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SLEEP (M. THORPY AND M. BILLIARD, SECTION EDITORS)

The Comorbidity of Migraine and Restless Legs Syndrome

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Abstract

Purpose of Review The purpose of this review is to discuss migraine and RLS diseases and explain the comorbidity of migraine and RLS and possible mechanisms leading to this comorbidity in the light of recent studies.

Recent Findings Many clinical and epidemiological studies and recent meta-analyses of these studies have revealed a higher prevalence of RLS in patients with migraine compared to individuals without migraine.

Summary There is an association between RLS and migraine in terms of some action mechanisms, especially the dopaminergic system, and some symptoms. They are associated concerning burden and economic cost. It will be extremely useful to take this situation into account in order to choose the appropriate drug for both, reduce the side effects of the drugs, increase patient satisfaction, and decrease the cost of treatment.

Keywords Migraine · Restless legs syndrome · RLS · Dopamine · Comorbidity

Introduction

Common diseases in neurology practice include migraine and restless legs syndrome (RLS). Migraine has an increased risk of RLS, particularly in patients who have migraine with aura [1••, 2••, 3–11]. The aim of this review is to discuss migraine and RLS diseases and explain migraine and RLS comorbidity and possible mechanisms causing this comorbidity.

Migraine

Being a chronic neurologic disease, migraine is characterized by attacks of throbbing and often unilateral headache that is exacerbated by physical activity and associated with phonophobia, photophobia, nausea, and vomiting [12]. A recent study has reported that migraine is the leading cause of disability for patients aged between 15 and 49 years [1••]. This result spotlights the adverse effects of migraine on patients' daily functioning and quality of life. Therefore, it is necessary to determine the factors that worsen headaches and have an effect on daily functioning of patients [1••]. Even though it may begin early in childhood, its prevalence increases gradually at 10 to 14 years of age and continues to increase until 40 years of age. After 40 years of age, it gradually diminishes, especially among women after menopause. Migraine is two to three times greater in women than men [13•] and its highest prevalence is more than 25% among women. About one-third of patients having migraine with aura precedes or develops during some attacks; whereas, nearly 75% of patients experience a premonitory stage before migraine headache [12].

Attacks of migraine have a broad spectrum of frequency and severity. Migraine is an effectively managed rare problem in some patients, but is frequent, disabling, and stubborn to latest treatment in many patients. Approximately 1 out of 25 women may have chronic migraine headache on more than fortnight per month [13•]. Migraine is a frequent cause of work lost and interrupted kinships and is associated with an impaired quality of life [13•]. Migraine is the second most incapacitating neurologic situation worldwide in terms of the time causing disability [12]. Migraine is associated with a remarkable financial burden and its total annual costs is estimated at 27 billion dollars in the USA [12].

Migraine is also connected with enhanced risks of many other diseases, including stroke, asthma, depression, anxiety, and other pain diseases [13•].

During the past 20 years, a lot of evidence have disproved the concept of migraine which was described as particularly a vascular disorder for a long term, in which

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dilation of blood vessels leads to throbbing headache, associated with the vascular throb [13•]. Now it has become apparent that constriction of blood vessels is not an essential mechanism of migraine treatment [13•]. Migraine has an increased relative risk of stroke and cardiovascular disease; however, its underlying mechanisms remain unclear and cerebral ischemia or infarction rarely occurs along with a migraine episode [14].

Vascular mechanisms alone are not responsible for migraine attacks. Current studies have provided important new information on the genetic causes, anatomical and physiological characteristics, and pharmacological mechanisms of migraine. The identification of more than 30 genes associated with migraine, the visualization of activated brain regions by PET and functional MRI studies in the early stages of a migraine attack, better understanding of the potential role of cervical nerves, and the recognition of the critical role for neuropeptides such as CGRP (calcitonin gene-related peptide) and PACAP (pituitary adenylate cyclase-activating polypeptide), are among the advances leading to new targets for the treatment of migraine [15].

The clinical approach towards migraine involves establishing a correct diagnosis, identifying and eliminating the aggravating factors, setting up a plan for the treatment of acute attacks, and identifying daily prophylactic therapy to prevent attacks.

