Received: 12 June 2023 | Accepted: 8 August 2023

DOI: 10.1111/ene.16038

european journal of neurology
the official journal of the european academy of neurology

REVIEW ARTICLE

Systematic review of drug therapy for chorea in *NXK2*-1-related disorders: Efficacy and safety evidence from case studies and series

Laia Nou-Fontanet[1] | Carmen Martín-Gómez[2,3] | Rebeca Isabel-Gómez[2] | Anne-Catherine Bachoud-Lévi[4,5,6] | Giovanna Zorzi[7] | Alessandro Capuano[8] | *NKX2-1*-Related Disorders Guideline Working Group | Juan Antonio Blasco-Amaro[2] | Juan Darío Ortigoza-Escobar[1,6,9]

[1]Department of Paediatric Neurology, Hospital Sant Joan de Déu, Barcelona, Spain

[2]Health Technology Assessment Area-AETSA, Andalusian Public Foundation for Progress and Health ("Fundación Progreso y Salud"-"FPS"), Seville, Spain

[3]Research Group HUM604: Lifestyle Development in the Life Cycle and Health Promotion, University of Huelva, Huelva, Spain

[4]Assistance Publique-Hôpitaux de Paris, Henri Mondor Hospital, National Center of Reference for Huntington's Disease, Créteil, France

[5]Département d'Etudes Cognitives, École Normale Supérieure, PSL University, Paris, France

[6]European Reference Network for Rare Neurological Diseases (ERN-RND), Tübingen, Germany

[7]Department of Pediatric Neuroscience, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

[8]Movement Disorders Clinic, Department of Neurosciences, Bambino Gesù Children's Hospital, Rome, Italy

[9]U-703 Centre for Biomedical Research on Rare Diseases (CIBER-ER), Instituto de Salud Carlos III, Barcelona, Spain

Correspondence
Juan Darío Ortigoza-Escobar, Movement Disorders Unit, Pediatric Neurology Department, Institut de Recerca, Hospital Sant Joan de Déu Barcelona, Passeig Sant

Abstract

Background: The *NKX2-1*-related disorders (*NKX2-1*-RD) is a rare disorder characterized by choreiform movements along with respiratory and endocrine abnormalities. The European Reference Network of Rare Neurological Disorders funded by the European Commission conducted a systematic review to assess drug treatment of chorea in *NKX2-1*-RD, aiming to provide clinical recommendations for its management.

Methods: A systematic pairwise review using various databases, including MEDLINE, Embase, Cochrane, CINAHL, and PsycInfo, was conducted. The review included patients diagnosed with chorea and *NKX2-1*-RD genetic diagnosis, drug therapy as intervention, no comparator, and outcomes of chorea improvement and adverse events. The methodological quality of the studies was assessed, and the study protocol was registered in PROSPERO.

Results: Of the 1417 studies examined, 28 studies met the selection criteria, consisting of 68 patients. The studies reported 22 different treatments for chorea, including carbidopa/levodopa, tetrabenazine, clonazepam, methylphenidate, carbamazepine, topiramate, trihexyphenidyl, haloperidol, propranolol, risperidone, and valproate. No clinical improvements were observed with carbidopa/levodopa, tetrabenazine, or clonazepam, and various adverse effects were reported. However, most patients treated with methylphenidate experienced improvements in chorea and reported only a few negative effects. The quality of evidence was determined to be low.

Conclusions: The management of chorea in individuals with *NKX2-1*-RD presents significant heterogeneity and lack of clarity. While the available evidence suggests that methylphenidate may be effective in improving chorea symptoms, the findings should be interpreted with caution due to the limitations of the studies reviewed. Nonetheless, more rigorous and comprehensive studies are necessary to provide sufficient evidence for clinical recommendations.

Laia Nou-Fontanet and Carmen Martín-Gómez contributed equally to this study.

Joan de Déu 2, 08950 Barcelona, Spain.
Email: juandario.ortigoza@sjd.es

KEYWORDS
chorea, clinical guideline, drug therapy, *NKX2-1*, systematic review

INTRODUCTION

NKX2-1-related disorder (*NKX2-1*-RD), also referred to as benign hereditary chorea, is a rare condition characterized by early-onset choreiform movements, respiratory complications, and endocrinological abnormalities, all of which result from variations or deletions in the *NKX2-1* gene [1–4]. The neurological phenotype of *NKX2-1*-RD is defined by hypotonia and associated movement disorders, including chorea, ataxia, dystonia, myoclonus, and others, which are debilitating symptoms that impede the psychomotor development of patients, causing a delay in motor development, gait and balance disturbances, and difficulties with daily activities. Chorea is the most common manifestation of these symptoms and has been the focus of most previous studies. Chorea typically has an onset at 2 years of age. Although there are no natural history studies, it has been observed that the condition often demonstrates improvement or remains stable during the second decade of life.

Despite the availability of pharmacological treatment options for *NKX2-1*-RD, the management of chorea, a hallmark symptom of the disorder, remains challenging. The current drug therapies, such as L-dopa, tetrabenazine, and methylphenidate, have shown limited efficacy in controlling chorea, leaving patients with impaired gait and manual dexterity. Owing to the rarity of the disease, controlled clinical trials investigating the efficacy of drugs for *NKX2-1*-RD are lacking. As a result, there are no clear guidelines on the selection, timing, or expected motor outcomes of these medications. Thus, the immediate focus should be on the integration of rehabilitation and medical therapies aimed at reducing the severity of chorea. Conversely, the use of some of these pharmacological treatments may lead to negative adverse effects.

This complex disorder has been the focus of extensive research, leading to a plethora of case studies and case series. However, a critical analysis of the literature indicates several inadequacies in the documentation of therapeutic interventions for this condition. As part of the European Program ERN Guidelines, the European Reference Network for Rare Neurological Disorders (ERN-RND) aims to create the first clinical practice guideline for *NKX2-1*-RD. Therefore, this systematic review intends to provide a comprehensive and detailed analysis of the pharmacological management of chorea in this disorder, consolidating the available evidence and addressing gaps in the literature.

METHODS

We conducted a systematic review, registered our study protocol with the PROSPERO database (CRD42022330910), and it is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [5]. Methods are summarized below. For more detailed information, refer to Supplementary material 1.

Search strategy

We conducted a search of core electronic databases as well as a targeted search of various websites on July 26, 2022, and updated thereafter on December 2, 2022 including records dating back to 2002, when the *NKX2-1* gene mutation was first discovered and named [6]. Our search strategy followed the PICO model (see Supplementary material 2). The search was first piloted in MEDLINE through Ovid and subsequently adapted for the other databases (see Supplementary material 3).

Eligibility criteria

The inclusion criteria were patients of all ages diagnosed with chorea who had genetic confirmation of the disease. The interventions of interest were drugs used to treat chorea. No comparator was established. Outcomes of interest included improvement in chorea measured by the Unified Huntington's Disease Rating Scale (UHDRS) or clinical observation, improvement in quality of life measured through questionnaires, adverse events described, and treatment adherence measured through questionnaires or clinical observation. Any study design was included except for narrative reviews, conference articles, and editorials. No restrictions were imposed regarding language or setting.

Study selection

After removing duplicates, the title, abstract, and full texts were independently screened by two researchers. Any discrepancies in the selection process were resolved through consultation with a third independent researcher. The entire process was conducted using the Covidence software [7].

