

INPLASY PROTOCOL

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Corresponding author:
Ying-Sheng Li

ejmjjj@hotmail.com

Author Affiliation:
Department of Neurology,
Kaohsiung Medical University
Hospital, Kaohsiung Medical
University, Kaohsiung, Taiwan.

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None declared.

Association of low serum ferritin levels with augmentation in patients with restless legs syndrome: A systemic review and meta-analysis

Li, YS¹; Yeh, WC²; Hsu, CY³.

Review question / Objective: P: patients with restless legs syndrome under dopaminergic agents; I: survey the serum ferritin level; low serum ferritin level as the case group; C: survey the serum ferritin level; high serum ferritin level as the case group; O: the association between serum ferritin levels and the development of augmentation.

Condition being studied: Although BID is the fundamental pathogenesis of RLS, the association of iron and augmentation has not been discussed in detail. Trenkwalder et al. stated that augmentation was associated with low serum ferritin [1]. Frauscher et al reported a significant inverse correlation between serum ferritin and augmentation [2]. To resolve the doubtful results, our meta-analysis aimed to confirm the association between augmentation and ferritin. [1]. Frauscher et al reported a significant inverse correlation between serum ferritin and augmentation; [2]. To resolve the doubtful results, our meta-analysis aimed to confirm the association between augmentation and ferritin.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 May 2023 and was last updated on 19 May 2023 (registration number INPLASY202350074).

INTRODUCTION

Review question / Objective: P: patients with restless legs syndrome under dopaminergic agents; I: survey the serum ferritin level; low serum ferritin level as the case group; C: survey the serum ferritin level; high serum ferritin level as the case group; O: the association between serum

ferritin levels and the development of augmentation.

Rationale: Restless leg syndrome (RLS) is a circadian rhythm related and sensorimotor disorder. Brain iron deficiency (BID) and dopaminergic dysregulation are two of the most well-established pathogeneses currently. However, augmentation in RLS,

which was regarded as an iatrogenic side effect, could occur after a period of treatment. Augmentation always led to treatment failure. The features of RLS augmentation contained earlier daily onset, increased intensity of the discomfort, extension to previous unaffected sites, and shorter latency to onset of symptoms [1]. Any risk factors of augmentation need to be avoided.

[1] Allen RP, Picchiotti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J, et al. 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.* 2003;4:101-19.

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[1] Trenkwalder C, Hogl B, Benes H, Kohnen R. Augmentation in restless legs syndrome is associated with low ferritin. *Sleep Med.* 2008;9:572-4.

[2] Frauscher B, Gschliesser V, Brandauer E, El-Demerdash E, Kaneider M, Rucker L, et al. The severity range of restless legs syndrome (RLS) and augmentation in a prospective patient cohort: association with ferritin levels. *Sleep Med.* 2009;10:611-5.

METHODS

Search strategy: Two authors (YS Li and WC Yeh) separately conducted systematic literature searches on PubMed, Cochrane Library, Embase, ClinicalKey, ScienceDirect, and ProQuest databases with the following keywords: (Restless legs syndrome OR Willis-Ekbom disease OR

RLS) AND (augmentation OR augmented restless legs syndrome) AND (ferritin OR iron OR iron profiles) to April 23, 2023. After removing duplicate studies, two authors screened the search results based on the title and abstract to evaluate the eligibility. A series of probably relevant studies were filtered out for a full-text review. Once any disagreements occurred, a discussion with a third author (CY Hsu) would help to reach a final consensus.

Participant or population: Patients with restless legs syndrome.

Intervention: Check the serum ferritin level.

Comparator: Serum ferritin level.

Study designs to be included: Observational studies: cohort and case control.

Eligibility criteria: 1) clinical studies in humans; and (2) patients with RLS augmentation diagnosed per criteria from National Institutes of Health (NIH) or Max Planck Institute (MPI); and (3) studies with iron profiles; and (4) studies with controls of RLS patients without augmentation.

Information sources: PubMed, Cochrane Library, Embase, ClinicalKey, ScienceDirect, and ProQuest databases.

Main outcome(s): Low serum ferritin was associated with the augmentation.

Quality assessment / Risk of bias analysis: Two investigators independently evaluated the quality of the selected cohort and case-control studies with the modified Newcastle-Ottawa Scale (NOS) [8]. The scale includes evaluation of qualities for three categories: participant selection, comparability, and exposure. The total score ranges from 0 to 9, and a higher score (≥ 7) indicates better methodological quality.

Strategy of data synthesis: Due to the anticipated heterogeneity, we selected a random-effects meta-analysis, which is more strict than a fixed-effects analysis to incorporate between-study variances [9].

The meta-analysis procedure was performed with Comprehensive Meta-Analysis software, version 3. Hedges' g and 95% confidence intervals (CIs) were optioned to combine the effect sizes. Effect sizes were defined as small, medium, and large when Hedges' g was 0.8, respectively. For each analysis, a two-sided P value <0.05 indicated significance.

Subgroup analysis: No subgroup meta-analysis.

Sensitivity analysis: Heterogeneity was examined with the p-values of Q-statistics. The I² statistic was used to evaluate the proportion of variation, with cutt-off value >50% indicating high heterogeneity. Possible publication bias were detected through funnel plots. Finally, we conducted the one-study-removal method to test the sensitivity and detect latent outliers, which resulted in confounding effects to the meta-analysis.

Language restriction: None.

Country(ies) involved: Taiwan - Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung.

Keywords: restless legs syndrome, augmentation, ferritin, iron deficiency, meta-analysis.

Contributions of each author:

Author 1 - Ying-Sheng Li, the first author, was responsible for drafting the manuscript and conducting the literature search.

Author 2 - Wei-Chih Yeh contributed to the literature search and data interpretation processes.

Author 3 - Chung-Yao Hsu is the corresponding author and was responsible for concept formation, manuscript revision, and manuscript submission.