The International Classification of Headache Disorders (ICHD) has mentioned the detailed criteria for the diagnosis of different types of headache [16]. The 3rd of the International Classification of Headache Disorders (ICHD-3) has been published in 2018 [17]. This categorization and the comparable diagnostic criteria were released as a beta document in 2014. After that date, they have been extensively accepted and should now be used for all diagnosis and management of headache disorders in clinical practice and in study. Like its formers, the ICHD-3 is not only hierarchical but also enables to establish diagnosis in different clinical settings [17].

Typical and atypical features for migraine were as shown in Table 1.

Attack treatments, prophylactic treatments, or their combination can be used to treat the pain and associated symptoms of migraine, as well as its life outcomes. However, because the intensity, frequency, and features of migraine vary among patients and, often, within persons in the course of time [18, 19], and symptom profiles or biomarkers foreseeing its efficacy and adverse effects have not been identified yet, it is challenging to optimize treatment for specific patients [20].

Before starting the treatment of migraine, during pharmacologic prophylactic and attack treatment, the points to be considered were as shown in Table 2.

Table 1 Typical and atypical features for migraine (Charles A. Migraine. N Engl J Med 2017;377(17):1698–1699. Doi: https://doi.org/10.1056/NEJMc1711803) [13•]

Migraine's typical features:
1) History of 4–72-h multiple stereotypical attacks
2) Lack of symptoms between attacks
3) Gradual onset of headache and neck pain
4) Vision, sensory, and language symptoms progressing gradually and lasting for less than an hour.
5) Yawning, fatigue, sensory sensitivity, neck pain, and mood change before and after headache
6) Positive family history for headache
Headache characteristics that do not suggest migraine
1) Newly onset of headache (particularly in patients older than 50 years of age)
2) Headache last more than 72 h
3) Vision, sensory, and language symptoms lasting more than an hour
4) Positive neurologic symptoms or very rapid onset of headache
5) Associated systemic disease and fever
6) Abnormal neurological examination

Neuromodulation and biobehavioral treatment may be suitable for prophylactic and attack therapy, based on the needs of persons. Neuromodulation is likely to be useful for migraine patients who choose nonpharmacological therapies, respond poorly, are not able to tolerate, or have contraindications to drugs [12].

Table 2 The following conditions should be considered when planning treatment of migraine, during pharmacologic prophylactic and attack treatment [12]

When planning treatment of migraine
1) The severity and frequency of attacks
2) The presence, type, and severity of its symptoms
3) Disability due to attack
4) Status of pregnancy or lactation, or planning to conceive
5) Response to previous treatment
6) The presence of comorbid and concomitant disease
7) Contraindications (such as liver and renal diseases)
8) Physiological measurements such as blood pressure, heart rate, and body habitus
9) The use of accompanying drugs
Pharmacologic prophylactic therapy of migraine with oral drugs
1) Using evidence-based treatments whenever possible and appropriate
2) Beginning with a low dose and tardily increase
3) Extending a therapeutic dose if possible
4) Allowing a sufficient treatment trial duration
5) To create therapeutic response and side effect expectations
6) Maximize patient compliance
Attack therapy
1) Utilizing evidence-based treatments whenever possible and appropriate
2) Treating early after the onset of a migraine attack
3) Choosing non-oral routes in selected patients
4) Considering tolerability and safety issues
5) Considering self-administered rescue therapies
6) Avoiding extreme of drugs

Restless Legs Syndrome (RLS)

RLS is a chronic neurological disease that is characterized by impaired rest and sleep, thus resulting in poor quality of life and performance. Sir Thomas Willis, a British anatomist and doctor, defined the disorder in 1685 for the first time. Karl Axel Ekbom, a Swedish doctor who later became a leader in RLS researches, described all the clinical characteristics of RLS, so he created the term RLS in 1944 [21].

RLS is a circadian disease with peerless clinical characteristics. Typically emerging in the evening or at night, symptoms can progressively aggravate but resolve at early morning hours. The symptoms develop after relative immobility for a while. The main clinical feature of RLS is the irrepressible impulse to move the legs, by itself or against comfortless paresthesia of the legs. The impulse relieves by moving the legs or walking [21, 22].

