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RESEARCH REPORT

Sleep Disturbance, Obstructive Sleep Apnoea and Abnormal Periodic Leg Movements: Very Common Problems in Fabry Disease

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Abstract *Objectives*: To assess the prevalence of sleep disorder(s) in males with Fabry disease and explore possible association with disease phenotype.

Background: Fabry disease, an X-linked lysosomal storage disease caused by deficiency in α-galactosidase, results in intracellular accumulation of globotriaosylceramide. It causes organ dysfunction, most significantly affecting renal, cerebrovascular and cardiovascular systems. Respiratory involvement may include obstructive lung disease, reduced diffusing capacity and thickened soft and hard palates. Patients commonly develop small-fibre sensory peripheral neuropathy manifested by acroparaesthesia and pain crises. Combined with self-reported sleep disturbance and snoring, these features suggest an increased risk of sleep disorders.

Methods: In-laboratory polysomnography (PSG) studies and sleep inventory assessments, including Epworth Sleepiness Scale (ESS), were performed in a cohort of male Fabry patients. PSGs were reviewed by a sleep physician. Sleep-disordered breathing and periodic leg movements were targeted for analysis. Associations with renal, cardiovascular and cerebrovascular function were sought.

Results: Twenty males underwent overnight PSG. Patient baseline characteristics included age 43.9 ± 10.7 years, BMI 24.3 ± 3.8 kg/m^2, neck circumference 39.7 ± 3.3 cm and ESS 9.8 ± 5.1 (7/20, abnormal ESS >10). Abnormal periodic leg movement index (PLMI) was present in 95% (mean frequency 42.4 ± 28.5/min) and sleep-disordered breathing in 50% patients. Periodic leg movements were associated with pain and depression but not with increased cortical arousal.

Conclusions: Sleep-disordered breathing and abnormal PLMI are highly prevalent in patients with FD. The presence of abnormal PLMI alone appears to have minimal impact on sleep disturbance, but is associated with depression and analgesic requirement.

Abbreviations

AHI	Apnoea–hypopnea index
EEG	Electroencephalogram
EMG	Electromyogram
ERT	Enzyme replacement therapy
FD	Fabry disease
Gb3	Globotriaosylceramide
OSA	Obstructive sleep apnoea
PLMI	Periodic leg movement index
PSG	Polysomnography

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Introduction

Fabry disease (FD) is an X-linked storage disorder caused by a mutation in the gene encoding the lysosomal enzyme α-galactosidase A (OMIM 300644) (Desnick et al. 2003). It leads to impaired glycosphingolipid metabolism and resultant intracellular accumulation of globotriaosylceramide

(Gb3). Metabolites of Gb3 induce inflammation, hypertrophy and fibrosis, especially of vascular endothelium and smooth muscle cells (von Scheidt et al. 1991). Clinical manifestations are widespread with the heart, kidneys, cerebrovascular system, peripheral nerves and skin most severely affected (Mehta et al. 2009; Zarate and Hopkin 2008).

Respiratory outcomes have been infrequently reported in Fabry disease, probably due to both reduced life expectancy, especially in males, and the fact that cardiovascular, renal and cerebrovascular complications, being prevalent and life threatening, dominate clinical care. Symptoms include dyspnoea in up to 69% of men and 65% of women (Mehta et al. 2004), cough, wheeze, reduced exercise tolerance (Lobo et al. 2008; Germain 2010) and fatigue (Lobo et al. 2008; Franzen et al. 2013). Obstructive airway disease has been reported in up to 26% of women and 61% of men (Rosenberg et al. 1980; Germain 2010; Franzen et al. 2013). In men, a significant decrease in all spirometric variables, including a reduced diffusion capacity, has been observed compared with unaffected controls (Magage et al. 2007), while women have decreased percent fixed vital capacity. The primary mechanism is likely to be Gb3 accumulation within the endothelial and bronchial smooth muscle cells resulting in hyperplasia of the pulmonary small airways combined with impaired smooth muscle relaxation (Magage et al. 2007; Raiman and Clarke 2010; Franzen et al. 2013).

