Title: Restless legs syndrome/Willis–Ekbom disease prevalence in beta thalassemia patients

Author(s): Euthimia Dimitriadou, Christoforos D. Giannaki, Maria Tsekoura, Ioannis Stefanidis, Georgios M. Hadjigeorgiou, Eleftherios Lavdas, Christina Karatzaferi, Giorgos K. Sakkas

Published in: Sleep and Breathing (2017)

DOI:10.1007/s11325-017-1497-2

Title Page

Title: Restless legs syndrome/Willis–Ekbom disease prevalence in beta thalassemia patients

Authors: Euthimia Dimitriadou[1], Christoforos D. Giannaki[2], Maria Tsekoura[3], Ioannis Stefanidis[4], Georgios M. Hadjigeorgiou[4], Eleftherios Lavdas[5], Christina Karatzaferi[3,6], Giorgos K. Sakkas[3,6]

Affiliations:[1]Department of Haematology, General Hospital of Trikala, Trikala, Greece; [2]Department of Life and Health Sciences, University of Nicosia, Nicosia, Cyprus,[3]Department of PE and Sport Science, University of Thessaly, Trikala, Greece;[4]School of Health Science, Department of Medicine, University of Thessaly, Larissa, Greece, [5]Department of Medical Radiological Technologists, Technological Education Institute of Athens, Athens, Greece, [6]School of Sport and Health Science, University of St Mark and St John, Plymouth, UK

Correspondence: Giorgos K. Sakkas PhD

University of St Mark and St John,

Faculty of Sport and Health Sciences,

Derriford Rd, PL68BH, Plymouth, UK

E-mail: gsakkas@marjon.ac.cy

Acknowledgements

We would like to thank all the patients participated in the current study as well as the medical and nursing staff of the hematology unit of the General Hospital of Trikala, Larissa and Karditsa.

Abstract:

Purpose: Both beta thalassemia and restless legs syndrome (RLS) patients share some common pathophysiological characteristics related to iron handling. In the present study, the aim was to explore the prevalence of RLS as well as to explore potential association between the syndrome and various quality of life-related parameters in a sample of beta thalassemia patients.

Methods: One hundred fourteen (age 40 ± 11yr, 59M/55F) beta thalassemia patients participated in this cross-sectional descriptive study. Patients were screened for RLS based to the international RLS study group diagnostic criteria as well as a battery of validated questionnaires.

Results: The prevalence of RLS in this sample of beta thalassemia patients was zero. The quality of life score was low (78± 18). Iron levels were within normal range (191 ± 66 mcg/dL) while ferritin levels were high as expected (1836 ± 225ng/dL).

Conclusions: Our sample of patients comes from central Greece where the prevalence of RLS in the general population is 4% while in renal failure patients is 27%. To our surprise there was no presence of RLS among this sample of beta thalassemia patients. The adequate levels of iron and ferritin often seen in these patients could be the reason of the absence of RLS symptoms.

Keywords: anemia; iron; ferritin; sleep disorders

Introduction

Beta thalassemia is a group of hereditary blood disorders characterized by reduced or absent synthesis of the beta chains of hemoglobin and anemia and leading therefore to unaffected erythropoiesis [1].Individuals with thalassemia major usually present within the first two years of life with severe anemia, requiring regular red blood cell transfusions. Regular transfusion therapy leads, among other, to iron overload-related complications.On the other hand, compliance with iron therapy mainly influences frequency and severity of the iron overload-related complications [2].

On the other hand, restless legs syndrome (RLS) (called also as Willis-Ekbom disease WED) is a sensorimotor neurological disorder related to dopaminergic pathways while the neuronal iron handling have been implicated in the pathophysiology of the syndrome [3]. RLS is characterized by an uncontrolled need to move extremities accompanied by unpleasant sensations, which frequently leads to sleep disturbances [4,5]. Symptoms are particularly troublesome in the evening and at night, and sleep disturbance is common [4].

RLS is categorized as either primary or secondary. Primary RLS is associated with family history with some genetic risk factors to have been identified recently [6]. RLS susceptibility is strongly related to iron levels, however, iron-related genes do not seem to affect serum iron parameters while the correlation between RLS and iron parameters in serum seems to be weaker than assumed [7].

RLS can be presented as secondary to or exacerbated by, a number of conditions associated with iron deficiency and anemia such as pregnancy and end-stage renal disease [8]. This is also the case in peripheral iron deficiency with or without anemia which appears to be an important environmental trigger of RLS symptoms [9].

