2.74% ($n=119$) of the subjects. Growing pains were reported in 54.5% of the subjects with definite RLS. Thirty percent of the subjects experienced growing pains 1 to 3 times per month, 15% less than once per month, and 9.5% once or more per week [18].

Older and more recent studies have suggested a genetic overlap between the two disorders and a family history common to both disorders [8,22] (Table 3). Although Ekbom [28] was the most recognized and well-published investigator of RLS in the mid-20th century, he only performed a small family study of a mother and her 3 sons investigating the relationship between RLS and growing pains and concluded that there was no relationship. However, Brenning [22], a contemporary of Ekbom, took these results much deeper and came to the opposite conclusion in an investigation of *molina crurum nocturna* (MCN), including restless legs [22]. Although this study is an older study which was previously reviewed, it is re-reviewed here due to its large size and important historical significance [1,22]. Brenning [22] identified MCN as “leg discomfort” which is precipitated by “sitting still, especially in the evening, and/or nightly horizontal position.” Notably, these descriptors are diagnostic features of our current definition of RLS [4]. Of 112 growing pains children with leg discomfort, only 12 had

exclusively daytime symptoms. The other 100 children had “leg troubles during the night and/or while sitting still in the evening.” Seventeen percent of children had discomfort that was never painful. Some growing pains children had creeping sensations suggestive of RLS; some had a sensation of cramps which were occasionally experienced in RLS patients, even though they had no spasm. Growing pains were experienced by one or both parents in 51% of growing pains children, in contrast to 12.5% of children without growing pains. Forty seven percent of one or both parents had adult MCN symptoms if they had a child with growing pains, but only 19.7% of one or both parents had adult MCN symptoms if they had a child with no growing pains. In addition, the prevalence of adult MCN was 39.7% in parents who had experienced growing pains as a child compared to only 12% in parents who had not experienced growing pains as a child. Leg discomfort was found in 45.4% of children who had parents with adult MCN compared to only 16.7% of children who had parents without adult MCN.

Using different methodology, Champion et al [8] came to remarkably similar conclusions as Brenning [22]. In a twin study, 73.5% of monozygotic twins had concordant growing pains compared to only 22.2% of dizygotic twins indicating a familial tendency for growing pains. Furthermore, 70% of all twins with growing pains had at least one parent with growing pains. Significantly more twins with concordant growing pains also met the criteria for RLS (18%) than twins with discordant growing pains (2%) ($P=.01$). When at least one twin had growing pains, 51.5% of mothers, 42% of fathers, and 50% of siblings had a history of growing pains; and 40% of mothers, 24% of fathers, and 18% of siblings had a history of RLS [8].

5. Conclusions

RLS and growing pains are both common disorders, with criteria for definite RLS met by 1.9% of children ages 8 to 11 years and 2% of children and adolescents ages 12 to 17 years [11]. The prevalence of growing pains widely varies from study to study, but conservative estimates suggest a prevalence of 4.7% [9]. This prevalence emphasizes the importance of exploring the relationship between these 2 commonly bothersome disorders, given their similarities. There is considerable overlap between the diagnostic criteria for RLS and growing pains; the 2 conditions more commonly occur together than one would expect based on chance alone, and the family histories of RLS and growing pains often are overlapping. Further studies exploring these similarities are warranted. Although the diagnostic criteria for RLS are standardized and universal [2-4], this is not the case for growing pains as different criteria are employed by various investigators [5-8]. To more accurately define the relationship between RLS and growing pains, standardized universally agreed on criteria for the diagnosis of growing pains also need to be established. Once standardized diagnostic criteria have been established for growing pains, a genome wide association study of all genes with particular attention to those genes identified as related to RLS should be performed in growing pain children. The genes include the BTB [POZ] domain containing 9 gene, *BTBD9*; the Meis homeobox 1 gene, *Meis 1*; the mitogen-activated protein kinase 5/LBXCOR1 homolog (mouse) genes, *MAP2K5/LBXCOR1*; and the protein tyrosine phosphatase, receptor type, D gene, *PTPRD*) [29,30]. It is possible that RLS and growing pains are different phenotypic expressions of the same disorder, as has been previously noted even within the RLS group itself [31]. Because of the clinical and genetic similarity of the 2 conditions, a therapeutic trial of medications known to be effective in RLS such as dopamine agonists or α 2- δ ligand anticonvulsant medications also are recommended in growing pains patients [32,33].