Sleep disturbance is a frequent clinical finding; up to 68% Fabry males have excessive daytime sleepiness (Duning et al. 2009). Possible causes include central sleep apnoea (CSA) and obstructive sleep apnoea (OSA), respectively, seen in 22% and 17% of patients (Duning et al. 2013), and restless legs secondary to painful peripheral neuropathy, reported in 36% patients (Dominguez et al. 2007). In comparison 2–4% of the adult normal population have OSA (Epstein et al. 2009), while 5–15% are affected by restless legs (Earley and Silber 2014; Becker and Novak 2014; Winkelman et al. 2013). Furthermore, 2.7% of the population meet criteria for clinically significant restless leg syndrome (Winkelman et al. 2013). Enzyme replacement therapy in Fabry disease has been shown to stabilise or alleviate bronchial obstruction and sleep apnoea (Franzen et al. 2013; Wang et al. 2008; Kim et al. 2007) and reduce neuropathic pain (Dominguez et al. 2007).

We aimed to explore the prevalence and possible causes of sleep disturbance in a cohort of Fabry patients using polysomnography. Known associated risk factors including cardiovascular disease, cerebrovascular disease and iron deficiency were also assessed.

Methods

Study Population

All male Fabry patients attending the Royal Melbourne Hospital Fabry clinic were invited to undergo overnight polysomnography (PSG). Inclusion criteria were confirmed genetic diagnosis of Fabry disease and ability to tolerate overnight PSG. Patients were not required to meet specific respiratory or sleep disturbance criteria. Informed consent was obtained for data analysis. Patient characteristics of height, weight, body mass index and smoking status were collected prior to the study. Disease severity was determined by validated health surveys and quality-of-life scores. Daytime sleepiness was determined by the Epworth Sleepiness Scale (ESS) (Johns 1992) with an abnormal score being >10. Symptoms of restless legs, defined by the International RLS Study Group (2012), were assessed at the time of recruitment.

Polysomnography

Patients underwent overnight PSG at the Department of Respiratory and Sleep Medicine at Royal Melbourne Hospital, conducted by qualified sleep scientists and reported by a sleep physician. Measurements were performed according to the American Academy of Sleep Medicine guidelines (AASM, Berry et al. 2012). A 17-channel PSG recorded readings from electrocardiogram, electroencephalogram (EEG), electrooculogram, chin and lower leg (anterior tibialis) electromyograms (EMG), chest and abdominal inductance respiratory belts, pulse oximetry, body position, airflow monitoring via oronasal thermistor and nasal cannula and a snore microphone positioned on the neck.

Sleep stages and physiological events were scored according to the 2012 AASM Rules (Berry et al. 2012), with apnoea defined as a $\geq$ 90% drop in oronasal airflow for $\geq$10 s and hypopnea defined as a $\geq$30% drop in nasal airflow amplitude lasting $\geq$10 s, leading to either a $\geq$3% oxygen desaturation or a cortical arousal. Apnoeas were scored as obstructive events (apnoeic event with increased or ongoing respiratory effort throughout the period of airflow cessation) or central events (apnoeic event with absent respiratory effort throughout the period of airflow cessation). The apnoea–hypopnea index (AHI) defined as the average frequency of events per hour of sleep, with an AHI of 5–14, 15–29 and $\geq$30 defined as mild, moderate and severe, respectively.

Periodic leg movements during sleep are defined as rhythmical extensions of big toe and dorsiflexion at the

ankle, knee and hip as in retraction response. Leg movements were scored on each leg channel when they reached an amplitude $\geq$8 μV and duration of 0.5–10 s. A series of periodic movements was defined by four or more leg movements, separated by 5–90 s. Normal periodic leg movement index (PLMI) is defined as <5/h (Somers et al. 2008). Cortical arousals were defined as an abrupt shift in EEG frequency (excluding spindles) lasting more than 3 s. During REM, a concurrent increase in chin EMG amplitude lasting at least 1 s was also required. Leg movements and arousals are associated when a period of <0.5 s occurs between the end of one event and the onset of another, irrespective of the order in which they appear.