Neurologists have still identified RLS as a disorder impairing significantly the quality of life at low rates. Therefore, when patients have either sensory symptoms in their legs (regardless of pain), an impulse to move at rest usually in the evening, or sleep disorders, a diagnosis is not usually established for them and they are not treated for years [23••].

There are no practical tests or clinically useable biomarkers for the diagnosis of RLS, completely based on the subjective definition of symptoms [21]. For this reason, new diagnostic criteria have been created by a consensus of RLS specialists from the International Restless Legs Syndrome Study Group (IRLSSG) [24], and later the American Academy of Sleep Medicine published a modified edition of these criteria in International Classification of Sleep Disorders (ICSD-3) [25]. Numerous studies have addressed the IRLSSG diagnostic criteria [24]; however, independent and somewhat different diagnostic criteria recommended by the American Psychiatric Association have been published in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The DSM-5 criteria do not distinguish episodic and chronic RLS, which is fundamental for clinical routine and long-term treatment management [26].

RLS is a familial illness. More than 60% of patients have at least one first degree relative suffering from the disorder. Although there is a powerful genetic contribution and many linkages identified, highly penetrant gene has been not defined. Genomewide association studies have determined that there are six different genes with single nucleotide polymorphisms (MAP2K5, BTBD9, PTPRD, SKOR1, MEIS1, and TOX) [21, 23].

Studies have increasingly determined possible situations whereby persons having medical or neurological disorders could also suffer from RLS in recent years. In the past, the term of secondary RLS was used in these situations. Doctors have a crucial role in the diagnosing and managing RLS in the early period; therefore, it is important to consider RLS comorbidities when a patient presents with such condition [27]. The frequency of RLS increases to a great extent when minimum three of medical comorbidities, such as cardiovascular disease, diabetes, arterial hypertension, or depression, are present. This can make diagnosis difficult [23••]. In our study of multiple sclerosis patients, RLS was seen 2.55 times greater in patients with multiple sclerosis than the control group [28].

Drugs have been evaluated via evidence-based medicine techniques, and algorithms have been produced for starting RLS treatment and managing a significant worsening of symptoms with longer term dopaminergic drugs. Even though a regulatory approval has not been given for iron preparations, guidelines for such therapy have been published. The fact that genome-wide association researches have considered newly coined risk loci for RLS could also result in new therapy options [23••].

Since most of patients mention inadequate treatment in the long-term, the biggest challenge is to find new treatments. Commonly prescribed combination treatments should be evaluated. The combinations of low-dose dopaminergic drugs, opioids, or $\alpha 2\delta$ ligands could be more secure, more effective, and cheaper than monotherapy. It is required to investigate these combinations in order to increase trustworthy and efficiency in long-term therapy and to lower the expenditures [23••].

Pregabalin, gabapentin enacarbil, and oxycodone/naloxone, and their classification are effective for the therapy of RLS and increasing therapy options for RLS. However, there is a need for further studies to assess their use for a long term and to compare them with dopaminergic treatments. Moreover, there has been no study investigating combined treatments or whether or not the order of the agents affects RLS [22, 23••, 29••].

Through the recognition of genetic risk variants and their functional follow-up, new concepts may appear for the pathophysiology of RLS. Future studies should assess the genomic profile of patients in order to provide a more special treatments for peculiar subgroups of RLS [29••].

Migraine and RLS Comorbidities

Comorbidity may be described as the association of two diseases in persons at a frequency higher than the statistically expected. Migraine and RLS are complicated due to the existence of several comorbidities.

It has been determined that headache and sleep have common neuro-physiological and neuro-anatomical substrates, and specific headache diagnoses and sleep disorders are highly correlated. This close correlation is associated with common neuro-anatomical structures and neuro-chemical processes in the pathophysiology of headaches and sleep [30, 31].

Many clinical and epidemiological researches and their meta-analyses have revealed a higher prevalence of RLS in patients with migraine compared to persons without migraine. Likewise, a higher prevalence of migraine was reported in patients with RLS [2–4]. Meta-analysis study by Yang et al. has showed that the pooled prevalence of RLS in migraine was 19% (16% among Asians and 21% among other races). The prevalence of RLS was higher in migraine with aura (MA) than migraine without aura (MO). This meta-analysis study showed that the prevalence of RLS was significantly higher among persons with migraine than controls [2••].

