Brain & Development 41 (2019) 250–256

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Restless Legs Syndrome in *NKX2-1*-related chorea: An expansion of the disease spectrum

A. Iodice [a,*], M. Carecchio [b,c], G. Zorzi [c], B. Garavaglia [b], C. Spagnoli [a], G.G. Salerno [a] D. Frattini [a], N.E. Mencacci [d], F. Invernizzi [b], L. Veneziano [e], E. Mantuano [e] M. Angriman [f], C. Fusco [a]

[a] *Child Neurology and Psychiatry Unit, Santa Maria Nuova Hospital IRCCS, Reggio Emilia, Italy*
[b] *Molecular Neurogenetics Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Via L. Temolo 4, 20126 Milan, Italy*
[c] *Department of Pediatric Neurology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Via Celoria 11, 20133 Milan, Italy*
[d] *Department of Neurology, Northwestern University, Feinberg School of Medicine, Chicago, 60611 IL, USA*
[e] *Institute of Translational Pharmacology, National Council of Research, Rome, Italy*
[f] *Child Neurology and Neurorehabilitation Unit, Department of Pediatrics, Hospital of Bolzano, Italy*

Received 14 March 2018; received in revised form 13 July 2018; accepted 1 October 2018

Abstract

Background: Molecular technologies are expanding our knowledge about genetic variability underlying early-onset non-progressive choreic syndromes. Focusing on *NKX2-1*-related chorea, the clinical phenotype and sleep related disorders have been only partially characterized.

Methods: We propose a retrospective and longitudinal observational study in 7 patients with non-progressive chorea due to *NKX2-1* mutations. In all subjects sleep and awake EEG, brain MRI with study of pituitary gland, chest X-rays, endocrinological investigations were performed. Movement disorders, pattern of sleep and related disorders were investigated using structured clinical evaluation and several validated questionnaires.

Results: In patients carrying *NKX2-1* mutations, chorea was mainly distributed in the upper limbs and tended to improve with age. All patients presented clinical or subclinical hypothyroidism and delayed motor milestones. Three subjects had symptoms consistent with Restless Legs Syndrome (RLS) that improved with Levodopa.

Conclusions: Patients with *NKX2-1* gene mutations should be investigated for RLS, which, similarly to chorea, can sometimes be ameliorated by Levodopa.

Keywords: Benign hereditary chorea; Restless legs syndrome; *NKX2-1*-related chorea; *ADCY5*; Levodopa

1. Background

In recent years, thanks to the advances in DNA sequencing technologies, the list of genetic non-progressive forms of hereditary choreas has expanded [1]. In 2002 mutations in *NKX2-1* (also known as TITF1 or TTF1) were linked to benign hereditary chorea (BHC) [2,3]. More recently, *ADCY5* mutations have been described as a cause of hyperkinetic movements with a non-progressive course and childhood onset [4–6]. Differentiating these genetic disorders on clinical

* Corresponding author at: Viale Risorgimento 80, Arcispedale Santa Maria Nuova, 42123 Reggio Emilia, Italy.
E-mail address: alle.iodice@gmail.com (A. Iodice).

https://doi.org/10.1016/j.braindev.2018.10.001
0387-7604/

grounds only, can be challenging due to the existence of several clinical overlaps, including delay in motor milestones, axial hypotonia and similar age at onset. Moreover, some phenotypic features of these genetic conditions have not been investigated in detail. Despite the elevated disability due to sleep-related disturbances in choreic syndromes and parkinsonisms with adult onset [7,8], data on sleep disorders in monogenic early onset non-progressive choreas are scarce. Patients with *ADCY5* mutations often show sleep-related episodic exacerbations of movement disorder [9].

The first descriptions of BHC reported the disappearance of hyperkinetic movement disorder during sleep with reappearance upon awakening [10]. Afterwards, this finding was recognized to be specific only in families carrying NKX2-1 mutations [11]. No other studies focusing on movement disorders during sleep was tried in this group of patients. The aim of the present study was to describe clinical movement sleep-awake patterns and to analyse sleep quality in patients with NKX2-1 gene mutation.