Studies carried out in populations with iron deficiency anemia report approximately 35% with RLS symptoms [10] compared to the general population prevalence of 5% [11]. Recent studies have shown that IV iron therapy offers a rapid solution to replenishing body iron stores and diminishes or eliminates RLS symptoms in those with comorbid iron deficiency anemia [9]. However, many studies have shown that the local brain iron levels seem to be more important than the serum levels for the development of RLS [12,13]. Low brain iron levels or deficiency has been found in patients with haemochromatosis indicating a possible role of local brain iron deficiency in the pathophysiology of RLS and PLMS, even in patients with systemic iron overload, such as in patients with hemochromatosis [14] or beta thalassemia.

So far, there are no published reports to support the notion that beta thalassemia patients will follow the example of hemochromatosis patients showing evidence of RLS. It is not clear whether iron overload-related complications often seen in beta thalassemia patients will include the development or absence of RLS. Therefore, the primary aim of the current study was to examine the prevalence of RLS in this sample of beta thalassemia patients in central Greece where the prevalence of RLS has been assessed recently [15]. Taking into account the association and presence of RLS in other conditions characterized by iron overload we expected to observe some cases of RLS in the examined sample of beta thalassemia patients. Secondary aims were to investigate potential associations – if any - of RLS with quality of life levels, sleep quality, daily sleepiness, fatigue and depression levels.

Materials and methods

Participants

From May of 2012 to May of 2013 a total of 114 patients (54 female) were recruited from the thalassemia units of Hospitals of Larissa, Trikala and Karditsa, Greece. Patients were screened for RLS by an expert Neurologist (GMH) based on the 4 international RLS study group diagnostic criteria [4] while the severity of RLS symptoms was evaluated using the IRLSSG severity scale [16].

The inclusion criteria for this study were: Participants with beta thalassemia aged between 18-70 years and with clinical stable condition. Exclusion criteria included diagnosed neuropathies or reasons for being in a catabolic state within 3 months prior to the start of the study.

All patients gave their written informed consent prior to study participation. The study was approved by the Ethics Committee of the University of Thessaly (29/03/2012-519), Greece and the associated hospitals.

Biochemical assessment

Hematological and biochemical indices included the levels of Hemoglobin, Hematocrit, Glucose, Urea, Creatinine, Serum glutamic oxaloacetic transaminase (SGOT), Albumin, Total cholesterol, Triglycerides, High density lipoprotein (HDL), Low density lipoprotein (LDL), C reactive protein (CRP), Ferritin, Iron, Potassium and Phosphorus. The biochemical analysis was performed at the clinical labs of hospitals of Trikala, Larissa and Karditsa under standard hospital procedures.

Questionnaires

All questionnaires were completed with the interview method by experienced personnel. We should note that all the questionnaires used in the current study have been used before in various RLS studies [17,18].

Fatigue levels were assessed using the fatigue severity scale (FSS)[19].The patients' depression levels were evaluated by using a questionnaire developed by Zung[20].The Epworth sleepiness scale (ESS) was used to assess the daily sleepiness level of the patients[21]. Patient's quality of sleep was evaluated using a weekly sleep diary. This diary is adapted from the University of Massachusetts Medical School website.

Finally, the patient's subjective QoL outcomes were evaluated by using a Short Form-36 Health Survey (SF-36) version modified for patients receiving HD therapy [22]. Data are presented in Table 1 & 2

Statistical analysis

Descriptive statistics and analysis of the data was carried out using the SPSS version 18 software and the level for statistical significance was set at $P<0.05$.Normality of data was assessed using the Kolmogorov-Smirnov test.

Results

The patients' characteristics are presented in Table 1. No patients with RLS or conditions mimic RLS were found in the current study. Since no RLS positive patients were found, the IRLS severity scale was not evaluated in none of the participants. As it was expected due to the nature of their disease, the patients present low hematocrit and hemoglobin levels, low HDL and increased ferritin levels. The data derived by the various questionnaires are presented in Table 2.

Discussion

To our surprise, no presence of RLS in this sample of patients with beta thalassemia was detected. We believe that the adequate levels of iron and ferritin which observed in the current study and often seen in these patients could be the reason of the absence of RLS symptoms.