Medication regimens could be developed on an on-demand basis for intermittent need or for more regular treatment when symptoms are frequent and severe, as needed by the patient. A similarity in therapeutic response for RLS and growing pains would not only be helpful to growing pains patients, but also might suggest a biochemical basis common to RLS. A severity rating scale for growing pains has already been developed and validated [6]. Such an instrument is a key approach in evaluating therapeutic response. Such instruments also have been developed for the assessment of RLS symptoms in adults and children, and this has been validated in the case of the adult scale [34,35]. Based on the therapeutic response of RLS to dopaminergic agents, several studies with different methodologies have investigated the role of dopamine in the pathogenesis of RLS [36]. It would be interesting to also perform similar studies in growing pains children. Polysomnographic studies to determine if growing pains children also have the repetitive involuntary kicking movements in sleep (periodic limb movements in sleep) seen in RLS children would help to determine if there is greater clinical similarity and genetic similarity between the two conditions by implication [2]. In addition to the cross-sectional, retrospective, and observational studies already mentioned, longitudinal prospective studies are needed to determine to what degree growing pains truly disappear in childhood. These longitudinal studies also are needed to determine if childhood growing pains ever return and if they are ever transformed in to some other disorder including RLS. Other studies of interest would be circadian rhythm studies in growing pains patients similar to those performed in RLS to determine if children with growing pains have worse symptoms at night because they are at rest (i.e., lying down), or if the biologic or circadian clock also plays a role in triggering symptoms [25-27]. Vitamin D is said to be deficient in both disorders [37,38] and vitamin D-binding

protein is increased in the cerebrospinal fluid of RLS patients [39]; therefore, further exploration of the role of vitamin D in both disorders also is warranted.

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Table 1

Diagnostic criteria for adult and childhood restless legs syndrome—Modified from Allen et al [2].

Essential diagnostic criteria for RLS (adults)

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs
 2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down 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 in the evening or night than during the day, or only occur during the evening or night
 5. Conditions such as positional discomfort and leg cramps
-

that meet all 4 criteria for RLS but are not RLS should be excluded

by asking additional relevant questions preferably during a personal patient interview.

Definite childhood RLS

1. The child meets all 4 essential adult criteria,

And

2. The child relates a description in his or her own words that is consistent with leg discomfort.

Abbreviation: RLS, restless legs syndrome.

Table 2

Growing pains criteria modified from Evans and Scutter [2] (left) and growing pains criteria modified from Champion et al [8] (right) and combined (center).

Features not shared in common with both sets of diagnostic criteria are shown in white.

Modified from Evans and Scutter [5,6]	Combined growing pains criteria	Modified from Champion et al [8]
Pain is intermittent and not persistent and there are some pain-free days and nights without increasing intensity	1. Pain in both legs	Pain in both legs
The pain is bilateral and not unilateral	2. Pain starts between the ages of 3 and 12 years	Pain starts between the ages of 3 and 12 years
The pain is in the anterior thigh, calf, and posterior knee and is felt in the muscles not in the joints	3. Pain typically occurs at the end of the day or during the night. Pain is not a problem in the morning	Pain typically occurs at the end of the day or during the night. Pain is not a problem in the morning
The onset of the pain is in the late afternoon of evening and is gone by the morning	4. There is no notable limitation of activity and no limping	There is no notable limitation of activity and no limping. No orthopedic problems, no abnormalities in X-rays and bone scans
The physical examination reveals no abnormalities and there is no evidence of swelling, erythema, tenderness, local trauma or infection, reduced joint range of motion or limping, or reduced physical activity	5. The typical distribution of the pain is anterior thigh, calf, and posterior knee. The pain is felt in the muscles and not in the joints	Pain persists at least 3 months
Laboratory tests are within reference range and there are no objective findings, e.g., erythrocyte sedimentation rate, X-ray, bone scan	6. The pain is intermittent with some pain-free days and nights. There are periods of days, weeks, or months without leg pains	There are periods of days, weeks, or months without leg pains
	7. Physical examination reveals no abnormalities with no evidence of orthopedic disorder, swelling, erythema, tenderness, local trauma, infection, or reduced range of motion	There is no associated lack of well-being
	8. The laboratory tests are within reference range with no objective findings, e.g., erythrocyte sedimentation rate, radiograph, bone scan	
	9. Pain persists at least 3 months	
	10. There is no associated lack of well-being	

3 of the first 4 features must be present

Table 3

Summary of recent studies investigating the link between Restless Legs Syndrome and growing pains.