Their meta-analyses of 11 case-control studies have indicated a 2.65-fold higher prevalence for RLS in those with migraine compared to controls. These results are compatible with those of a systematic review in 2014 [4] and higher than a study stating 1.42-fold higher risk for RLS among persons with migraine in a population-based cohort study in Taiwan [3]. In our study, the prevalence of RLS was found to be 33% in the migraine group and 9.5% in the control group. Additionally, there was a statistical difference between the migraine patients and control groups in terms of incidence of RLS ($p = 0.0001$). Incidence rates of fibromyalgia and depression were also higher in migraine patients compared to the control group ($p = 0.0001$). These increases may be associated with dopaminergic pathways. Concerning the association between headache characteristics and RLS, it was found in our study that generalized anxiety before migraine headache was statistically higher in the migraine patients with RLS ($p = 0.018$). We thought that generalized anxiety was also associated with dopaminergic symptoms. In addition, traveling not only caused the symptoms of RLS but also triggered migraine attacks in migraine patients with RLS ($p = 0.009$). Even though all the patients were thoughtfully interviewed about the characteristics of their migraine, any association was not identified between the characteristics of migraine and RLS [5].

In our study, RLS was statistically higher in migraine patients with nonspecific lesions in the brain MRI ($p = 0.005$) [5]. After all, increased frequency of the MRI lesions in the brain has been reported in both depression and fibromyalgia patients [32, 33].

The available evidence has indicated a significant difference between migraine with aura (MA) and migraine without aura (MO) in terms of the prevalence of RLS. Pooled prevalence of RLS is 18.8% in MA persons and 18.5% in MO persons. Meta-analyses of 11 studies have reported that the prevalence of RLS was higher in MA group than MO group ($p = 0.037$). The reasons for this situation are still elusive [2••]. In our study, the prevalence of RLS was statistically higher in MA than MO ($p = 0.001$) [5].

It has been reported that children with migraine have also a higher prevalence of RLS [6, 7]. A population-based study by Cho et al. indicated that migraine and RLS were associated in adults under age 50 but not in adults over 50. Their results suggest that RLS and migraine are differently related in terms of age [8].

Interestingly, a diary study conducted on migraine patients with RLS revealed that migraine attacks were associated with RLS attacks on the following night, and RLS attacks triggered migraine attacks on the following day. These data showed that there was a bidirectional triggering association among RLS and migraine attacks [9]. RLS attacks following migraine attacks or migraine attacks following RLS attacks were more robust and lasted for a longer time [1, 9]. In addition, the migraineurs with RLS were probably to have photophobia, phonophobia, vertigo, dizziness, tinnitus, and neck pain as well as exacerbation associated with physical activities [10]. The results suggest that severity of headache is associated with frequency of RLS and explain the reason why the tendency of RLS is higher in clinic-based studies than community-based studies [10].

While there is no prospective study assessing the effect of RLS on clinical factors in patients with migraine, Suzuki et al. recently conducted a 7-year follow-up study. In their study, they confirmed a significant correlation between RLS and migraine. Comorbidity of RLS was a significant predictor for headache associated disabilities in migraine patients [1••].

Lin et al. studied the relation among migraine and RLS frequency and found that higher frequency of migraine was correlated with the higher prevalence of RLS, especially among migreineurs with auras [11].

The poor quality or poor sleep duration could be trigger of migraine attack, and a higher frequency of headache has been reported in migraine patients with poor sleep [34]. In the study by van Oosterhout et al., the rate of poor sleepers was higher among migraine patients (50.1% vs. 25.6%; $p < 0.001$). Poorer quality of sleep was independently correlated with prevalence (odds ratio 1.08; $p < 0.001$) and severity ($p < 0.001$) of RLS in patients with migraine [35]. In the study by Gozubatik-Celik et al., the severity of RLS was significantly higher in migraine patients. Furthermore, the family history of RLS was higher in migraine patients [36].