Cardiac Function

Transthoracic Echocardiography

Transthoracic echocardiography is routinely performed annually in adult male Fabry patients. Measurements were performed according to American Society of Echocardiography recommendations (Lang et al. 2005) and included interventricular septal and posterior wall diameters and left atrial diameter. Standard assessment of diastolic function was performed, including tissue Doppler imaging, to determine estimated left ventricular filling pressure. Heart failure was defined as presence of systolic and/or diastolic dysfunction. Diastolic dysfunction is defined as a left ventricular filling pressure (E/Ea) >15 or deceleration time >220 ms.

Magnetic Resonance Imaging

Presence of cardiac fibrosis was determined by late gadolinium enhancement on cardiac magnetic resonance imaging (MRI) after intravenous injection of gadobenate dimeglumine 0.1 mmol/kg.

Renal Function

Glomerular filtration rate was measured yearly by renal clearance of radionuclide ^{51}Cr-EDTA, normalised to body surface area.

Cerebrovascular Disease

Multiplanar, multisequence images were obtained through the brain of each patient using 3-Tesla system and included time of flight magnetic resonance angiography. The presence of white matter lesions, above the age appropriate level, infarct(s) and/or dolichoectasia was determined as markers of cerebrovascular disease.

Metabolic Studies

Calcium, magnesium, 25OH vitamin D and iron levels, including total iron and ferritin, were measured prior to each PSG. Anaemia was defined as haemoglobin <130 g/l, iron <10 μmol/l, ferritin <20 μg/l or transferrin saturation <20%.

Health and Quality-of-Life Scores

Disease severity index was measured according to validated scoring systems:

1. SF-36 Health Survey – The 36-item short-form health status questionnaire measured the level of disability at the time of each PSG.
2. EQ5D Generic QOL – Five dimension simple quality-of-life status questionnaire recorded at the time of each PSG.

A diagnosis of depression was made clinically, based on subjective symptoms and response to antidepressant agents.

Statistical Analysis

Statistical analysis and graphical presentation utilised GraphPad Prism v6.0c for Mac OSX (1994–2013 GraphPad Software Inc). Descriptive statistics were presented as median with interquartile range or mean and (standard deviation). Shapiro–Wilk test assessed continuous variables for normality prior to data analysis. Patient groups were compared using Mann–Whitney *U* tests. Wilcoxon rank or Fishers exact tests were used to compare the frequencies of recorded parameters within patient groups. Spearman's matrix was used to determine correlations between continuous variables. A p value <0.05 was considered statistically significant.

Results

Study Population

Thirty-two male patients with genetically confirmed Fabry disease who attended the outpatient clinic between June 2008 and June 2015 were invited to undergo nocturnal polysomnography. PSG studies were undertaken in 21 of these, with one study terminated early due to insomnia. Of the remaining 11 patients, four were international candidates unable to participate, four declined investigation and three dialysis patients were unable to attend. Patient characteristics at the time of PSG are shown in Table 1.

Table 1 Parameters of patients with and without obstructive sleep apnoea (OSA)

Variable	OSA $N = 8$	No OSA $N = 12$	p
Age	44.9 ± 11.9	42.5 ± 10.5	0.65[a]
BMI	24.3 ± 5	24 ± 2.8	0.98[a]
Neck circumference (cm)	40 (37.1–45.8)	39 (37.5–40.9)	0.51[a]
Mallampati score	3 (1–3)	3 (2–4)	0.39[a]
ESS	10.5 (6–18)	9 (4–13)	0.34[a]
DT (ms)	207.7 (183–235)	197 (182–238)	0.84[a]
IVWT (mm)	10.5 (9.3–17.3)	14 (10–15.8)	0.099[a]
PWT (mm)	10 (9–13.5)	13 (10–16)	0.16[a]
LVMI (g/m^2)	110 (84–153)	125 (96–198)	0.26[a]
E/Ea	8 (6–10)	12 (9–15)	0.08[a]
LAD (mm)	4 (3.4–4.8)	3.9 (3.3–4.6)	0.63[a]
GFR (ml/min/1.73 m^2)	86.5 (66.3–100)	82.5 (42.3–87.3)	0.33[a]
Cerebrovascular disease (n)	4 (50%)	5 (45.5%)	0.85[b]

BMI body mass index, *DT* ventricular deceleration time, *IVWT* interventricular wall thickness, *PWT* posterior wall thickness, *E/Ea* estimated left ventricular filling pressure, *LAD* left atrial diameter, *GFR* glomerular filtration rate
[a] Mann–Whitney *U*-test
[b] Fishers Exact Test

Periodic leg movements were not available in one PSG recording due to a technical difficulty.