Beta thalassemia is a hereditary blood disorder and is particularly prevalent among people living in Mediterranean countries, including Greece. The prevalence of beta thalassemia in Greece is 0,04% while RLS is affecting the 3,9% of the Greek general population [15], and the 27% of the Greek hemodialysis patients [23].

According to the most accepted hypothesis, the pathophysiology of RLS is centered on dopaminergic dysfunction in the central nervous system [24]. In addition, there is evidence to suggest that defect in the brain iron metabolism may contribute to the pathogenesis of the disease [24]. Iron is a cofactor for tyrosine hydroxylase, which is a rate-limiting step in the conversion of levodopa to dopamine[25].In animals iron deficiency anemia is associated with D2 receptorshypofunction and should be treated with iron therapy. In addition, RLS severity reported to worsen in patients with low ferritin levels [24]. It is noteworthy that published data reveal that treatment with intravenous iron could successfully ameliorate the RLS symptoms both in primary and secondary RLS patients [26].

Patients with beta thalassemia have increased iron levels in blood serum [27], in cerebrospinal fluid[28]and in the brain while regular transfusion therapy could lead to iron overload with negative impact to overall health[29,30]. Deposition of iron in the brain can contribute to the formation of free radicals, leading to lipid peroxidation and

neurotoxicity[31]. Iron deposition in the central nervous system can occur in thalassemia, Parkinson disease and other diseases [30]. It was for that reason that we believed that RLS could be present in patients with beta thalassemia, however, the findings reject our original hypothesis as no RLS case was found in this sample of beta thalassemia patients in Greece.

Various physiological mechanisms could explain at least in part the lack of RLS symptoms in this group of patients. It seems that neurotoxicity which can be present in patients with thalassemia does not influence the dopaminergic system of the brain which is may be responsible for idiopathic RLS[24].In addition, we do not examined the levels of iron in the brain, which is considered to be another possible pathophysiological pathway responsible for RLS [24]. The high ferritin value of the patients may also lead to the no RLS symptoms presence in our sample. Those levels are explained due to increased iron absorption from the gastrointenstinal system and also because of the overload of the patients due to frequent transfusions.

Some limitations in the current study need to be acknowledged. The lack of control group seems to be a major pitfall. In the original design will have included as a control group all RLS negative patients, however, in the case of negative findings (0% RLS prevalence) this is less of importance.

In conclusion, the data of the present study reveal no RLS cases in this sample of beta thalassemia patients. One of the more direct possibilities to be explored is whether the iron over loading will result in no RLS prevalence in these patients and also if it could lead to the discovery of new treatment approaches.

Funding

No funding was received for this research.

Conflict of Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent:

Informed consent was obtained from all individual participants included in the study.

References

1. Danjou F, Anni F, Galanello R (2011) Beta-thalassemia: from genotype to phenotype. Haematologica 96 (11):1573-1575. doi:haematol.2011.055962 [pii] 10.3324/haematol.2011.055962

2. Galanello R, Origa R (2010) Beta-thalassemia. Orphanet J Rare Dis 5:11. doi:1750-1172-5-11 [pii] 10.1186/1750-1172-5-11

3. Montplaisir J, Godbout R, Poirier G, Bedard MA (1986) Restless legs syndrome and periodic movements in sleep: physiopathology and treatment with L-dopa. Clin Neuropharmacol 9 (5):456-463

4. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J (2003) Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 4 (2):101-119

5. Esposito M, Parisi P, Miano S, Carotenuto M (2013) Migraine and periodic limb movement disorders in sleep in children: a preliminary case-control study. J Headache Pain 14:57. doi:10.1186/1129-2377-14-57

6. Schormair B, Plag J, Kaffe M, Gross N, Czamara D, Samtleben W, Lichtner P, Strohle A, Stefanidis I, Vainas A, Dardiotis E, Sakkas GK, Gieger C, Muller-Myhsok B, Meitinger T, Heemann U, Hadjigeorgiou GM, Oexle K, Winkelmann J (2011) MEIS1 and BTBD9: genetic association with restless leg syndrome in end stage renal disease. Journal of medical genetics 48 (7):462-466. doi:10.1136/jmg.2010.087858

7. Oexle K, Schormair B, Ried JS, Czamara D, Heim K, Frauscher B, Hogl B, Trenkwalder C, Martin Fiedler G, Thiery J, Lichtner P, Prokisch H, Specht M, Muller-Myhsok B, Doring A, Gieger C, Peters A, Wichmann HE, Meitinger T, Winkelmann J (2013) Dilution of candidates: the case of iron-related genes in restless legs syndrome. Eur J Hum Genet 21 (4):410-414. doi:10.1038/ejhg.2012.193