However, how RLS might be associated with migraine is unclear since they appear to be neurologic disorders. Both of them are likely associated with dysfunction of the dopaminergic system [1••]. RLS is thought to include the A11 dopaminergic nucleus of the dorsal posterior hypothalamus, which is the single source of spinal dopamine [2••]. Similar to the RLS features in humans, A11-lesioned rats show the increased hyperactive alertness across the rest-activity cycle and a reduced sensory threshold. A11 nucleus obtains an inhibitory dopaminergic signal to the medulla spinalis and may provoke a dysregulation of peripheral somatosensory processing [2••]. In this way, A11 nucleus abnormality may symbolize a general feature in RLS and migraine even though pathogenesis of both disorders is more complex and includes other

neurotransmitters and brain parts [6, 37]. Further, the prodromal symptoms including mood changes, drowsiness, yawning, and food craving; concomitant symptoms including nausea, vomiting, and hypotension; and postdromal symptoms including mood changes, tiredness, and drowsiness of migraine may be associated with dopaminergic stimulation [2••]. Interestingly, dopaminergic agents are effective to prodromal symptoms of migraine. RLS symptoms disappear after therapy with dopaminergic agents and treating patients with accompanying migraine RLS and using immediate release pramipexole recovers not only RLS symptoms but also migraine frequency [1••, 2••]. These various studies point out joint matters in the pathophysiology of migraine and RLS. In our study published in 2016, Dopamine Beta Hydroxylase gene +1603C > T polymorphism was more common in migraine patients. But we did not evaluate the presence of RLS in migraine patients [38].

Moreover, both migraine and RLS may include iron insufficiency [1••, 2••] although further studies are needed to prove this. Enhanced iron depositions in multiple deep cerebral nuclei are associated with repeated headache attacks [2••], whereas cerebral iron deficiency has a critical role in the RLS pathogenesis [1••]. It has been also revealed that severity of RLS is associated with peripheral iron deficiency [39].

The function of the spreading depression model may be an additional common way. Formerly, MA has been only regarded as a vascular process after vasoconstriction [39]. This definition refers to the spreading depression theory, which recommended that there is a spreading decrease in brain blood flow or spreading oligemia in patients with MA. Such an approach led to a reform in thoughts about migraine aura [39].

Valente et al. reported that was associated with the presence of RLS in migraine patients. Serotoninergic overload developed depending on the combined use of selective serotonin reuptake inhibitors, norepinephrine reuptake inhibitors, and serotonin antagonists, and the presence of triptan misuse. The authors have recommended that serotoninergic instabilities may have impact on RLS comorbidity in migraine patients [40]. Mutual interactions among the dorsal raphe serotonin system and the substantia nigra dopamine and ventral tegmental systems further complicate the comorbidity mechanisms of RLS and migraine [1••].

When considering familial predispositions for RLS and migraine, genetic or environmental elements may also be effective in this predisposition. Among the six tested loci (MAP2K5, PTPRD, MEIS1, TOX3, BTBD9, and an intergenic region on chromosome 2p14), only MEIS1 variants were connected with an increased risk of RLS in patients with migraine [41]. In this study, it was investigated whether or not the comorbid situations including migraine had more RLS-risk alleles. There was no significant difference between carriers of any of the RLS risk alleles and noncarriers in terms of the mean number of comorbidities [42].

Another common mechanism of migraine and RLS is cerebral hypersensitivity. Hypersensitivity to pain and central sensitization and sensory stimuli are involved in the pathophysiology of RLS and migraine, respectively [1••]. The hypersensitivity of corticostriatal glutamatergic terminals in a cerebral iron insufficiency model of RLS has been studied in the recent time [1••].

Yang et al. conducted a resting-state functional MRI and network wise analysis of functional connectivity in migraineurs with and without RLS and controls. Their network-based statistic results indicated that both of migraine patients with and without RLS had lower functional connectivity than controls in the dorsal attention, salience, visual, default mode, cingulo-opercular, auditory, sensory-somatomotor, and frontoparietal networks [43].

Possible mechanisms for the comorbidity of RLS and migraine are summarized in Table 3.