2. Material and methods

We performed a retrospective longitudinal observational study including 7 consecutive patients diagnosed with benign hereditary chorea due to *NKX2-1* mutations belonging to four different pedigrees (three sporadic cases and four related patients). The institutional research ethics committee approved the study and informed consent was obtained from the parents of the children enrolled. All patients presented a non-progressive hyperkinetic movement disorder mainly characterized by generalized chorea with onset before the age of 20 months, without other major neurological features. All subjects had been referred to our Department of Child Neurology from 2010 to 2017 and underwent an extensive diagnostic workup including sleep and awake EEG, brain MRI with study of pituitary gland, chest X-ray, cardiac ultrasound and endocrinologic investigations (TSH, FT3 and FT4 in serum TSH, FT3 and FT4 in serum TSH, FT3, FT4, cortisolemia, ACTH, serum glucose).

Movement disorders were analysed through clinical and video-taped evaluation and Abnormal Involuntary Movement Scale (AIMS) questionnaire was administered [12]. Written informed consent to perform genetic testing was obtained from the parents of enrolled children and directly from adult subjects included in the study. All participants were assessed by neurologists with expertise in movement disorders.

Genomic DNA was extracted from peripheral blood lymphocytes according to standard procedures and the 3 coding exons of *NKX2-1* gene were Sanger sequenced as described by Breedveld and colleagues [2]. Sleep quality and sleep disorders were investigated using validated questionnaires and a structured clinical interview: for subjects in the paediatric age, Sleep Disturbance Scale for Children (SDSC) [13], Paediatric Restless Legs Syndrome (RLS) Severity Scale and the paediatric version of the Epworth Sleepiness Scale were used; in adults, Epworth Sleepiness Scale, Berlin questionnaire, a validated Restless Legs Syndrome (RLS) single question [14–17] and Pittsburgh Sleep Quality Assessment (PSQI) were administered. Subjects with confirmed different sleep disorders were investigated for the influences of anti-dyskinetic pharmacological treatment on sleep patterns.

3. Results

Patients included in the study carried four different mutations in the *NKX2-1* gene; three sporadic cases harboured *de novo* missense mutations causing a single amino acid substitution (p.Leu230Pro; p.Pro291Arg) or a premature stop codon (p.Tyr100*), whereas four affected children, belonging to the same dominant kindred, carried a frameshift mutation causing a premature stop codon (p.Trp238Cysfs*9). All patients presented with chorea between 6 and 15 months with a mean age of onset of 10.4 months; all exhibited mild to moderate hypotonia and delayed motor milestones at time of first evaluation. Chorea had a generalized distribution over the whole disease course, although its severity was variable, also depending on the patients' age and pharmacological treatment; a significant spontaneous improvement was observed from childhood to adolescence in one patient. Some features were consistently observed: prominent arm involvement was recognized in 6 subjects and particularly in 3 belonging to the same family with a positive AIMS examination receiving a score of 3 or 4 in upper extremity movements. One subject displayed myoclonic jerks in the upper limbs, more prominent upon awakening and decreased in severity during the day with a circadian pattern whereas none reported drop attacks. Abnormal involuntary movements were absent at rest in 3 subjects whereas spontaneous darting movements were seen in the others. Dysarthric speech (moderate modification of fluency) was reported in two patients (Table 1).

With regards to respiratory manifestations, only one patient required mechanical ventilation due to neonatal respiratory distress and chest X-rays (performed at the time of first evaluation) were unremarkable in all subjects. Subclinical or clinical hypothyroidism with high serum thyrotropin concentration was documented in all subjects at the time of diagnosis and hormone replacement therapy was started in five out of seven patients.

Results coming from analysis of sleep scales and questionnaires are reported in Table 2. The SDSC is a quantitative paediatric scale which identifies an overall

Table 1
Phenotypic features and sleep patterns of *NKX2.1* positive subjects.