The mean age of the 20 males completing the study was 43.9 ± 10.7 years (range 23–71 years). Body mass index was 24.3 ± 3.3 kg/m^2 (range 17.1–31.6) and neck size 39.7 ± 3.3 cm (range 33–46). Enzyme replacement therapy was being used by 16 (80%) of patients. Sleepiness scores by ESS were 9.8 ± 5.1, with 7/20 having abnormal results.

Polysomnography

Sleep-Disordered Breathing

Sleep-disordered breathing with AHI $\geq$ 5 and $\geq$15 events/h was, respectively, present in 10 (50%) and 5 (25%) of the 20 patients studied. The severity of OSA was mild in three, moderate in five and severe in two cases. No obvious demographic differences were found between patients with sleep-disordered breathing and those without. Age, BMI, neck size, and Mallampati scores were not statistically different in patients with OSA (see Table 1).

Abnormal PLMI and Restless Legs

Fifteen of the 20 patients (75%) assessed described symptoms consistent with restless leg syndrome, with none taking preventative medications. Nineteen patients had periodic leg movement syndrome having recorded abnormal PLMI >5/h. Only two males had cortical arousals that were attributable to abnormal PLMI. There were no obvious demographic differences associated with increasing PLMI (see Table 2). Increased PLMI was associated with depression (Mann–Whitney $p = 0.0166$), with increased neuropathic pain, as measured by anti-epileptic drug requirements (Mann–Whitney, $p = 0.0412$), and with markers of cardiomyopathy – left ventricular mass index and left atrial diameter (Spearman's rho = 0.53, df 16, $p = 0.035$ and rho = 0.66, $p = 0.006$, respectively). Ferritin and PLMI were negatively correlated (Spearman's rho = −0.58, df 19, $p = 0.01$), but no other metabolic parameters nor the presence of cerebrovascular disease correlated with increased PLMI.

Cardiac Function

Mean interventricular and posterior wall thicknesses for the entire cohort were 13.6 ± 4.7 and 12.2 ± 3 mm, respectively. Deceleration time and E/Ea, markers of diastolic function, were 226 ± 92 and 11.2 ± 4.8 ms, respectively. There were no differences in any cardiac parameters or diastolic dysfunction between those with or without OSA. Two patients had systolic dysfunction but neither had OSA. Neither the presence of heart failure (diastolic or systolic

Table 2 Correlation of PLMI scores with presence of risk factors for secondary restless legs

	PLMI score factor present	PLMI score factor not present	p^a
Anti-epileptic drug use	54.6 (25.1–73)[a]	36.5 (15.4–41.1)	0.041
Depression	62.9 (40.7–77)	27 (12–42)	0.017
Cardiac dysfunction	44.8 (40.3–70)	27 (12–42.1)	0.051
IVWT or PWT >12 mm	42.1 (27–67)	27.9 (12.2–57.5)	0.201
Cardiac fibrosis (MRI)	56.8 (34.6–83.4)	31.8 (12.2–42.8)	0.059
Cerebrovascular disease	46.5 (26.5–75)	38.5 (11.5–42.3)	0.094
Anaemia	27 (19.2–67)	42.1 (24–58.7)	0.624
25OH-vitamin D <55 nmol/l	42.1 (24.9–66.8)	39.7 (15.6–55)	0.486

Anti-epileptic drugs were prescribed for neuropathic analgesia with no patient having a seizure history. Depression diagnosed with clinical symptoms requiring treatment with anti-depressive agents

IVWT, interventricular wall thickness; *PWT* posterior wall thickness; cerebrovascular disease – cerebrovascular accident or dolichoectasia; anaemia – haemoglobin <130 g/l, transferrin saturation <20% or iron <10 μmol/l

[a] Median and interquartile range

[b] Mann–Whitney *U*-test

dysfunction), cardiac fibrosis measured by MRI nor cerebrovascular disease was associated with increased OSA.