Finally, the case is precisely depending on the disease burden and cost. Migraine is one of the most difficult diseases, the first cause of disability among persons under 50 years of age, and causes a considerable economic burden. The average annual cost per migraine patient is estimated to be over 1200 Euros. When comparing with migraine, the burden and cost of RLS have been less systematically investigated but RLS leads to a significant impairment in patients of life quality and has been associated with an annual cost of over 2000 Euros [44].

Table 3 Possible mechanisms for the comorbidity of RLS and migraine

Possible mechanisms	References number
Headache and sleep have common physiological and anatomical substrates	[30, 31]
Both of them are likely associated with dysfunction of the dopaminergic system	[1••, 2••, 6, 37]
Both migraine and RLS may include iron insufficiency	[1••, 2••]
The function of the spreading depression model may be an additional common way	[39]
Mutual interactions among the dorsal raphe serotonin system and the substantia nigra dopamine and ventral tegmental systems	[1••, 40]
Common genetic factors (such as MEIS1 variants)	[41]
Cerebral hypersensitivity	[1••]

Conclusion

RLS and migraine are common neurological disorders. RLS and migraine are connected with some common action mechanisms and some symptoms as well as relevant burden and economic cost. Regardless of suffering from migraine or RLS, it will be extremely useful to question the presence of another disease in the patient, choose the appropriate drug for both, reduce the side effects of the drugs, increase patient satisfaction, and decrease the treatment expenses.

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent This article does not include any study conducted by the author with human or animal subjects.

Conflict of Interest The author declares no conflict of interests concerning the publication of this article.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Suzuki K, Suzuki S, Haruyama Y, Kobashi G, Shiina T, Hirata K. Restless legs syndrome is associated with headache-related disabilities in patients with migraine: a prospective 7-year follow-up study. Eur J Neurol. 2019;26(2):238–45. https://doi.org/10.1111/ene.13796. **The authors reported that RLS had a significant impact on headache-related disability in patients with migraine. This is the first prospective study on this subject.**

2.•• Yang X, Liu B, Yang B, Li S, Wang F, Li K, et al. Prevalence of restless legs syndrome in individuals with migraine: a systematic review and meta-analysis of observational studies. Neurol Sci. 2018;39(11):1927–34. https://doi.org/10.1007/s10072-018-3527-7. **This study comprehensively evaluated the available evidence to estimate the prevalence of RLS in subjects with migraine and non-migraine controls. Their meta-analysis provides the first reliable pooled estimate of RLS prevalence among individuals with migraine, and it provides strong evidence that RLS risk is higher among individuals with migraine than among controls.**

3. Yang FC, Lin TY, Chen HJ, Lee JT, Lin CC, Huang WY, et al. Increased risk of restless legs syndrome in patients with migraine: a nationwide population-based cohort study. Medicine (Baltimore). 2016;95(5):e2646. https://doi.org/10.1097/MD.0000000000002646.

4. Schürks M, Winter A, Berger K, Kurth T. Migraine and restless legs syndrome: a systematic review. Cephalalgia. 2014;34(10):777–94. https://doi.org/10.1177/0333102414537725.

5. Akdag Uzun Z, Kurt S, Karaer UH. The relationship with restless legs syndrome, fibromyalgia, and depressive symptoms in migraine patients. Neurol Sci. 2018;39(8):1409–14. https://doi.org/10.1007/s10072-018-3438-7.

6. Angriman M, Cortese S, Bruni O. Somatic and neuropsychiatric comorbidities in pediatric restless legs syndrome: a systematic review of the literature. Sleep Med Rev. 2017;34:34–45. https://doi.org/10.1016/j.smrv.2016.06.008.

7. Sevindik MS, Demirci S, Göksan B, Özge A, Savrun FK, Onur H, et al. Accompanying migrainous features in pediatric migraine patients with restless legs syndrome. Neurol Sci. 2017;38(9):1677–81. https://doi.org/10.1007/s10072-017-3045-z.

8. Cho SJ, Chung YK, Kim JM, Chu MK. Migraine and restless legs syndrome are associated in adults under age fifty but not in adults over fifty: a population-based study. J Headache Pain. 2015;16:554. https://doi.org/10.1186/s10194-015-0554-0.