NKX2-1 patients	Family 1/subject II-A1*	Family 1/subject III-A2*	Family 1/subject III-A3*	Family 1/subject III-B1*	Sporadic case/subject 1	Sporadic case/subject 2	Sporadic case/subject 3
Ethnic origin	IT-Caucasian	IT-Caucasian	IT-Caucasian	IT-Caucasian	IT-Caucasian	IT-Caucasian	IT-Caucasian
Age at onset	6 months (post-vaccination)	10 months	11 months	9 months	13 months	10 months	14 months
Age at last examination	35 years	8 years	4 years	3 years	16 years	5 years	7 years
Mutation (affected transcript Ref. Seq. NM_001079668.2)	c.714del G	c.714del G	c.714del G	c.714del G	c.689T>C	c.872C>G	c.300C>G
Affected protein (Ref. Seq. NP_001073136.1)	p.Trp238Cysfs*9	p.Trp238Cysfs*9	p.Trp238Cysfs*9	p.Trp238Cysfs*9	p.Leu230Pro	p.Pro291Arg	p.Tyr100*
Symptoms at onset	Motor delay	Motor and language delay	Motor delay	Motor delay	Motor and language delay	Motor delay	Motor and language delay
Episodic mov dis exacerbations	No	No	No	No	No	No	No
Choreic features (pattern and distribution)	Prominent arm involvement	Prominent arm involvement	Prominent arm involvement	No dyskinetic movement at rest		No dyskinetic movement at rest	No dyskinetic movement at rest
AIMS (higher score)	Extremity movements (upper: arms, wrist, hand, finger) score 3	Extremity movements (upper: arms, wrist, hand, finger) score 4	Extremity movements (upper: arms, wrist, hand, finger) score 3	Extremity and trunk movements: score 2	Extremity and trunk movements: score 1	Facial, oral, Extremity and trunk movements: score 1	Extremity and trunk movements: score 1
Other Movement disorders	Darting movement of the legs at rest	Darting movement of the legs at rest	Darting movement of the legs at rest	Jerky movements	Darting movement of the legs at rest and during sleep	–	–
MRI	Normal	Little pituitary gland	Normal	Normal	Normal	Hippocampal dysmorphism	Normal
EEG awake and sleep	Sleep apnoeas						
Endocrinological alterations	Hypothyroidism	Hypothyroidism	Subclinical hypothyroidism	Hypothyroidism	Hypothyroidism	Subclinical hypothyroidism	Hypothyroidism; neonatal respiratory distress
Therapy	Tetrabenazine (50 mg/day) Levodopa (3 mg/kg/day)	Levodopa (4 mg/kg/day)	Levodopa (3 mg/kg/day)	Levodopa (5 mg/kg/day)	Levodopa (3 mg/kg/day)	Trihexifenydil (2 mg/kg/day) discontinued at 5 years of age	Levodopa (3 mg/kg/day)

*Pedigree referring to family 1 with autosomal dominant *NKX2-1* mutation: four affected subjects (black); one female carrier with mild movement disorder (light gray); one founder (dark grey).

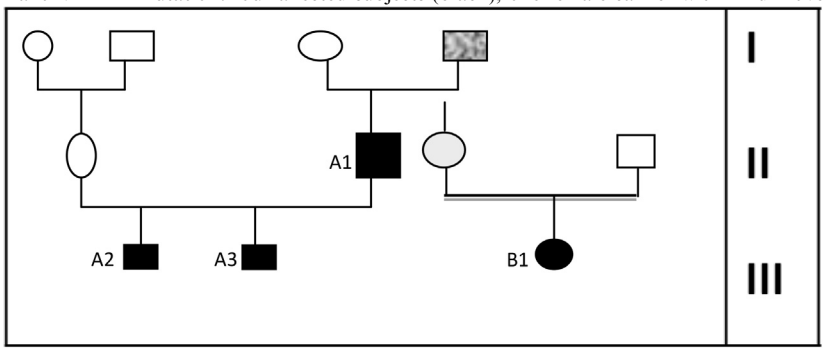

Table 2
Retrospective and longitudinal sleep analyses.