Renal Function

Overall renal function (as measured by renal clearance of radionuclide ^{51}Cr-EDTA) was 75.7 ± 26.3 ml/min/1.73 m^2 and was not statistically different between patients with or without OSA (83.9 ± 22.4 versus 70.3 ± 28.2 ml/min/1.73 m^2, $p = 0.26$).

Cerebrovascular Disease

Nine (45%) of the studied males patients had evidence of cerebrovascular disease on brain MRI. Seven of these patients had established infarcts, with white matter lesions greater than expected for age. Four patients had dolichoectasia, two of these also having had infarcts. There was no association of cerebrovascular disease, defined by the presence of white matter lesion, dolichoectasia or established infarcts, with either OSA (Fisher exact $p = 0.85$) or increased PLMI (Mann–Whitney, $p = 0.094$). No patient experienced seizures or had been diagnosed with epilepsy.

Metabolic Studies

Calcium and magnesium were within normal ranges. Three patients were anaemic with a haemoglobin <130 g/l and another four were iron deficient (either iron <10 μmol/l or transferrin saturation <20%). Ferritin level was negatively correlated with increased PLMI in this cohort. Eleven patients had suboptimal vitamin D with level in range 26–54 nmol/l and three of these were deficient with level < 25 nmol/l, but no association with increased PLMI was found.

Health and Quality-of-Life Scores

The mean and median SF-36 scores of this male cohort, across all domains, were lower than reported normative controls, but there was no association between PLMI and any domain.

EQ5D generic quality-of-life average score was 62 ± 17, with no association between EQ5D score and PLMI. Ten patients were being treated with antidepressant agents for clinical diagnoses of depression.

Discussion

We have identified very high prevalence of sleep-disordered breathing, OSA (50%) and abnormal periodic leg movements (94.7%), in our cohort of male Fabry patients. Our patients had wide phenotypic variation, but significant disease severity was well represented, with 59% having cardiomyopathy and 37% cerebrovascular disease. Limited data has previously been available regarding the severity of sleep disorders in Fabry disease. Duning et al. 2013, in a mixed-gender cohort of 23 Fabry patients, reported an incidence of OSA (17%) and CSA (23%). However, this group had only mild to moderate disease with no cerebrovascular events and a low incidence of cardiomyopathy (22%). We found no cases of CSA in our male cohort despite greater disease severity. The single published study of restless legs in Fabry disease (Dominguez et al. 2007)

reported an overall incidence of 36% in a mixed cohort of 11 Fabry patients. In their study only 50% of males were affected, but these were significantly younger (age range 19–32) than our patients.

None of the traditional risk factors for OSA, including BMI, neck size and Mallampati score, explained the high incidence of obstructive sleep apnoea in our cohort. Indeed despite the high prevalence of both heart failure and hypertrophic cardiomyopathy, no association with OSA was present for any cardiovascular parameter. In addition there was no association of OSA with cerebrovascular disease, impaired renal function or vitamin D deficiency. Likely contributors to the high incidence of OSA in Fabry disease are facial dysmorphology (Cox-Brinkman et al. 2007; Ries et al. 2006) including prominent nasal bridge and pseudo-acromegalic features with prognathism (Hogarth et al. 2012) and possible thickening of upper airway. While pharyngeal diameters in our cohort were within the normal range, and Mallampati scores normal, the upper airways may well be less compliant, possibly contributing to snoring.

Abnormal PLMI, or periodic leg movement syndrome, and restless leg syndrome are common afflictions affecting 5–15% of the general population (Earley and Silber 2014; Becker and Novak 2014; Winkelman et al. 2013) and associated with insomnia in 50–85% of people (Becker and Novak 2014). We identified only two patients having cortical arousals secondary to periodic leg movement that were greater than expected age norms. Increased PLMI within our cohort could not be explained by secondary factors including anaemia, iron deficiency, cerebrovascular or cardiovascular disease. Increased PLMI was significantly associated with left atrial diameter and left ventricular mass and approached significance with cardiac dysfunction. These factors probably reflect the overall burden of disease. Ferritin itself was inversely correlated with PLMI in this study. PLMI was also significantly higher in patients with OSA, as seen in previous studies (Baran et al. 2003). It is possible that OSA itself increases the risk of developing abnormal PLMI through increased catecholamine or other hormone release.