8. Inoue Y (2009) [Diagnosis and symptom rating scale of restless legs syndrome]. Brain and nerve = Shinkei kenkyu no shinpo 61 (5):533-538

9. Mehmood T, Auerbach M, Earley CJ, Allen RP (2014) Response to intravenous iron in patients with iron deficiency anemia (IDA) and restless leg syndrome (Willis-Ekbom disease). Sleep Med 15 (12):1473-1476. doi:10.1016/j.sleep.2014.08.012

10. Allen RP, Auerbach S, Bahrain H, Auerbach M, Earley CJ (2013) The prevalence and impact of restless legs syndrome on patients with iron deficiency anemia. Am J Hematol 88 (4):261-264. doi:10.1002/ajh.23397

11. Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, Ferini-Strambi L (2005) Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med 165 (11):1286-1292. doi:10.1001/archinte.165.11.1286

12. Li X, Allen RP, Earley CJ, Liu H, Cruz TE, Edden RA, Barker PB, van Zijl PC (2016) Brain iron deficiency in idiopathic restless legs syndrome measured by quantitative magnetic susceptibility at 7 tesla. Sleep Med 22:75-82. doi:10.1016/j.sleep.2016.05.001

13. Unger EL, Bianco LE, Jones BC, Allen RP, Earley CJ (2014) Low brain iron effects and reversibility on striatal dopamine dynamics. Experimental neurology 261:462-468. doi:10.1016/j.expneurol.2014.06.023

14. Haba-Rubio J, Staner L, Petiau C, Erb G, Schunck T, Macher JP (2005) Restless legs syndrome and low brain iron levels in patients with haemochromatosis. J Neurol Neurosurg Psychiatry 76 (7):1009-1010. doi:10.1136/jnnp.2003.030536

15. Hadjigeorgiou GM, Stefanidis I, Dardiotis E, Aggellakis K, Sakkas GK, Xiromerisiou G, Konitsiotis S, Paterakis K, Poultsidi A, Tsimourtou V, Ralli S, Gourgoulianis K, Zintzaras E

(2007) Low RLS prevalence and awareness in central Greece: an epidemiological survey. Eur J Neurol 14 (11):1275-1280. doi:ENE1966 [pii]

10.1111/j.1468-1331.2007.01966.x
16. Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, Trenkwalder C (2003) Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med 4 (2):121-132
17. Giannaki CD, Sakkas GK, Karatzaferi C, Hadjigeorgiou GM, Lavdas E, Kyriakides T, Koutedakis Y, Stefanidis I (2013) Effect of exercise training and dopamine agonists in patients with uremic restless legs syndrome: a six-month randomized, partially double-blind, placebo-controlled comparative study. BMC Nephrol 14 (1):194. doi:1471-2369-14-194 [pii]10.1186/1471-2369-14-194

18. Giannaki CD, Sakkas GK, Karatzaferi C, Hadjigeorgiou GM, Lavdas E, Liakopoulos V, Tsianas N, Koukoulis GN, Koutedakis Y, Stefanidis I (2011) Evidence of increased muscle atrophy and impaired quality of life parameters in patients with uremic restless legs syndrome. PLoS One 6 (10):e25180. doi:10.1371/journal.pone.0025180 PONE-D-11-12475 [pii]

19. Bonner A, Wellard S, Caltabiano M (2008) Levels of fatigue in people with ESRD living in far North Queensland. J Clin Nurs 17 (1):90-98. doi:JCN2042 [pii] 10.1111/j.1365-2702.2007.02042.x