NKX2-1 patients	Family 1/subject II-A1	Family 1/subject III-A1	Family 1/subject III-A2	Family 1/subject III-B3	Sporadic case/subject 1	Sporadic case/subject 2	Sporadic case/subject 3
Restless legs syndrome diagnostic criteria	**RLS** *Positive RLS single question. International RLS Study Group consensus diagnostic criteria for restless legs syndrome.*	No unpleasant, restless feelings in the legs during evening or sleep.	**Possible RLS** *P-RLS-SS: suspected RLS. The child is observed to have behavior manifestations of lower extremity discomfort when sitting or lying, accompanied by movement of the affected limbs. The discomfort is characterized by RLS criteria 2–5*	No legs movements during sleep. No behaviour supporting uncomfortable sensation transiently relieved by movement	**Possible RLS** *P-RLS-SS: suspected RLS. Between 5 and 9 years of age the child is observed to have behavior manifestations of lower extremity discomfort when sitting or lying, accompanied by movement of the affected limbs. The discomfort is characterized by RLS criteria 2–5*	No unpleasant, restless feelings in the legs during evening or sleep.	No unpleasant, restless feelings in the legs during evening or sleep.
Sleep Disturbance Scale for Children	NP	TOTAL T score 54 normal/near normal	TOTAL T score 50 normal/near normal	TOTAL T score 68 Subdomains: Sleep wake transition disorder 84 T score (hypnic myoclonias; nocturnal hyperhidrosis) – T score 93	TOTAL T score 66 Subdomains: Sleep wake transition disorder – T score 70	TOTAL T score 54 Subdomains: Disorders of arousal – T score 82 (enuresis)	TOTAL T score 48: normal/near normal
Pittsburgh Sleep Quality Assessment	Global PSQI (overall score 10) Items: Cannot get to sleep within 30 min (score 2); Wake up in the middle of the night or early morning (score 2); Have pain (score 2); medicine to help you sleep (score 3)	**NP**	**NP**	**NP**	**NP**	**NP**	**NP**
Berlin questionnaire	no categories with a positive score	no categories with a positive score	no categories with a positive score	no categories with a positive score	no categories with a positive score	Low risk OSAS Category 1 (score 2): snoring as loud as talking	no categories with a positive score
Epworth Sleepiness Scale	TOTAL score: 6 (normal)	TOTAL score: 8 (normal)	TOTAL score: 0 (normal)	TOTAL score: 4 (normal)	TOTAL score: 6 (normal)	TOTAL score: 6 (normal)	TOTAL score: 8 (normal)
Effect of Levodopa on RLS and sleep pattern	Levodopa ameliorated RLS criteria 3 (urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement)	Regular sleep-wake pattern	Levodopa ameliorated RLS criteria 3 and 4 (unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day)	Regular sleep-wake pattern	Levodopa ameliorated RLS criteria 3 and 4 (unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day)	Enuresis still present with seasonal course	Regular sleep-wake pattern

RLS: Restless Legs syndrome; P-RLS-SS: Pediatric Restless Legs Syndrome Severity Scale; NP: not performed due to age.

score and five subdomains, based on a Likert-type scoring. In our sample we detected a mild impairment in global score for two subjects due to hypnic myoclonias and nocturnal hyperhidrosis in one case and to sleep-wake transition disorder in the other case. One subject presented enuresis with seasonal relapse.

The Epworth Sleepiness Scale, the Berlin questionnaire and the Pittsburgh Sleep Quality Assessment also are quantitative scales and give the opportunity to gather information about daytime sleepiness, sleep apneas or other sleep disorders commonly relevant in clinical practice. Results of these scales in our sample were within normal limits in all patients. On the other side Paediatric Restless Legs Syndrome (RLS) Severity Scale and validated Restless Legs Syndrome (RLS) single question were useful to satisfy clinical diagnostic criteria for RLS. In line with current validated scales and RLS International diagnostic criteria, two children displayed symptoms consistent with a diagnosis of possible Restless Legs Syndrome (RLS) [14–16]. In fact, both patients showed lower extremity discomfort when sitting or lying, which worsened during rest and sleep and were transiently relieved by voluntary movements of the affected limbs. We used the Pediatric Restless Legs Syndrome Severity Scale (P-RLS-SS) as a qualitative measure of RLS sensations intending to identify clinically relevant symptoms. In one subject RLS was still present at the time of the last evaluation (4 years) with only mild impairment on sleep and awake activities. In the teen subject despite his age (16 years old) pediatric criteria for RLS were applied due to language disorder; moreover clinical follow-up documented clear sleep impairment, due to the leg discomfort, during the period between 5 and 9 years before starting therapy with Levodopa. In both pediatric patients, sleep disturbances improved after the introduction of Levodopa (therapeutic range between 3 and 5 mg/kg with maximum daily dose of 300 mg): based on caregivers' report, the ongoing movements RLS-related improved during rest and inactivity even in the evening or night. The single question for the rapid screening of RLS was positive in the adult patient [14]; subsequently deep investigation based upon the clinical history confirmed all 5 criteria for RLS [17]. In that case Levodopa ameliorated only the unpleasant sensation and the urge to move the legs.