Abnormal PLMI is usually multifactorial and is frequently found in chronic pain conditions and peripheral neuropathies. However, PLMI scores do not correlate well with pain scores (Winkelman et al. 2013), perhaps reflecting the difficulties involved in scoring pain. Depression and anxiety are both highly prevalent in Fabry disease, ranging from 15% to 62% people, and are strongly associated with neuropathic pain (Bolsover et al. 2014). Within our cohort, associations between higher PLMI and both depression and increased use of neuropathic analgesics were present, but did not extend to quality-of-life scores. Sequelae of elevated PLMI and restless legs include greater risks of depression, cerebrovascular disease and cardiovascular disease (Ferini-Strambi et al. 2014). Depression was highly prevalent in our study group, and the strong association with increased PLMI is likely to reflect the overall burden of disease and presence of peripheral nerve injury. Presence of cardiovascular and cerebrovascular disease did not correlate with either PLMI or OSA, but our small cohort size may limit this observation.

There are inherent limitations in studying Fabry patient cohorts. Firstly, phenotype is heterogeneous even within a small patient group. Secondly reported neuropathic pain is subjective, with frequent exacerbations resulting in variable neuralgic requirements. No data on nerve conduction studies or nerve biopsy data were available to further determine neuropathic involvement in individual patients.

Male Fabry patients carry a high burden of multi-organ disease in addition to significant pain and increased risk of depression. The very high prevalences of abnormal PLMI, OSA and restless legs that we observed are likely to further impact on patients' well-being, and treatment may improve quality of life. The impact of sleep disturbance on individual partners of the studied Fabry patients was not assessed. Extrapolation from the general community, however, would suggest a negative influence. This may add further strain to relationships dealing with a chronic and progressive disease.

Future investigation with repeated PSG may determine the level of response but is limited by availability. As for many manifestations of Fabry disease, it will be instructive to follow changes in abnormal PLMI and OSA as disease-specific treatment evolves and is instituted earlier.

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Take-Home Message

Sleep-disordered breathing and abnormal periodic leg movements are highly prevalent in male Fabry patients and significantly impact on patient well-being.

Compliance with Ethics Guidelines

Details of Contributions of Individual Authors

Andrew Talbot was primarily responsible for planning the study, patient recruitment and primary data interpretation, including statistical analysis and original manuscript preparation.

Gary Hammerschlag conducted patient data collection, initial sleep study analysis and data interpretation including manuscript editing.

Jeremy Goldin performed sleep study interpretation, data collection and manuscript editing.

Kathy Nicholls contributed to patient recruitment and consent for study, data interpretation and original manuscript preparation.

Conflict of Interest: Nil Direct

Andrew Talbot has received research support, speaker honoraria and travel assistance from Shire Corporation and Sanofi Corporation, speaker honoraria and travel assistance from Dainippon Sumitomo Pharma Co and research support from Amicus Therapeutics and Protalix Biotherapeutics.

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Gary Hammerschlag declares that he has no conflict of interest relevant to this project.

Jeremy Goldin declares that he has no conflict of interest relevant to this project.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000(5). Informed consent was obtained from all patients for data analysis of results included in the study.

This article does not contain any studies with animal subjects performed by any of the authors.

References

Baran AS, Richert AC, Douglass AB, May W, Ansarin K (2003) Change in periodic limb movement index during treatment of obstructive sleep apnoea with continuous positive airway pressure. Sleep 26(6):717–720

Becker PM, Novak M (2014) Diagnosis, comorbidities, and management of restless legs syndrome. Curr Med Res Opin 30 (8):1441–1460

Berry RB, Budhiraja R, Gottlieb DJ et al (2012) Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. J Clin Sleep Med 8 (5):597–619

Bolsover FE, Murphy E, Cipolotti L, Werring DJ, Lachmann RH (2014) Cognitive dysfunction and depression in Fabry disease: a systematic review. J Inherit Metab Dis 27:177–187

Cox-Brinkman J, Vedder A, Hollak C et al (2007) Three dimensional face shape in Fabry disease. Eur J Hum Genet 15:535–542