Data extraction

Data were extracted into a structured form, including author, publication year, country of origin, targeted population features, treatment approaches for chorea, effectiveness of the treatments, UHDRS score or other objective measures found, clinical observations, quality of life outcomes, adverse events, treatment adherence, and study type. Any discrepancies were resolved through a consensus-based approach.

Quality assessment

The Murad et al. [8] tool was utilized to assess the risk of bias of the included studies, and to facilitate interpretation of the score, we

followed the qualitative categories proposed by Moura-Coelho et al. [9] (see Supplementary material 4). To evaluate the overall quality of evidence, we used the GRADE system (Grade of Recommendation, Assessment, Development, and Evaluation) [10, 11].

RESULTS

Studies selection

A total of 1726 records were identified, which were reduced to 1427 after removing duplicates. Following a full-text review of 57 articles, 28 studies were included in this systematic review based on the selection criteria. The flowchart is provided in Figure 1, while Supplementary material 5 lists all included and excluded studies after full-text review.

Studies characteristics

The included studies were published between 2005 and 2019 and were conducted in Spain [12–16], Japan [17–20], USA [21–23], Italy [24, 25], France [2, 26], Germany [27, 28], Portugal [29], Norway [30], Canada [31], Israel [32], Hungary [33], UK [34–36], Ireland [37], and the UK and Ireland [38]. Of these, 8 were case reports and 22 were case series, with a valid sample size ranging from 1 to 12 patients (median = 2). The detailed characteristics of these studies are presented in Table 1.

Patient demographics and clinical characteristics

In total, 68 patients were included (42.65% were male), with 91.18% of patients exhibiting mutations and 8.82% exhibiting deletions.

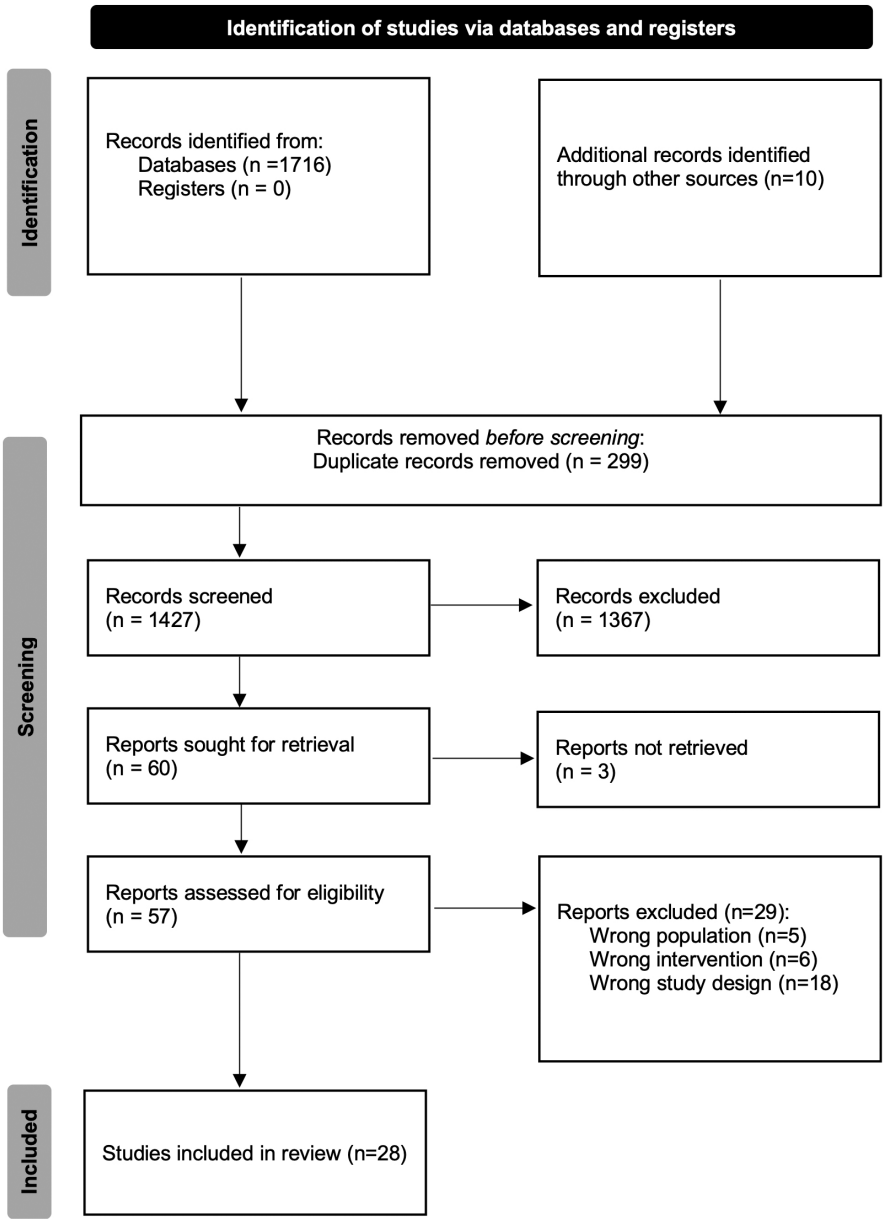

FIGURE 1 PRISMA flowchart depicting the identification, screening, and inclusion of articles for the systematic review of drug therapy for chorea in *NXK2-1*-related disorders. *Source*: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71.

TABLE 1 Study characteristics.

Author, year	Country	Study type	Patient included/full patients[a]	Study target population[b]
Asmus et al., 2005	Germany	Case series	2 (4)	Members of a family with a *TITF-1* mutation
Asmus et al., 2007	UK	Case series	1 (4)	Patients with BHC and/or myoclonus-dystonia, two members of a family and index patients in two additional pedigrees
Asmus et al., 2009	Ireland	Case series	1 (23)	Cohort of index patients with hyperkinetic dystonia
Balicza et al., 2018	Hungary	Case series	2 (2)	Members of a family with a pathogenic stop variation in the *NKX2-1* gene
Barreiro et al., 2011	Spain	Case report	1 (1)	–
Blumkin et al., 2018	Israel	Case series	1 (4)	Patients with pediatric early onset of chorea of different causes
de Gusmao et al., 2016	USA	Case report	1 (1)	–
Devos et al., 2006	France	Case series	1 (3)	Members of a family with BHC
Ferrara et al., 2012	USA	Case series	2 (10)	Members of a family with BHC
Fons et al., 2012	Spain	Case report	1 (1)	–
Gauquelin et al., 2017	Canada	Case report	1 (1)	–
Gras et al., 2012	France	Case series	12 (28)	Patients with BHC from five families and sporadic cases
Koht et al., 2016	Norway	Case series	7 (8)	Members of a family with BHC
Konishi et al., 2013	Japan	Case series	2 (6)	Members of a family with BHC
Nakamura et al., 2012	Japan	Case series	1 (3)	Members of a family with BHC
Parnes et al., 2019	USA	Case series	5 (5)	Patients with BHC
Peall et al., 2013	UK/Ireland	Case series	6 (10)	Patients with BHC
Provenzano et al., 2016	Spain	Case report	1 (1)	–
Rosati et al., 2015	Italy	Case series	1 (2)	Patients with BHC
Salvado et al., 2013	Spain	Case series	2 (3)	Patients with BHC
Salvatore et al., 2010	Italy	Case series	2 (3)	Members of a family with BHC
Santos-Silva et al., 2019	Portugal	Case series	1 (79)	Cohort of pediatric patients with congenital hypothyroidism
Sempere et al., 2013	Spain	Case series	2 (5)	Members of a family with BHC
Shiohama et al., 2018	Japan	Case report	1(1)	–
Tübing et al., 2018	Germany	Case series	1 (2)	Pediatric patients with *NKX2-1* and *ADCY5* mutation
Uematsu et al., 2012	Japan	Case series	2 (3)	Patients with BHC, two from the same family and one sporadic
Veneziano et al., 2014	UK	Case series	1 (3)	Members of a family with BHC
Williamson et al., 2014	UK	Case series	2 (3)	Members of a family with BHC

Abbreviation: BHC, benign hereditary chorea.