4. Discussion

In this study, we retrospectively evaluated seven patients with genetically confirmed *NKX2-1* related chorea with a special focus on sleep disorders. Our case series provides four novel frameshift and missense pathogenic *NKX2-1* variants, of which one co-segregating with disease status in an autosomal dominant pedigree and three arising *de novo* in sporadic cases. Clinically, all patients presented mild to moderate motor delay in infancy followed by the onset of chorea, as observed in most patients previously reported in the literature [18].

Our *NKX2-1* positive patients showed a variable severity of chorea over disease course, with a trend to gradually improve with age. In terms of distribution, choreic movements were more prominent in the upper limbs with phenotypic variability, whereas during growth no inter-subjective changes in pattern and side distribution were documented. In the youngest child, we did not observe classic chorea but mild jerky movements overcoming voluntary movements and partially relieved by therapy with Levodopa. This pattern was also reported until three years of age, in the other two children belonging to the same pedigree. Recently, mutations in the *ADCY5* gene have been described as an additional cause of BHC but, unlike *NKX2-1* mutation carriers, patients often display a characteristic pattern of movement disorders with episodic exacerbations mostly upon awakening and falling asleep [4]. Previous descriptions of BHC patients reported a generalized distribution of chorea with no further characterization [19]; in our series, choreic movements were classically generalized but with a more specific pattern characterized by marked involvement of extremities, partially sparing the face and trunk. Jerky movements presumed to be choreic in origin could be seen in toddlers. A clinical painstaking analysis of movement disorder may be of further help in discriminating *NKX2-1* mutation carriers from other forms of genetic chorea [8,18,19]. Sleep quality was investigated with different scales and questionnaires. Except for RLS suspicion in three subject (Validated RLS single question in the adult patient and P-RLS-SS in present or past clinical history of other two children), no other sleep disorders commonly relevant in clinical practice were identified. Diagnostic criteria for possible or definite RLS [15,17] were clinically fulfilled in three out of seven (43%) subjects; however 2 (50%) of the 4 NKX-2-1 variants described here were associated with RLS. Due to the limited number of patients included in our sample, clear correlation of specific clinical aspects with different genetic variants in the same gene is hampered. In all NKX2-1 mutation carriers a clinical or subclinical hypothyroidism was also documented, consistently with previous studies [19]. Hypothyroidism, especially together with low serum ferritin, can contribute to the development of RLS-like symptoms [20]. All three subjects with possible or definite RLS were taking hormonal replacement therapy since the onset of movement disorders but with normal blood thyroid hormones, ferritin levels and no iron deficiency at the time of diagnosis. This feature has never been described in patients carrying *NKX2-1* gene mutations; this might be related to the difficulty in differentiating subtle chorea in the legs from voluntary movements due to discomfort perceived in the lower

limbs by patients with RLS, especially in the pediatric age. The classical clinical presentation of RLS in children consists in a compelling urge to move the legs, often accompanied by uncomfortable dysesthesias. Revised and simplified diagnostic criteria for pediatric RLS specifically indicate that "the description of these symptoms should be in the child's own words". For non-verbal children, "diagnosis by behavioral observation" is suggested, supported by home-video-recording [21,22].

Language and cognitive development determine the applicability of the RLS diagnostic criteria, rather than age [15]; for this reason, it was a challenging diagnosis in our group of pediatric subjects due to psychomotor and language delay. In BHC patients, only the adult subject included in this study reported uncomfortable sensation transiently relieved by movement, but behavioral observation and information obtained from caregivers supported the hypothesis of possible RLS in 2 additional children.

Another important item required for RLS diagnosis is the presence of sensory-motor symptoms at rest with increased severity at night [15–17]. Accordingly, RLS diagnosis in our patients was suggested by the strict correlation between movements of legs and sleep, whereas choreic movements were not seen at rest or during sleep.

In patients with movement disorders who have difficulty in communicating subjective sensations, symptoms of RLS may be confused with other sleep disturbances (e.g. bedtime resistance and limit setting-type behaviors) and primary conditions such as bruises, growing pains, positional numbness or dermatitis which deserve to be considered for the differential diagnosis [23].