9. Chen PK, Fuh JL, Wang SJ. Bidirectional triggering association between migraine and restless legs syndrome: a diary study. Cephalalgia. 2016;36(5):431–6. https://doi.org/10.1177/0333102415596444.

10. Chen PK, Wang SJ. Non-headache symptoms in migraine patients. F1000Res. 2018;7:188. https://doi.org/10.12688/f1000research.12447.1 eCollection 2018.

11. Lin GY, Lin YK, Lee JT, Lee MS, Lin CC, Tsai CK, et al. Prevalence of restless legs syndrome in migraine patients with and without aura: a cross-sectional, case-controlled study. J Headache Pain. 2016;17(1):97. https://doi.org/10.1186/s10194-016-0691-0.

12. American Headache Society. The American headache society position statement on integrating new migraine treatments into clinical practice. Headache. 2019;59(1):1–18. https://doi.org/10.1111/head.13456.

13.• Charles A. Migraine. N Engl J Med. 2017;377(17):1698–9. https://doi.org/10.1056/NEJMc1711803. **The author summarized the diagnosis and treatment of migraine in a very nice and understandable way**.

14. GBD, Neurological Disorders Collaborator Group. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the global burden of disease study 2015. Lancet Neurol. 2015;2017(16):877–97. https://doi.org/10.1016/S1474-4422(17)30299-5.

15. Charles A. The pathophysiology of migraine: implications for clinical management. Lancet Neurol. 2018;17(2):174–82. https://doi.org/10.1016/S1474-4422(17)30435-0.

16. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition (beta version). Cephalalgia. 2013;33:629–808. https://doi.org/10.1177/0333102413485658.

17. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. Cephalalgia. 2018;38(1):1–211. https://doi.org/10.1177/0333102417738202.

18. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. Headache. 2015;55:3–20. https://doi.org/10.1111/head.12499.

19. Silberstein SD. Preventive migraine treatment. Continuum (Minneap Minn). 2015;21(4 Headache):973–89. https://doi.org/10.1212/CON.0000000000000199.

20. Serrano D, Lipton RB, Scher AI, Reed ML, Stewart WBF, Adams AM, et al. Fluctuations in episodic and chronic migraine status over the course of 1 year: implications for diagnosis, treatment and clinical trial design. J Headache Pain. 2017;18:101. https://doi.org/10.1186/s10194-017-0787-1.

21. Wijemanne S, Ondo W. Restless legs syndrome: clinical features, diagnosis and a practical approach to management. Pract Neurol. 2017;17:444–52. https://doi.org/10.1136/practneurol-2017-001762.

22. Kwatra V, Khan M, Quadri SA, Cook TS. Differential diagnosis and treatment of restless legs syndrome: a literature review. 2018;10(9):e3297. https://doi.org/10.7759/cureus.3297.

23.•• Trenkwalder C, Allen R, Högl B, Clemens S, Patton S, Schormair B, et al. Comorbidities, treatment, and pathophysiology in restless legs syndrome. Lancet Neurol. 2018;17(11):994–1005. https://doi.org/10.1016/S1474-4422(18)30311-9. **The authors examined new insights from genetics, and iron and hypoxic pathways to elucidate the strong biological component of RLS**.

24. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, et al. International restless legs syndrome study group. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated international restless legs syndrome study group (IRLSSG)consensus criteria–history, rationale, description, and significance. Sleep Med. 2014;15(8):860–73. https://doi.org/10.1016/j.sleep.2014.03.025.

25. American Academy of Sleep Medicine. The international classification of sleep disorders: diagnostic & coding manual (ICSD-3). 3rd ed. Darien: American Academy of Sleep Medicine; 2014.

26. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Association; 2013.

27. Becker PM, Novak M. Diagnosis, comorbidities, and management of restless legs syndrome. Curr Med Res Opin. 2014;30(8):1441–60. https://doi.org/10.1185/03007995.2014.918029.

28. Aydar G, Kurt S, Karaer Unaldi H, Erkorkmaz U. Restless legs syndrome in multiple sclerosis. Eur Neurol. 2011;65(5):302–6. https://doi.org/10.1159/000327315.