[a]The patients considered in this review are indicated, and the total number of patients in the study is shown in square brackets. The reason for not including some patients in this review is that they did not meet the predefined inclusion criteria.

[b]No target population information is added to the case reports because the subjects meet all the inclusion criteria.

Among the group with mutations, missense mutations were observed in 36.76% of patients, frameshift mutations in 33.82% of patients, splicing mutations in 8.82% of patients, nonsense mutations in 5.88% of patients, insertion–deletion mutations in 4.41% of patients, and duplication mutation in one patient. Mutations were de novo in 33.82% of the cases, although in 13.24% of patients this information was not reported. Regarding the age at genetic diagnosis, 7.35% of patients were diagnosed between 2 and 3 years of age, 5.9% between 12 and 28 years of age, and 1.47% after 28 years of age. For the majority of patients (57%) this information has not been reported.

Data related to independent walking was available in 84.02% of the cases. The onset of independent walking was before 24 months in 22.06% of patients, between 25 and 36 months in 10.29% of

TABLE 2 Patient demographics and clinical characteristics.

Patient	Sex[a]	NKX2-1 mutation or deletion (diagnosis method[c])	Inherited[d]	Age/at genetic diagnosis/at independent walking (months)/at onset of chorea[b]
Asmus_2005_III2[1]	M	c.523G>T (p.Asp178Tyr) (gene sequencing)	M	8/NA/30/2
Asmus_2005_III4	F	c.523G>T (p.Asp178Tyr) (gene sequencing)	M	4/NA/48/1
Asmus_2007_UK_II:1	F	c.376-2A>C (gene sequencing)	D	NA/NA/NA/I
Asmus_2009_IR9	F	c.432C>A (p.Tyr144Ter) (gene sequencing)	D	6/NA/NA/1.5
Balicza_2018_III1[2]	F	c.338G>A (p.Trp113Ter) (WES)	P	20/20/18/20
Balizca_2018_II2[3]	M	c.338G>A (p.Trp113Ter) (WES)	M	46/46/24/6
Barreiro_2011_P1	M	c.374-1G>A (NA)	NA	3/3/22/1.33
Blumkin_2018_P1	M	c.1206A>C (p.Ter402CysTer*63) (gene sequencing)	M	10/NA/30/3
de Gusmao_2016_P1	F	c.524C.A (p.Ser175Ter) (WES)	D	2.75/NA/24/NA
Devos_2006_II3	M	Deletion (analysis of short tandem repeat markers)	P	44/NA/36/2
Ferrara_2012_II2	M	C.617T>A (p.Leu206Gln) (N)	M	30/NA/36/5
Ferrara_2012_III1	F	C.617T>A (p.Leu206Gln) (NA)	P	4/NA/NA/1–2
Ferrara_2012_III2	F	C.617T>A (p.Leu206Gln) (NA)	P	2.5/NA/NA/1–2
Ferrara_2012_III6	M	C.617T>A (p.Leu206Gln) (NA)	M	9/NA/NA/1
Ferrara_2012_III7	M	C.617T>A (p.Leu206Gln) (NA)	M	3.5/NA/NA/1
Fons_2012_P1	F	c.463+1G>A (gene sequencing)	D	6/NA/20/NA
Gauquelin_2017_P1	F	c.626G>C (p.Arg209Pro) (NA)	D	10/2/NA/NA
Gras_2012_P1	F	c.257dupA (p.Tyr86Ter) (NA)	M	6/NA/30/2
Gras_2012_P11	F	c.373+1_373+4del (NA)	M	4/NA/36/4
Gras_2012_P13	F	c.581T>G (p.Leu224Arg) (NA)	M	35/NA/15/childhood
Gras_2012_P2	F	c.257dupA (p.Tyr86Ter) (NA)	M	30/NA/NA/childhood
Gras_2012_P20	F	c.671T>G (p.Leu224Arg) (NA)	NA	59/NA/48/childhood
Gras_2012_P23	F	c.786_787del (c.Leu263GlyfsTer145) (NA)	D	5/NA/not achieved/3
Gras_2012_P24	F	c.643T>G (p.Tyr215Asp) (NA)	D	6/NA/60/4
Gras_2012_P25	F	14q13.2q22.1 deletion 13.8 Mb (NA)	D	12/NA/48/4
Gras_2012_P27	F	14q13.2q21.2 deletion 6.2 Mb (NA)	D	20/NA/20/1.5
Gras_2012_P28	F	14q13.3 deletion 0.3 Mb (NA)	D	17/NA/21/8
Gras_2012_P4	M	c.732C>A (p.Tyr244Ter) (NA)	M	12/NA/21/0.66
Gras_2012_P7	F	c.732C>A (p.Tyr244Ter) (NA)	NA	53/NA/NA/childhood
Koht_2016_II7	F	c.671T>G (p.Leu224Arg) (NA)	M	NA/NA/NA/1
Koht_2016_III6_index	F	c.671T>G (p.Leu224Arg) (NA)	M	36/NA/NA/1
Koht_2016_III7	M	c.671T>G (p.Leu224Arg) (NA)	M	NA/NA/NA/1
Koht_2016_III8	M	c.671T>G (p.Leu224Arg) (NA)	M	NA/NA/NA/1
Koht_2016_IV1	M	c.671T>G (p.Leu224Arg) (NA)	M	NA/NA/NA/1
Koht_2016_IV2	M	c.671T>G (p.Leu224Arg) (NA)	M	NA/NA/NA/1
Koht_2016_IV3	M	c.671T>G (p.Leu224Arg) (NA)	M	NA/NA/NA/1
Konishi_2013_II1[4]	M	c.464-9C>A (NA)	P	52/NA/NA/8
Konishi_2013_III1	M	c.464-9C>A (gene sequencing)	P	25/NA/3/8
Nakamura_2012_P1	F	c.294C>G (p.Tyr98Ter) (genomic DNA)	M	19/19/>24/2.9
Parnes_2019_P1	M	c.754_755insT (p.Asp252ValTer187) (WES)	D	8/3/Late/3
Parnes_2019_P2	F	c.390.C>G (p.Tyr130Ter) (WES)	M	2/2/late/2