20. Zung WW, Richards CB, Short MJ (1965) Self-rating depression scale in an outpatient clinic. Further validation of the SDS. Archives of general psychiatry 13 (6):508-515
21. Johns MW (1991) A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 14 (6):540-545
22. Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH (2001) Association among SF36 quality of life measures and nutrition, hospitalization, and mortality in hemodialysis. J Am Soc Nephrol 12 (12):2797-2806
23. Stefanidis I, Vainas A, Dardiotis E, Giannaki CD, Gourli P, Papadopoulou D, Vakianis P, Patsidis E, Eleftheriadis T, Liakopoulos V, Pournaras S, Sakkas GK, Zintzaras E, Hadjigeorgiou GM (2013) Restless legs syndrome in hemodialysis patients: an epidemiologic survey in Greece. Sleep Med 14 (12):1381-1386. doi:10.1016/j.sleep.2013.05.022
24. Allen RP (2007) Controversies and challenges in defining the etiology and pathophysiology of restless legs syndrome. Am J Med 120 (1 Suppl 1):S13-21
25. Winkelman JW (2006) Considering the causes of RLS. Eur J Neurol 13 Suppl 3:8-14
26. Sakkas GK, Giannaki CD, Karatzaferi C, Maridaki M, Koutedakis Y, Hadjigeorgiou GM, Stefanidis I (2015) Current trends in the management of uremic restless legs syndrome: A systematic review on aspects related to quality of life, cardiovascular mortality and survival. Sleep Med Rev 21:39-49. doi:10.1016/j.smrv.2014.07.006
27. Srichairatanakool S, Thephinlap C, Phisalaphong C, Porter JB, Fucharoen S (2007) Curcumin contributes to in vitro removal of non-transferrin bound iron by deferiprone and desferrioxamine in thalassemic plasma. Med Chem 3 (5):469-474
28. Zheng W, Monnot AD (2012) Regulation of brain iron and copper homeostasis by brain barrier systems: implication in neurodegenerative diseases. Pharmacology & therapeutics 133 (2):177-188. doi:10.1016/j.pharmthera.2011.10.006
29. Papadimas J, Mandala E, Pados G, Kokkas B, Georgiadis G, Tarlatzis B, Bontis J, Sinakos Z, Mantalenakis S (1996) Pituitary-testicular axis in men with beta-thalassaemia major. Hum Reprod 11 (9):1900-1904

30. Haacke EM, Cheng NY, House MJ, Liu Q, Neelavalli J, Ogg RJ, Khan A, Ayaz M, Kirsch W, Obenaus A (2005) Imaging iron stores in the brain using magnetic resonance imaging. Magnetic resonance imaging 23 (1):1-25. doi:10.1016/j.mri.2004.10.001
31. Brass SD, Chen NK, Mulkern RV, Bakshi R (2006) Magnetic resonance imaging of iron deposition in neurological disorders. Topics in magnetic resonance imaging : TMRI 17 (1):31-40. doi:10.1097/01.rmr.0000245459.82782.e4

Table 1.Patients characteristics and biochemical data

Variable	**Mean ± SD**
N	114
Men/Women	59/55
Age (Years)	39.6±11.4
Weight (Kg)	64.4±11.8
Height (m)	1.67±0.08
Body Mass Index	22.9±3.4
Hemoglobin (g/dl)	9.8±1.1
Haematocrit (HCT) (%)	29.9±3.03
Glucose (mg/dl)	95.4±23.4
Urea (mg/dl)	35.3±10.5
Creatinine (mg/dl)	0.7±0.2
Serum glutamic oxaloacetic transaminase (SGOT) (IU/l)	34.1±20.7
Albumin (g/dl)	4.5±0.4
Total cholesterol (mg/dl)	125.5±31.7
Triglycerides (mg/dl)	124±68.1
High density lipoprotein (HDL) (mg/dl)	34.7±11.2
Low density lipoprotein (LDL) (mg/dl)	63.5±26.3
C reactive protein (CRP) (mg/dl)	0.5±0.3
Ferritin (ng/dl)	1836.7±2251
Iron (mg/dl)	202.5±61
Potassium (mmol/l)	4.5±0.4
Phosphorus (mg/dl)	3.9±0.7

Table 2. Quality of life, depression score, sleep quality and fatigue data in patients with beta thalassemia.

Variables	**Mean ± SD**
Zung Depression Scale	35.5±8.3
Sleep Quality	6.5±2.9
Epworth Sleepiness Scale	6.6±3.5
Fatigue Severity Scale	3.1±1.6
SF-36 questionnaire data	
Physical function scale	87.8±20.9
Role-physical scale	84.8±32.8
Body pain scale	80.1±27.8
General health scale	60.9±24.7
Vitality scale	75.5±18.9
Social functioning scale	88.0±24.8
Role emotional scale	85.5±32.0
Mental health scale	72.8±18.8
Physical health Component summary	77.8±18.7
Mental health Component summary	76.5±17.5
Total SF 36 Score	79.4±18.0