29.•• Winkelmann J, Allen RP, Högl B, Inoue Y, Oertel W, Salminen AV, et al. Treatment of restless legs syndrome: Evidence-based review and implications for clinical practice (Revised 2017)(§). Mov Disord. 2018;33(7):1077–91. https://doi.org/10.1002/mds.27260. **The authors updated the previous evidence-based medicine review of treatments for RLS. All randomized, controlled trials (level I) with a high quality score published between January 2007 and January 2017 were reviewed.**

30. Dosi C, Figura M, Ferri R, Bruni O. Sleep and headache. Semin Pediatr Neurol. 2015;22(2):105–12. https://doi.org/10.1016/j.spen.2015.04.005.

31. Nesbitt AD, Leschziner GD, Peatfield RC. Headache, drugs and sleep. Cephalalgia. 2014;34(10):756–66. https://doi.org/10.1177/0333102414542662.

32. Mitelman SA. Transdiagnostic neuroimaging in psychiatry: a review. Psychiatry Res. 2019;277:23–38. https://doi.org/10.1016/j.psychres.2019.01.026.

33. Sawaddiruk P, Paiboonworachat S, Chattipakorn N, Chattipakorn SC. Alterations of brain activity in fibromyalgia patients. J Clin Neurosci. 2017;38:13–22. https://doi.org/10.1016/j.jocn.2016.12.014.

34. Ferini-Strambi L, Galbiati A, Combi R. Sleep disorder-related headaches. Neurol Sci. 2019;40(Suppl 1):107–13. https://doi.org/10.1007/s10072-019-03837-z.

35. van Oosterhout WP, van Someren EJ, Louter MA, Schoonman GG, Lammers GJ, Rijsman RM, et al. Restless legs syndrome in migraine patients: prevalence and severity. Eur J Neurol. 2016;23(6):1110–6. https://doi.org/10.1111/ene.12993.

36. Gozubatik-Celik G, Benbir G, Tan F, Karadeniz D, Goksan B. The prevalence of migraine in restless legs syndrome. Headache. 2014;54(5):872–7. https://doi.org/10.1111/head.12288.

37. Zanigni S, Giannini G, Melotti R, Pattaro C, Provini F, Cevoli S, et al. Association between restless legs syndrome and migraine: a population-based study. Eur J Neurol. 2014;21(9):1205–10. https://doi.org/10.1111/ene.12462.

38. Sezer S, Kurt S, Ates O. Analysis of dopamine beta hydroxylase gene polymorphisms in migraine. Clin Neurol Neurosurg. 2016;145:96–100. https://doi.org/10.1016/j.clineuro.2016.02.002.

39. Acar BA, Acar T, Alagöz AN, Karacan A, Varım C, Uyanık MŞ, et al. Relationship between primary restless legs syndrome and migraine with aura. Kaohsiung J Med Sci. 2016;32(8):420–6. https://doi.org/10.1016/j.kjms.2016.06.003.

40. Valente M, Janes F, Russo V, Fontana A, Travanut A, Sommaro M, et al. Prevalence of restless legs syndrome in migraine patients: a case-control study. Analysis of risk factors for restless legs syndrome in migraine patients. Headache. 2017;57(7):1088–95. https://doi.org/10.1111/head.13124.

41. Fuh JL, Chung MY, Yao SC, Chen PK, Liao YC, Hsu CL, et al. Susceptible genes of restless legs syndrome in migraine. Cephalalgia. 2016;36(11):1028–37. https://doi.org/10.1177/0333102415620907.

42. Szentkirályi A, Völzke H, Hoffmann W, Winkelmann J, Berger K. Lack of association between genetic risk loci for restless legs syndrome and multimorbidity. Sleep. 2016;39(1):111–5. https://doi.org/10.5665/sleep.5328.

43. Yang FC, Chou KH, Hsu AL, Fuh JL, Lirng JF, Kao HW, et al. Altered brain functional connectome in migraine with and without restless legs syndrome: a resting-state functional MRI study. Front Neurol. 2018;9:25. https://doi.org/10.3389/fneur.2018.00025.

44. Raggi A. Can we now say that commonalities between restless leg syndrome and migraine exist? Neurol Sci. 2019;40(1):227–8. https://doi.org/10.1007/s10072-018-3591-z.