Other neurological findings[e]	Hypotiroidism (age at onset)[f]	Neonatal respiratory distress/pulmonar affection	Intellectual disability/ learning difficulties[g]	Abnormal brain MRI
h, Dy, choreoathetosis, G	Y (NA)	Y/Y (pneumonia)	N	N
h, G	Y (1.16)	Y/Y (pneumonia)	N	N
G	N	N/N	N	N
D	N	NA/NA	NA	NA
M	N	N/N	Y	Y
A, Dk, D	Y (45)	N/Y (asthma)	NA	Y
D; h	Y (neonatal)	Y/Y (bronchiolitis, bronchial hyperactivity)	NA	N
Dk	NA	N/NA	Y (ADHD/LD/behavioral problem)	NA
A, D	Y (neonatal)	N/N	N	NA
H	Y (NA)	N/Y (interstitial pneumopathy; asthmatic bronchitis episodes)	N	N
Dy, D, A	Y (NA)	N/NA	Y (executive disfunction)	N
D	Y (NA)	N/NA	Y	N
D	Y (NA)	N/NA	Y	NA
D	Y (NA)	N/NA	Y	N
D	Y (NA)	Y/NA	Y	N
A	Y (2)	N/Y (recurrent airway infections and pneumonia)	N	N
M, D	Y (2)	Y/Y (asthma)	Y(ADHD)	NA
h, D	N	N/Y (asthma)	Y (ADHD/LD)	NA
h	Y (4)	N/Y (asthma)	Y (GD)	NA
motor tics; M	Y (34)	N/N	Y (LD)	NA
h, D	Y (14)	N/Y (asthma)	Y (LD)	NA
h, D	Y (54)	N/Y(asthma)	Y (LD)	NA
h, D, M	Y (neonatal)	Y/N	Y (GD)	NA
h	Y (neonatal)	N/N	Y (LD)	NA
h	N	N/N	Y (LD)	NA
h	Y (1)	N/N	Y (ADHD/LD)	NA
h, motor and vocal tics	Y (1.5)	N/N	Y (LD)	NA
h	Y (8)	N/N	Y (ADHD/LD)	
M	Y (childhood)	N/N	N	NA
D, A	Y (NA)	NA/Y (asthma)	NA	NA
M, A	NOR fT4, elevated TSH	NA/Y (asthma)	N	NA
D	NOR fT4, elevated TSH	NA/Y (frequent infections)	NA	NA
D, tics, stuttering	NOR	NA/N	NA	NA
N	NOR	NA/Y (asthma)	N	NA
N	NOR	NA/Y (asthma)	N	NA
N	Subclinical hypothyroidism	NA/Y (asthma)	N	NA
Choreoathetosis	N	N/N	NA	N
Choreoathetosis	N	N/N	NA	N
N	Y(neonatal)	N/Y (pneumonia)	Y (WAIS-III very low)	N
G	Y (neonatal)	Y/Y upper-respiratory infections, bronchitis, bronchiolitis and reactive airway disease)	Y (ADHD, OCD)	N
Joint laxity	Y (neonatal)	Y/Y (pulmonary hypertension)	N	NA

(Continues)

TABLE 2 (Continued)

Patient	Sex[a]	NKX2-1 mutation or deletion (diagnosis method[c])	Inherited[d]	Age/at genetic diagnosis/at independent walking (months)/at onset of chorea[b]
Parnes_2019_P3	F	c.390.C>G (p.Tyr130Ter) (WES)	D	31/NA/late/3
Parnes_2019_P4	F	c.344delG (p. Gly115AlaTer10) (gene sequencing)	NA	2/NA/not achieved/0.34
Parnes_2019_P5	M	c.397dupA (p.Thr133AsnTer306) (gene sequencing)	NA	7/NA/late/2
Peall_2013_P2	M	c. 612delC (p.Tyr204Ter) (gene sequencing)	D	1.5/NA/NOR/1
Peall_2013_P3	F	c.428G>A (p.Trp143Ter) (gene sequencing)	M	3/NA/late/3
Peall_2013_P5	M	c.872C>T (p.Pro291Lys) (gene sequencing)	D	12/NA/late/3
Peall_2013_P6	F	c.1204T>A (p.Ter402ArgTer63) (gene sequencing)	D	18/NA/late/1
Peall_2013_P7	F	c. 1161C>G (p.Tyr387Ter) (gene sequencing)	D	16/NA/late/2
Peall_2013_P9	F	c. 1022C>T (p.Ala341Val) (gene sequencing)	D	5/NA/NOR/NA
Provenzano_2016_P1[5]	F	c.516G>T (p.Gln172His) (genomic DNA)	NA	32/28/24/2
Rosati_2015_P1	F	c.634C>T (p.Gln212Ter) (gene sequencing)	D	3/3/24/3
Salvado_2013_1	F	c.915del (p.Ala306ArgfsTer75) (NA)	M	19/18/23/NA
Salvado_2013_2	F	c.915del (p.Ala306ArgfsTer75) (NA)	M	13/12/NA/NA
Salvatore_2010_P1[6]	F	c.524C>A (p.Ser145Ter) (gene sequencing)	P	26/NA/18/7
Salvatore_2010_P2[7]	M	c.524C>A (p.Ser145Ter) (gene sequencing)	NA	56/NA/60/NA
Santos-Silva_2019_P10	F	c.859_860insTGCC (p. Arg287LeuTer) (gene panel)	D	7/NA/late/3
Sempere_2013_P1	M	c.319_320delCAinsGC (p.Gln107Ala) (gene sequencing)	P	42/NA/late/few days after birth
Sempere_2013_P2	M	c.319_320delCAinsGC (p.Gln107Ala) (gene sequencing)	P	41/NA/late/few days after birth
Sempere_2013_P3	M	c.319_320delCAinsGC (p.Gln107Ala) (gene sequencing)	P	39/NA/late/few days after birth
Shiohama_2018	M	14q deletion 1,8 Mb (gene sequencing)	D	NA/NA/24/NA
Tübing_2018_P1	M	c.204C>G (p.Tyr68Ter) (gene sequencing)	NA	15/NA/LATE/0.5
Uematsu_2012_P1	F	14q12-13 2.6 Mb deletion (Array CGH)	D	7/NA/38/4
Uetmatsu_2012_P2	F	c.613G>T (p.Val205Phe) (genomic DNA)	M	5/NA/30/NA
Uetmatsu_2012_P3	M	c.613G>T (p.Val205Phe) (genomic DNA)	M	6/NA/24/NA
Veneziano_2014_P1[8]	F	c.727A>T (p.Lys211Ter) (gene sequencing)	NA	49/NA/late/16
Williamson_2014_P1	M	c.626G>C (p.Arg209Pro) (gene sequencing)	D	24/NA/48/4
Williamson_2014_P2	M	c.626G>C (p.Arg209Pro) (gene sequencing)	D	20/NA/NA/1

Abbreviations: N, no; NA, not available; Y, yes.

[a]Sex. F, female; M, male.

[b]Age. Age (in years) when the data were collected/age at genetic diagnosis (years)/age at independent walking (months)/age at onset of chorea (years). I, infancy.

[c]Diagnosis method (array CGH, array comparative genomic hybridization, gene panel, gene sequencing; NA, not available; WES, whole exome sequencing).

[d]Inherited. D, de novo; M, maternal; NA, not available; P, paternal.

[e]A, ataxia; B, ballismus; DD, developmental delay; Dy, dysarthria; Dk, dyskinesia/hyperkinesia; D, dystonia; G, gait disorders; h, hypotonia; M, myoclonus; T, tremor.

[f]S, subclinical.

[g]ADHD, attention deficit-hyperactive disorder; CDD, cognitive developmental delay; GD, global delay; LD, learning difficulties; OCD, obsessive compulsive disorder; WAIS-II, Weschler intelligence scale for children.

[1]Asmus_2005_III2. Malignancies: pre-B-cell acute lymphocytic leukemia (onset 5 years). Died of a second leukemia relapse.

[2]Balizca_2018_III1. Brain MRI: empty sella.

[3]Balizca_2018_II2. Brain MRI: empty sella.