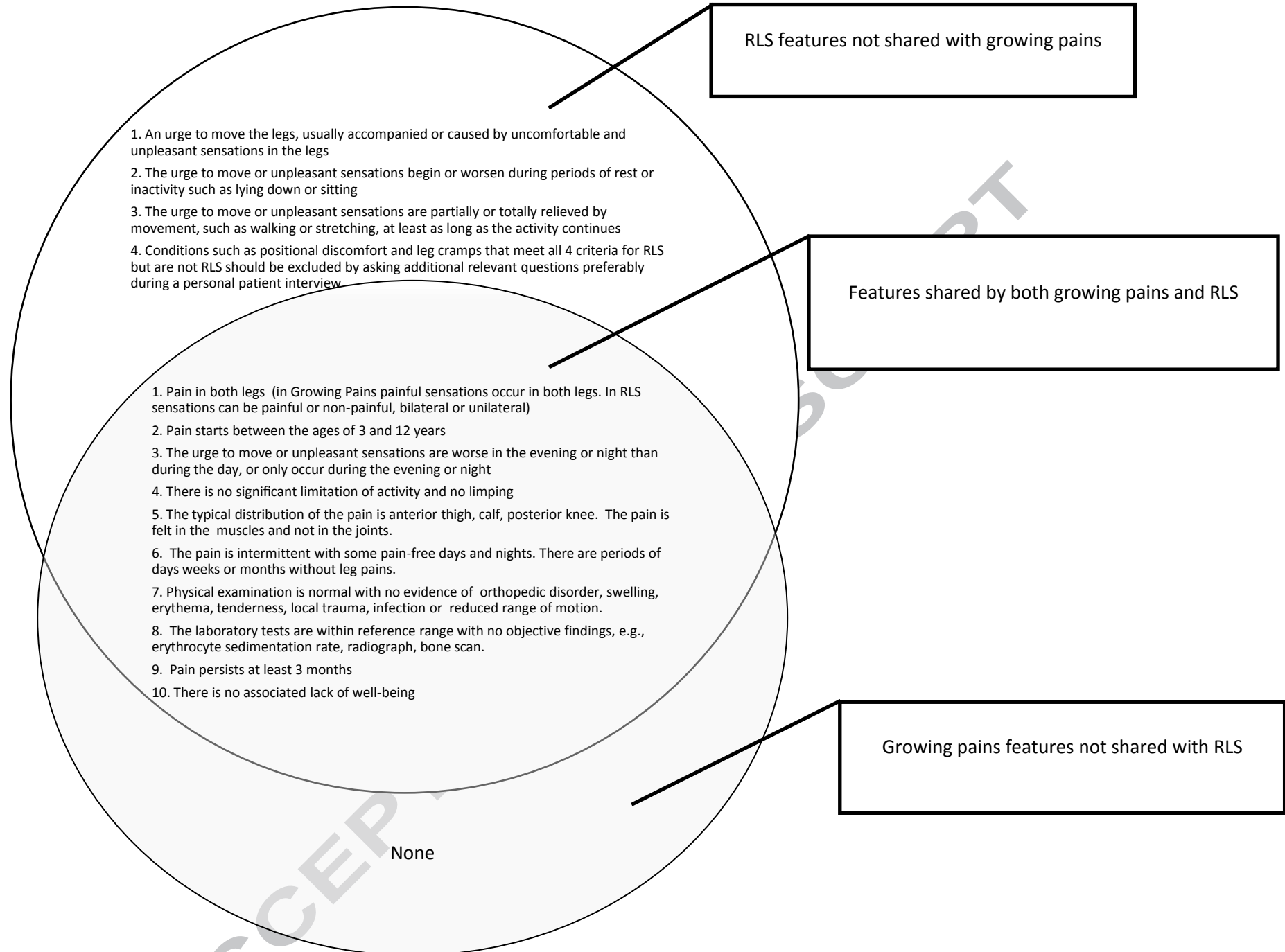
Study author (year)	Type of study	Findings
Bassetti et al [15] (2001)	Case control	Growing pains are more frequent in RLS patients with onset <20 years of age (27%) than in those with onset >20 years of age (3%) ($P=.005$)
Chervin et al [13] (2002)	Cross-sectional	No relationship between RLS and growing pains
Rajaram et al [12] (2004)	Case series	Growing pains was a misdiagnosis for RLS in 10 cases
Gamaldo et al [20] (2007)	Case control family history	No relationship between RLS and growing pains
Picchietti et al [11] 2007	Cross-sectional	A history of growing pains is more common in children with RLS (80.6%) than in those without RLS (63.2%)($P<.001$)
Picchietti et al [19] (2008)	Retrospective Chart review	10/18 (55.5%) of children with RLS had a history of growing pains
Balendran et al [14] (2011)	Case control	A history of growing pains more frequently is reported by pregnant women with RLS (17%) than pregnant women without RLS (6.7%)($P=.042$)
Turkdogan et al [18] (2011)	Cross-sectional	Growing pains are experienced in 54.5% of children with RLS

Champion et al [8] Twin study 18% of twins with concordant growing pains met
(2012) criteria for RLS as opposed to only 2% of twins with
discordant growing pains ($P=.01$).

Abbreviations: RLS, restless legs syndrome.

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Fig 1. Overlapping and nonoverlapping clinical features of restless legs syndrome and growing pains.



Highlights

- The overlap between the diagnostic criteria of RLS and growing pains is high.
- RLS and growing pains occur more commonly together than by chance alone.
- The overlap between the family histories of RLS and growing pains is high.
- A unification of the varying definitions of growing pains is recommended.
- Genetic and therapeutic studies may clarify the relationship between both entities.