From a pathophysiological perspective, the dopaminergic theory of RLS supports a role for both dopaminergic imbalance and iron deficiency, well documented from brain autopsy, magnetic resonance imaging and cerebrospinal fluid studies in adults [24,25]. Moreover, there is evidence for decreased spinal dopamine D3 receptor (D3R) signaling in RLS [26] and a role for brain dopaminergic signaling in RLS is suggested by the efficacy of dopaminergic drugs in treating this disorder, demonstrated in multiple randomized clinical trials [27]. Regarding *NKX2-1*-mutated subjects the hypothesis that levodopa could compensate for underdeveloped dopaminergic pathways is supported by the fact that choreic movements usually improve in adolescence and by the evidence of developmental defects of the basal ganglia in *NKX2.1*-knock-out mice [10,19,28]. From this point of view, the co-presence of chorea ad RLS in *NKX2-1* mutation carriers and the response of both to treatment with Levodopa may suggest a common underlying pathophysiology involving imbalance in dopaminergic transmission. The limitation of this study are: 1) the reduced number of recruited subjects, preventing the possibility of generalizing conclusions 2) lacking of polysomnography to document Periodic Limb Movements in Sleep, which will be the aim of incoming studies.

5. Conclusion

Childhood-onset chorea has a wide differential diagnosis, including rare genetic conditions such as *NKX2-1*-related benign hereditary chorea. In this study, we showed that patients with *NKX2-1* mutations present generalized chorea, but with a distribution mainly affecting upper limbs, with variable degrees of (spontaneous) improvement in adolescence. Moreover, we suggest investigating patients with paediatric-onset chorea for RLS, given the significant disability caused by this disorder, which can benefit from drug therapy, including Levodopa that has proven effective also for chorea.

Author roles

Alessandro Iodice: concept and design, data collection, data analysis, drafting of manuscript, manuscript revision; *Miryam Carecchio*: data analysis, language formatting, manuscript revision; *Giovanna Zorzi*: data analysis; manuscript revision *Barbara Garavaglia*: data analysis, manuscript revision; *Carlotta Spagnoli*: data analysis, language formatting; *Grazia Gabriella Salerno*: data analysis; *Daniele Frattini*: data analysis; *Mencacci Niccolo*: data analysis; manuscript revision; *Federica Invernizzi*: data analysis; *Liana Veneziano*: data analysis, manuscript revision; *Elide Mantuano*: data analysis; *Marco Angriman*: concept and design; manuscript revision; *Carlo Fusco*: concept and design, manuscript revision.

Financial disclosures/conflict of interest

None to declare.

Acknowledgment

The authors would like to thank the patient's family for their kind collaboration and our patients who fight since first year of life with such disabling disorder.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2018.10.001.

References

[1] Mencacci NE, Carecchio M. Recent advances in genetics of chorea. Curr Opin Neurol 2016;29:486–95.
[2] Breedveld GJ, van Dongen JW, Danesino C, Guala A, Percy AK, Dure LS, et al. Mutations in TITF-1 are associated with benign hereditary chorea. Hum Mol Genet 2002;11:971–9.