[4]Konishi_2013_II1. Lung tumor (adenoma) – successfully treated (surgical removal) (onset 64 years).

[5]Provenzano_2016_P1. Malignancies: glioblastoma multiforme (onset at 32). Brain MRI: mild cerebella atrophy.

[6]Salvatore_2010_P1. Brain MRI: ventricular dilatation, more marked in the posterior part of lateral ventricles and partial empty sella.

[7]Salvatore_2010_P2. Brain MRI: slight, asymmetrical ventricular dilatation, more marked in the right sight and the posterior part of lateral ventricles and complete empty sella.

[8]Veneziano_2014_P1. Brain MRI: cystic structure within an expanded pituitary fossa, abutting but not compromising the anterior visual pathways.

Other neurological findings[e]	Hypotiroidism (age at onset)[f]	Neonatal respiratory distress/pulmonar affection	Intellectual disability/ learning difficulties[g]	Abnormal brain MRI
M, D, joint laxity	Y (neonatal)	Y/N	Y (CDD)	N
Motor tics	N	Y/NA	Y (CDD)	N
Epilepsy	Y (neonatal)	N/N	Y (CDD)	N
h, M, D	Y (neonatal)	N/Y (recurrent lower respiratory infection)	N	NA
h, D, Dy, DD	Y (neonatal)	Y/N	N	NA
h, D, Dy, DD	N	Y/N	N	NA
h, M, A, DD	N	N/N	N	NA
h, M, D, Dy, DD	N	N/N	N (OCD)	NA
T	N	N/N	N	NA
A, B, M, D, nystagmus	Y (18)	N/N	N	Y
Drop attacks, A, D, eye blinking	N	N/N	N	N
Chorea, Dy, M	Y (neonatal)	NA/NA	Y	N
A, Dy	Y (1.5)	Y/NA	Y	NA
N	Y (23)	NA/NA	N	Y
Dy	Y (56)	NA/NA	Y	Y
h, A, choreoathetosis	Y (NA)	N/N	N	N
D	N	N/N	Y	N
D	N	N/N	Y	N
D	N	N/N	Y	N
h, drop attacks	Y (3.5 diagnosis-asymptomatic)	NA/NA	N	N
D	Y	N/N	Y (ADHD)	NA
Choreoathetosis	Y (0)	N/Y (recurrent lung infections)	N	N
Choreoathetosis	Y (0)	N/N	N	N
Choreoathetosis	Y (5)	N/N	N	N
A, D	Y (40)	N/N	N	Y
A; T	Y (0–5)	N/N	N	NA
NA	Y (2)	N/N	N	NA

patients, between 25 and 36 months in 10.29% of patients, between 37 and 48 months in 5.9% of patients, and between 49 and 60 months in 2.95% of patients; 2.95% had not achieved it at the time of the study (they are 2 and 5 years old). Other articles described walking onset qualitatively, reporting a delayed onset of walking in 10.29% of the cases and normal onset in 19.29% of the cases. As for the onset of chorea, it occurred before the first year of life for 8.82% of patients, during infancy for 75% of patients, the vast majority of them before the age of 4 years, and 1.47% during adulthood.

In addition to chorea, dystonia was the most frequently reported movement disorder, observed in 44.12% of cases, followed by myoclonus in 17.65% of cases, and ataxia in 13.24% of cases. Tics were reported in 7.35% of patients, while tremor, drop attacks, and ballismus were reported less frequently (2.94% each). It is noteworthy that other neurological symptoms were also reported, including hypotonia in 36.76% of cases, dysarthria in 11.76% of cases, and gait abnormalities in 5.88% of cases. Additionally, stuttering, nystagmus, and epilepsy were each reported in only one patient.

Also, 66.8% of patients had hypothyroidism, 19.1% had neonatal respiratory distress, and 29.4% had other pulmonary affections. Brain MRI information was only available for half of the patients. Up to 40% had a normal brain MRI. Patient characteristics are described in Table 2.

Drug therapy and adverse effects

Chorea was treated with the following drugs: amantadine ($n=1$), benztropine ($n=1$), beta-blockers ($n=1$); carbamazepine ($n=3$); clobazam ($n=1$) levodopa/carbidopa–levodopa (L-dopa) ($n=36$); clonazepam ($n=7$); diazepam ($n=1$): L3-4-dihydroxyphenylaalanine ($n=2$); L-thyroxine ($n=1$); fluphenazine ($n=1$); haloperidol ($n=2$); levetiracetam ($n=1$); methylphenidate ($n=8$); olanzapine ($n=1$); propanol hydrocholoride ($n=1$); risperidone ($n=2$); ropinirole hydrochloride ($n=1$); sodium valproate ($n=2$); sulpiride ($n=1$); tetrabenazine ($n=21$); topiramate ($n=4$), and trihexyphenidyl ($n=3$). It is worth noting that alcohol was used in two patients to relieve chorea. The dosages used in the studies are presented in Table 3. Figure 2 displays the prescription of different drugs separated into two time intervals from 2002 to 2012 and from 2013 to the present. As observed, certain drugs are no longer being prescribed, while others have been prescribed during the most recent time period. The most frequently used drugs and their corresponding dose ranges were L-dopa (20–33 mg/kg/day or 100 mg/6 h to 600 mg/24 h), tetrabenazine (up to 25 mg/24 h), and methylphenidate (15 mg/kg/24 h or 72 mg/24 h). In some cases, several drugs were combined, or administered consecutively, so the number of drugs exceeded the number of patients. The most frequent combinations were the following: (i) tetrabenazine and L-dopa, (ii) L-dopa and methylphenidate, and (iii) L-dopa and carbamazepine.

In this study, the improvement achieved with drug treatment was 34 of 63 patients (53%). The success rates for drug treatment, listed in descending order, were: methylphenidate (86%), clonazepam (57%), tetrabenazine (53%), and L-dopa (47%). These results, which appear in Table 4, are based on clinical observations of the patients.

Of the studies analyzed, only four of them (14 patients), utilized objective assessment scales to assess chorea. They were the UHDRS, items 12a–12g and 13) [22], Movement Disorder-Childhood Rating Scale [13], and the Scale for the Assessment and Rating of Ataxia (SARA) [30, 35]. Ferrara et al. observed a range of improvements in UHDRS scores across different patients, with reductions ranging from 14% to 66% [22]. Fons et al. reported a 75% improvement (as measured by a decrease in Movement Disorder-Childhood Rating from 4 to 1) in chorea with levodopa treatment [13]. Some studies used scales to assess chorea but not the response to the treatment employed [30, 35].

Limited information is available regarding the age of onset for drug treatment of chorea, with only a few articles mentioning the use of L-dopa starting at 2 years of age [27] or methylphenidate starting at 5 years of age [31]. Follow-up was reported for only 25% of patients, ranging from 2 weeks to 6 years (mean = 1.8 years).

In terms of adverse effects, the administration of L-dopa was associated with the manifestation of adverse events in a subset of patients. Among the cohort of 36 patients receiving L-dopa, a total of five individuals presented with adverse effects. These included dyskinesia, nausea, and sedation, each observed in one patient. Similarly, tetrabenazine treatment resulted in adverse events in 12 of 21 patients (57.14%), including asthenia, depression, instability, nocturnal bed-wetting, gait freezing, and insomnia. Clonazepam was administered to a subset of seven patients, with two (28.57%) patients exhibiting adverse effects (i.e., eye itching and dizziness or fatigue). Finally, 1 of 7 (14.29%) patients receiving methylphenidate reported experiencing appetite loss. No severe adverse effects were observed with any of the treatments used. It is important to note that for more than half of the patients ($n=44$, 64.70%), information regarding adverse effects was not reported. Specifically, for L-dopa, while only 5 of 36 patients reported adverse effects, it should be noted that adverse effect data were missing for many patients, and as such the results may be biased. This should be taken into consideration when interpreting the results for each drug. Amantadine, benztropine, diazepam, L3-4-dihydroxyphenylaalanine, fluphenazine, and L-thyroxine were associated with improvement without adverse effects. The list of adverse effects appears in Table 4.