Desnick RJ, Brady R, Barranger J et al (2003) Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. Ann Intern Med 138:338–346

Dominguez RO, Michref A, Tanus E, Amartino H (2007) Restless legs syndrome in Fabry disease: clinical feature associated to neuropathic pain is overlooked. Rev Neurol 45(8):474–478

Duning T, Deppe M, Keller S et al (2009) Excessive daytime sleepiness is a common symptom in Fabry disease. Case Rep Neurol 1:33–40

Duning T, Deppe M, Brand E et al (2013) Brainstem involvement as a cause of central sleep apnea: pattern of microstructural cerebral damage in patients with cerebral microangiopathy. PLoS One 8 (4):e60304

Earley CJ, Silber MH (2014) Restless legs syndrome: understanding its consequences and the need for better treatment. Sleep Med 11:807–815

Epstein LJ, Kristo D, Strollo PJ et al (2009) Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med 5(3):263–276

Ferini-Strambi L, Walters AS, Sica D (2014) The relationship among restless legs syndrome (Willis–Ekbom Disease), hypertension, cardiovascular disease, and cerebrovascular disease. J Neurol 261:1051–1068

Franzen D, Krayenbuehl PA, Lidove O, Aubert J-A, Barbey F (2013) Pulmonary involvement in Fabry disease: overview and perspectives. Eur J Intern Med 24:707–713

Germain DP (2010) Fabry disease. Orphanet J Rare Dis 5:30

Hogarth V, Hughes D, Orteu CH (2012) Pseudoacromegalic facial features in Fabry disease. Clin Exp Dermatol 38:137–139

International Restless Leg Syndrome Study Group. Revised IRLSSG diagnostic criteria for RLS 2012. http://irlssg.org/diagnosric-criteria. Last accessed 19 Jan 2016

Johns MW (1992) A new method for measuring daytime sleepiness. The Epworth sleepiness scale. Sleep 14:540–545

Kim W, Pyeritz RE, Bernhardt BA, Casey M, Litt HI (2007) Pulmonary manifestations of Fabry disease and positive response to enzyme replacement therapy. Am J Med Genet 143:377–381

Lang RM, Bierig M, Devereux RB et al (2005) Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 18:1440–1463

Lobo T, Morgan J, Bjorksten A et al (2008) Cardiovascular testing in Fabry disease: exercise capacity reduction, chronotropic incompetence and improved anaerobic threshold after enzyme replacement. Intern Med 38:407–414

Magage S, Lubanda JC, Susa Z et al (2007) Natural history of the respiratory involvement in Anderson-Fabry disease. J Inherit Metab Dis 30:790–799

Mehta A, Ricci R, Widmer U et al (2004) Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur J Clin Invest 34(3):236–242

Mehta A, Clarke JT, Giugliani R et al (2009) Natural course of Fabry disease: changing pattern of causes of death in FOS Outcome Survey. J Med Genet 46:548–552

Raiman JAJ, Clarke TM (2010) Pulmonary, ear and less commonly appreciated manifestations (Chap. 18). In: Elstein D (ed) Fabry disease. Springer, New York

Ries M, Moore DF, Robinson CJ et al (2006) Quantitative dysmorphology assessment in Fabry disease. Genet Med 8(2):96–101

Rosenberg DM, Ferrans VJ, Fulmer JD et al (1980) Chronic airflow obstruction in Fabry's disease. Am J Med 68(6):898–905

Somers VK, White DP, Amin R et al (2008) Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation 118:1080–1111

von Scheidt W, Eng CM, Fitzmaurice TF et al (1991) An atypical variant of Fabry's disease with manifestations confined to the myocardium. N Engl J Med 324:395–399

Wang RY, Abe JT, Cohen AH, Wilcox WR (2008) Enzyme replacement therapy stabilizes obstructive pulmonary Fabry disease associated with respiratory globotriaosylceramide storage. J Inherit Metab Dis 31:S369–S374

Winkelman JW, Gagnon A, Clair AG (2013) Sensory symptoms in restless legs syndrome: the enigma of pain. Sleep Med 14:934–942

Zarate YA, Hopkin RJ (2008) Lysosomal storage disease 3: Fabry's disease. Lancet 372:1427–1435