[3] Kleiner-Fisman G, Lang AE. Benign hereditary chorea revisited: a journey to understanding. Mov Disord 2007;22:2297–305.
[4] Carecchio M, Mencacci NE, Iodice A, Pons R, Panteghini C, Zorzi G, et al. ADCY5-related movement disorders: frequency, disease course and phenotypic variability in a cohort of paediatric patients. Parkinsonism Relat Disord 2017;2017(41):37–43.
[5] Chen YZ, Friedman JR, Chen DH, Chen YZ, Friedman JR, Chen DH, et al. Gain-of-function ADCY5 mutations in familial dyskinesia with facial myokymia. Ann Neurol 2014;75:542–9.
[6] Chen HD, Méneret A, Friedman JR, Korvatska O, Gad A, Bonkowski ES, et al. ADCY5-related dyskinesia: broader spectrum and genotype-phenotype correlations. Neurology 2015;85:2026–35.
[7] Driver-Dunckley ED, Adler CH. Movement disorders and sleep. Neurol Clin 2012;30:1345–58.
[8] Piano C, Bentivoglio AR, Cortelli P, Della Marca G. Motor-related sleep disorders in Huntington disease. A comment on: Neute et al.: "Nocturnal agitation in Huntington disease is caused by arousal-related abnormal movements rather than by rapid eye movement sleep behavior disorder" by Neutel et al.. Sleep Med 2016;20:172–3.
[9] Friedman JR, Méneret A, Chen DH, et al. ADCY5 mutation carriers display pleiotropic paroxysmal day and nighttime dyskinesias. Mov Disord 2016;31:147–8.
[10] Haerer AF, Currier RD, Jackson JF. Hereditary nonprogressive chorea of early onset. N Engl J Med 1967;276:1220–4.
[11] Inzelberg R, Weinberger M, Gak E. Benign hereditary chorea: an update. Parkinsonism Relat Disord 2011;17:301–7.
[12] Guy WA. Abnormal Involuntary Movement Scale (AIMS) ECDEU assessment manual for psychopharmacology. Washington, DC: U.S. Department of Health Education and Welfare; 1976. p. 534–7.
[13] Bruni O, Ottaviano S, Guidetti V, Romoli M, Innocenzi M, Cortesi F, et al. The Sleep Disturbance Scale for Children (SDSC). Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. J Sleep Res 1996;5:251–61.
[14] Ferri R, Lanuzza B, Cosentino FI, Iero I, Tripodi M, Spada RS, et al. A single question for the rapid screening of restless legs syndrome in the neurological clinical practice. Eur J Neurol 2007;14:1016–21.
[15] Picchietti DL, Bruni O, De Weerd A, Durmer JS, Kotagal S, Owens JA, et al. Pediatric restless legs syndrome diagnostic criteria: an update by the International Restless Legs Syndrome Study Group. Sleep Med 2013;14:1253–9. https://doi.org/10.1016/j.sleep.2013.08.778.
[16] Arbuckle R, Abetz L, Durmer JS, Ivanenko A, Owens JA, Croenlein J, et al. Development of the Pediatric Restless Legs Syndrome Severity Scale (P-RLS-SS): a patient-reported outcome measure of pediatric RLS symptoms and impact. Sleep Med 2010;11:897–906. https://doi.org/10.1016/j.sleep.2010.03.016.
[17] Allen RP, Picchietti 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.
[18] Peall HJ, Kurian MA. Benign hereditary chorea: an update. Tremor Other Hyperkinet Mov 2015;5:314.
[19] Moya CM, Perez de Nanclares G, Castaño L, Potau N, Bilbao JR, et al. Functional study of a novel single deletion in the TITF1/NKX2.1 homeobox gene that produces congenital hypothyroidism and benign chorea but not pulmonary distress. J Clin Endocrinol Metab 2006;91:1832–41.
[20] Tan EK, Ho SC, Eng P, Loh LM, Koh L, Lum SY, et al. Restless legs symptoms in thyroid disorders. Parkinsonism Relat Disord 2004;10:149–51.
[21] Peall KJ, Lumsden D, Kneen R, Madhu R, Peake D, Gibbon F, et al. Benign hereditary chorea related to *NKX2.* 1: expansion of the genotypic and phenotypic spectrum. Dev Med Child Neurol 2014;56:642–8.
[22] Ipsiroglu OS, Hung YH, Chan F, Ross ML, Veer D, Soo S, et al. "Diagnosis by behavioral observation". Home-videosomnography – a rigorous ethnographic approach to sleep of children with neurodevelopmental conditions. Front Psychiatry 2015;6:39.
[23] Waln O, Jankovic J. Paroxysmal movement disorders. Neurol Clin 2015;33:137–52.
[24] Connor JR, Ponnuru P, Wang XS, Patton SM, Allen RP, Earley CJ. Profile of altered brain iron acquisition in restless legs syndrome. Brain 2011;134:959–68.
[25] Connor JR, Wang XS, Allen RP, Beard JL, Wiesinger JA, Felt BT, et al. Altered dopaminergic profile in the putamen and substantia nigra in restless leg syndrome. Brain 2009;132:2403–12.
[26] Trenkwalder C, Paulus W. Restless legs syndrome: pathophysiology, clinical presentation and management. Nat Rev Neurol 2010;6:337–46.
[27] Garcia-Borreguero D, Stillman P, Benes H, Buschmann H, Chaudhuri KR, Gonzalez Rodríguez VM, et al. Algorithms for the diagnosis and treatment of restless legs syndrome in primary care. BMC Neurol 2011;11:28.
[28] Fons C, Rizzu P, Garcia-Cazorla A, Martorell L, Ormazabal A, Artuch R, et al. TITF-1 gene mutation in a case of sporadic non-progressive chorea. Response to levodopa treatment. Brain Dev 2012;34:255–7.