Quantitative synthesis of results was not possible due to the low number of objectively evaluated patients and the variability of the scales used. While adherence to pharmacological treatment and improvement of quality of life were considered outcomes in the PICO question, no data were available for these variables.

Methodological quality of the included studies

Fourteen studies ($n=28$) were deemed to have poor methodological quality [15, 16, 18, 20, 23–25, 27–31, 33, 37], while five had very

TABLE 3 Pharmacological interventions for chorea at the patient level: summary of treatment strategies.

Article reference and patient	Pharmacological treatment[a]	Dosage	Age at onset of treatment (years)	Follow-up	Effective	Clinical effect	Adverse events
Asmus_2005_III2	L-dopa	20 mg/kg/day	2.5	Until 8 years old	Y, when discontinued chorea worsening	20 mg/kg/day improved the walking substantially	NA
Asmus_2005_III4	L-dopa	21–33 mg/kg/day	2	10 weeks	Y	Therapy initiated at age 48 months After 6 weeks on L-dopa 21 mg/kg/day, she was able to walk without assistance for up to 20 m and could draw and drink from a glass without a straw. In combination with regular physiotherapy and 1 mg of TPN, her walking and slight residual chorea of the upper limbs further improved after 4 weeks. She was then able to climb stairs and could balance on one leg. Only occasionally were mild choreatic movements in the upper limbs detected	Increasing L-dopa up to 33 mg/kg/day led to dyskinesias of lower limbs with gait worsening
	TPN	1 mg/24 h	NA		Y		N
Asmus_2007_UK_II:1	Alcohol	NA	NA	NA	Y	Alcohol improves movement disorder up to 50%	NA
Asmus_2009_IR9	Alcohol	NA	NA	NA	N	NA	NA
Balizca_2018_III1	TBZ	NA	NA	NA	Y, mild	Mild improvement	NA
Balicza_2018_II2	TBZ (chorea)	NA	NA	NA	NA	NA	N
	BT (cervical dystonia)	NA	NA	NA	NA	NA	N
Barreiro_2011_P1	L-dopa	NA	NA	NA	NA	NA	Dyskinesia
Blumkin_2018_P1	CZP	0,5 mg/12 h	NA	NA	Y	NA	Eye itching
	LEV	500 mg/12 h	NA	NA	N	NA	Instability
	MPH	54 mg/24 h	NA	NA	Y	Improvement of chorea, non behavioral problems	N
de Gusmao_2016_P1	TBZ	1.5 mg/kg/24 h	NA	3 months	N	NA	Asthenia (dosage × 1.5)
	L-dopa	3 mg/kg/24 h	NA	2 months	N	NA	N
Devos_2006_II3	MPH	NA	NA	NA	Improved	Effective	NA
Ferrara_2012_II2	DZP	40 mg/24 h	NA	NA	UHDRS 15 to 7 (53% improvement)	DZP: Markedly lessen chorea with optimal and durable chorea control	N
	RIS	NA	NA	NA	N	NA	Falls
	TBZ	12.5 mg/12 h	NA	NA	N	NA	Instability
	C-L	NA	NA	NA	Y	NA	Sedation (>100 mg).

(Continues)

TABLE 3 (Continued)

Article reference and patient	Pharmacological treatment[a]	Dosage	Age at onset of treatment (years)	Follow-up	Effective	Clinical effect	Adverse events
Ferrara_2012_III1	C-L	100 mg/6 h	NA	NA	UHDRS 7 to 6 (14% improvement)	NA	NA
Ferrara_2012_III2	C-L	600 mg/24 h	NA	NA	UHDRS 12 to 4 (66% improvement)	NA	NA
Ferrara_2012_III6	C-L	100 mg/12 h	NA	NA	UHDRS 10 to 7 (30% improvement)	NA	NA
Ferrara_2012_III7	C-L	100 mg/12 h	NA	NA	UHDRS 10 to 7 (30% improvement)	NA	NA
Fons_2012_P1	L-dopa	3.5 mg/kg/12 h	3,5	3 years	Movement Disorder Childhood Rating Scale: 4 to 1 (75% improvement)	After 6 months of treatment and physiotherapy, the patient presented a significant neurological improvement	NA
Gauquelin_2017_P1	MPH	20 mg/24 h	5	3 years	Y	Immediate reduction chorea and dystonia, especially in the limbs. All tasks were carried out faster and with more precision after receiving the medication	Hyporexia
	MPH hydrochloride	30 mg/24 h	NA		Y	MPH hydrochloride: significant reduction of chorea and dystonia within 30 min after receiving her daily dose, with consequent improvement in her gait, speech, and fine motor skills. These benefits last throughout the day. The involuntary movements only become more bothersome in the evening and peak in the morning prior to MPH ingestion. This is consistent with the reported duration of action (8–12 h) of extended-release forms of stimulant medications and MPH hydrochloride	

TABLE 3 (Continued)

Article reference and patient	Pharmacological treatment[a]	Dosage	Age at onset of treatment (years)	Follow-up	Effective	Clinical effect	Adverse events
Gras_2012_P1	TBZ	0.5–1 mg/kg/24 h	NA	1 year	Y	Marked improvement with more natural walking and less frequency of falls	Asthenia (1 mg/kg/24 h) Titration was required with good tolerance 0.7 mg/kg/24 h
Gras_2012_P11	TBZ	0.5 mg/kg/24 h	NA	2 weeks	Y	Marked improvement with L-dopa	Y
	L-dopa	1 mg/kg/24 h	NA	1 year	NA	NA	NA
Gras_2012_P13	TPM	100 mg/24 h	NA	6 months	Y	Mild improvement	N
Gras_2012_P2	CBZ	1 g/24 h	NA	2 years	N	NA	NA
	VPA	1 g/24 h	NA		N	NA	NA
	TBZ	3.75 mg/24 h	NA		Y	Marked improvement with TBZ	NA
Gras_2012_P20	TPM	100 mg/24 h	NA	NA	Y	Mild improvement	Depression
Gras_2012_P23	TBZ	1 mg/kg/24 h	NA	2.5 years	Y	Marked improvement	N
Gras_2012_P24	TBZ	0.5/mg/kg/24 h	NA	6 months	Y	Marked improvement	N
Gras_2012_P25	L-dopa	NA	NA	6 years	Y (L-dopa)	Moderate improvement	N
	TBZ	1 mg/kg/day	NA		N	NA	Y
Gras_2012_P27	L-dopa	NA	NA	NA	Y	Moderate improvement	N
	MPH	60 mg/24 h	NA	NA	Y	Moderate improvement	N
Gras_2012_P28	TPN	NA	NA	3 months	NA	NA	N
	Haloperidol	NA	NA		Y	Mild	Tics
	TBZ	0.5 mg/kg/24 h	NA		Y	Marked improvement	Tics and chorea
Gras_2012_P4	CBZ	20 mg/kg/24 h	NA	NA	NA	NA	NA
	CLB	0.5 mg/kg/24 h	NA	NA	NA	NA	NA
	MPH	15 mg/kg/24 h	NA	NA	Y	Moderate improvement	N
Gras_2012_P7	TBZ	25 mg/24 h	NA	2 weeks	N	NA	Y
Koht_2016_II7	L-dopa	1.5–3 mg/kg/24 h	NA	NA	N	NA	NA
	CZP	CZP 0.5 mg/kg/24 h	NA	NA	Y (in some degree)	Improve involuntary movements	N
Koht_2016_III6_index	L-dopa	1.5–3 mg/kg/24 h	NA	NA	N	Improve involuntary movements	N
	CZP	0.5 mg/kg/24 h	NA	NA	N	NA	Dizziness and fatigue
Koht_2016_III7	CZP	0.5 mg/kg/24 h	NA	NA	Y	Partial improvement. Relieved hyperkinetic symptoms to some degree	NA

(Continues)

TABLE 3 (Continued)

Article reference and patient	Pharmacological treatment[a]	Dosage	Age at onset of treatment (years)	Follow-up	Effective	Clinical effect	Adverse events
Koht_2016_III8	TPM	NA	NA	NA	Y	Partial. Some reduction in involuntary movements	Depressive symptoms and fatigue
Koht_2016_IV1	TPM	NA	NA	NA	Y	Partial. Some reduction in involuntary movements	Depressive symptoms and fatigue
Koht_2016_IV2	TBZ	0.35 mg/kg/24 h	NA	NA	N	NA	Nocturnal bed-wetting
Koht_2016_IV3	TBZ	0.35 mg/kg/24 h	NA	NA	N	NA	Depressive symptoms
Konishi_2013_II1[4]	L-dopa	3 mg/kg/24 h	NA	6 months	N	NA	Nausea
Konishi_2013_III1	L-dopa	12 mg/kg/24 h	22	NA	N	NA	Nausea
	Haloperidol	2.25 mg/24 h	23	NA	N	Worsening of chorea.	Worsening of chorea
Nakamura_2012_P1	L-dopa	600 mg/24 h	NA	NA	N	NA	NA
	Olanzapine	5 mg/24 h	NA	NA	N	NA	NA
	Ropinirole	2 mg/24 h	NA	NA	Y	Partially reduced chorea	N
	Propranolol	60 mg/24 h	NA	NA	Y	Partially reduced chorea	Induction of asthma attack
Parnes_2019_P1	RIS	NA	NA	NA	N	NA	Somnolence, drooling
	L-dopa	NA	NA	NA	N	NA	N
	TBZ	NA	NA	NA	Y	Modest motor benefit	N
Parnes_2019_P2	CZP	NA	NA	NA	Y	Partial improvement of chorea	NA
Parnes_2019_P3	TBZ	NA	NA	NA	N	NA	Gait freezing
	L-dopa	NA	NA	NA	Y	Modest motor benefit	Gait freezing
Parnes_2019_P4	CZP	NA	NA	NA	N)	NA	N
	Fluphenazine	NA	NA	NA	Y	Modest motor benefits	N
Parnes_2019_P5	CZP	NA	NA	NA	N	NA	NA
	L-dopa	NA	NA	NA	N	NA	NA
	TBZ	NA	NA	NA	Y	Modest motor benefits	NA
Peall_2013_P2	TBZ	72 mg/24 h	NA	NA	NA	NA	Y
	L-dopa	72 mg/24 h	NA	NA	NA	NA	Y
	VPA	360 mg/24 h	NA	NA	N	NA	N
	Sulpiride	200 mg/24 h	NA	NA	N	NA	N
Peall_2013_P3	L-dopa	20 mg/24 h	NA	NA	N	NA	Y
	CZP	500 μg/24 h	NA	NA	Y	Moderate improvement of the movement disorders	N

TABLE 3 (Continued)

Article reference and patient	Pharmacological treatment[a]	Dosage	Age at onset of treatment (years)	Follow-up	Effective	Clinical effect	Adverse events
Peall_2013_P5	L-dopa	375 mg/24 h	NA	NA	N	No change to movement disorder	NA
Peall_2013_P6	L-dopa	187.5 mg/24 h	NA	NA	N	No change to movement disorder	NA
Peall_2013_P7	TPN	24 mg/24 h	NA	NA	Y	Moderate improvement of the movement disorder	NA
Peall_2013_P9	Beta-blockers	80 mg/24 h	NA	NA	NA	NA	Side effects
Provenzano_2016_P1	L-dopa	NA	NA	4 years	N	NA	NA
	Amantadine	200–400 mg/24 h	NA		Y	70% improvement of hyperkinetic movement without effect on cerebellar symptoms and dystonic postures	NA
Rosati_2015_P1	L-dopa	7 mg/kg/day	NA	NA	Y	Reduction in drop attacks and chorea, disappearance of eye blinking	NA
	C-L	7 mg/kg/day	NA	NA	Y		NA
Salvado_2013_1	C-L	100 mg/12 h	NA	NA	Y	Chorea decreases and improved manual dexterity, especially in writing	NA
Salvado_2013_2	C-L	100 mg/12 h	NA	NA	Y	Chorea decreases and improved manual dexterity, especially in writing	NA
	MPH	NA	NA	NA	Y	Maintenance of the response observed with C-L, with better tolerance and more comfortable dosage	NA
Salvatore_2010_P1	TBZ	75 mg/24 h	NA	NA	Y	Mild motor benefit	NA
Salvatore_2010_P2	TBZ	50 mg/24 h	NA	NA	NA	NA	Insomnia and nervousness
Santos-Silva_2019_P10	TBZ	0.5 mg/kg/24 h	NA	NA	Y	"Good response"	NA
Sempere_2013_P1	L-dopa	750 mg/24 h	NA	NA	N	NA	NA
Sempere_2013_P2	L-dopa	750 mg/24 h	NA	NA	N	NA	NA
Sempere_2013_P3	L-dopa	750 mg/24 h	NA	NA	N	NA	NA
Shiohama_2018	L-dopa	2–5 mg/kg/24 h	NA	NA	N	NA	N A
	Carbamazepine	6 mg/kg/24 h	NA	NA	N	NA	NA
	L-thyroxine	1 μg/kg/day	NA	NA	Y	Resolved drop attacks, however chorea during movement was not markedly resolved	Longstanding euthyroidisim
Tübing_2018_P1	MPH	72 mg/day	NA	>1 year	Y	Effective in high doses. Further improvement (walk unassisted and attend sport lessons) Walking aid only for longer distances. Handwriting also improved and became legible. A year later, the positive effect decreased (more frequent falls and hyperactivity)	NA

(Continues)

TABLE 3 (Continued)

Article reference and patient	Pharmacological treatment[a]	Dosage	Age at onset of treatment (years)	Follow-up	Effective	Clinical effect	Adverse events
Uematsu_2012_P1	L-dopa	NA	NA	NA	N	NA	NA
Uematsu_2012_P2	L-dopa	NA	NA	NA	N	NA	NA
Uematsu_2012_P3	L-dopa	NA	NA	NA	N	NA	NA
Veneziano_2014_P1	Benztropine	NA	17	NA	Y	NA	NA
Williamson_2014_P1	L-3,4-dihydroxyphenylaalanine	NA	NA	NA	N	NA	NA
Williamson_2014_P2	L-3,4-dihydroxyphenylaalanine	NA	NA	NA	N	NA	NA

Abbreviations: BT, botulin toxin; CBZ, carbamazepine; C–L, carbidopa–levodopa; CLB, clobazam; CZP, clonazepam; DZP, diazepam; LEV, levetiracetam; MPH, methylphenidate; N, no; NA, not available; RIS, risperidone; TBZ, tetrabenazine; TPM, topiramate; TPN, trihexyphenidyl; VPA, sodium valproate; Y, yes.

[a]In cases where a patient received multiple drugs for chorea, the order of appearance in the table reflects the order in which they were administered.

poor quality [12, 26, 34–36], six had average quality [14, 19, 21, 22, 32, 38], and three had good quality [2, 13, 17]. A detailed evaluation is presented in Table 5.

Quality of evidence

The initial assessment of the quality of the evidence was low due to the inclusion of only observational studies, such as case reports and case series. The overall risk of bias was low. Although it has not been possible to quantitatively calculate heterogeneity, the results obtained show a wide variability, with benefits or no effect for the same drug administered. The indirectness of the study was low, as the target population, interventions, and outcome did not differ from those of primary interest. Given that the condition studied is a rare disease, imprecision was inevitable due to the small sample sizes and limited reporting of results of interest. Regarding publication bias, the impossibility of performing a meta-analysis with the data obtained prevents an objective assessment. However, based on a qualitative analysis of the results, it can be inferred that there is no publication bias since many studies did not report any benefits of treatment and reported adverse events; and although the searches conducted were robust, it would also be possible that some studies with more positive results were not retrieved. The overall quality of the evidence is low due to several factors previously mentioned.

DISCUSSION

This is the first comprehensive review to systematically analyse individual genetic, clinical, and treatment response data in a cohort of 68 patients with 53 pathogenic variants, which were extracted from an extensive screening of over 1417 scientific articles. This systematic review explored studies from the most relevant databases in the field using a broad range of search terms to achieve a highly sensitive search. Notably, no exclusion criteria based on language or setting were applied during the search and selection process, which is a strength of this study, as language barriers can often limit the scope and generalizability of research findings. The number of patients included is not very high, but considering that the condition studied is a rare disease, and that the studies included are from 2002 onwards due to the discovery of the gene that causes it, we could consider it an optimal number of participants, who also come from different contexts and present different clinical characteristics. This provides external validity to the study. In addition, the strict inclusion criteria of analysing only individuals with genetic confirmation provide the study with internal validity. Study selection, data extraction, and risk of bias assessment were performed by trained, independent reviewers. We applied a laborious methodology to conduct the systematic review process and to evaluate the quality of the evidence. Through our rigorous analysis of the available literature, we have gained valuable insights into the current state of drug treatment for *NKX2-1*-RD,

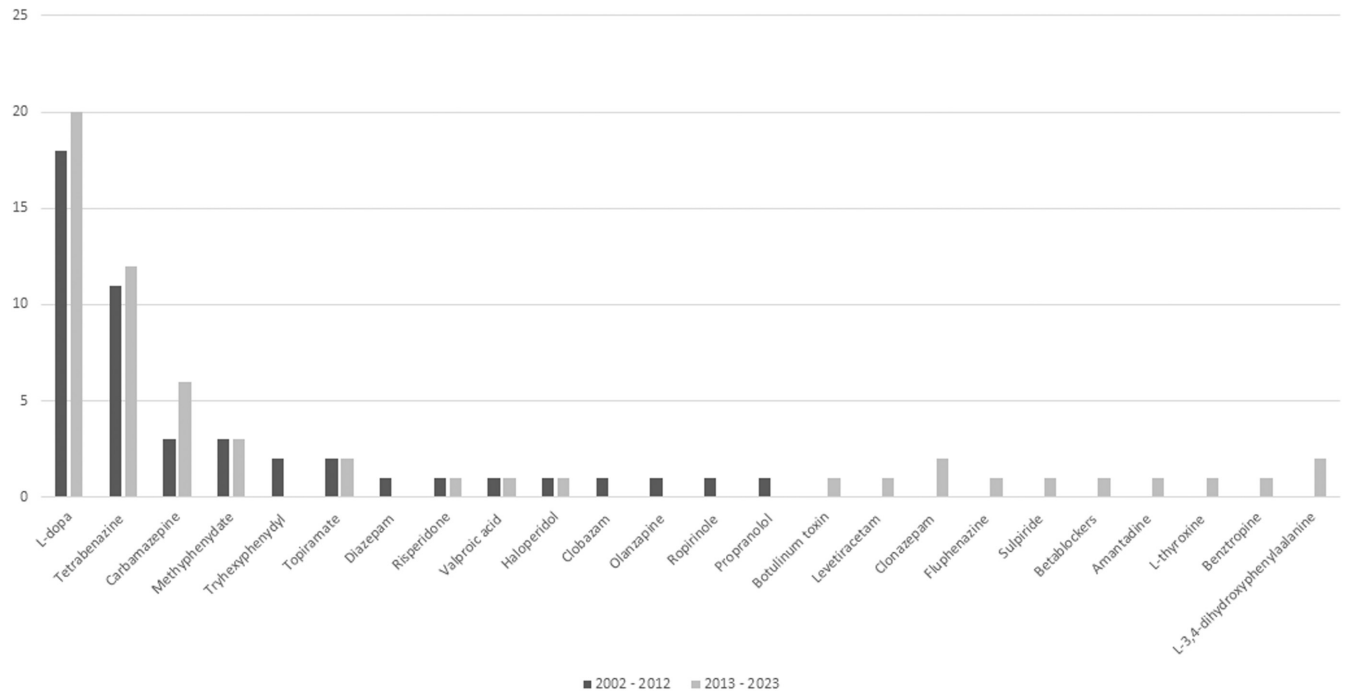

FIGURE 2 Frequency of drug utilization in included articles, segregated into two time periods (2002–2012 and 2013–2023), for the systematic review of drug therapy for chorea in *NXK2-1*-related disorders.

identified gaps in knowledge, and proposed potential avenues for future research.

Based on the available literature, L-dopa [2, 12–20, 22–24, 27, 30, 38], tetrabenazine [2, 21, 23, 25, 29, 30, 33], methylphenidate [2, 15, 26, 28, 31, 32], carbamazepine [2], and topiramate [2, 30] appear to be among the most commonly prescribed medications for the treatment of chorea in patients with *NKX2-1*-RD. Studies have reported that these medications can lead to an improvement in chorea symptoms in approximately 53% of patients. However, it should be noted that treatment response can vary widely between patients and that these medications may not be effective or appropriate for all patients. Furthermore, these results have to be interpreted with caution due to the design of the included studies, their overall low methodological quality, and the fact that they are not comparative trials.

Other medications and treatment approaches, including physical therapy, botulinum toxin for cervical dystonia [33] and L-thyroxine for drop attacks [19], may also be considered depending on the clinical presentation and response to therapy.

The optimal age for initiation of drug treatment for chorea in *NKX2-1*-RD is not well established and may vary depending on the individual clinical presentation and disease course. In some cases, medication may be initiated early in the course of the disease, particularly in patients with severe symptoms that are significantly impacting their quality of life. In other cases, medication may be deferred until later stages of the disease, particularly in patients with milder or less progressive symptoms or in cases where the potential risks of medication outweigh the potential benefits.

The recommended duration of treatment for chorea in *NKX2-1*-RD may vary depending on the clinical presentation and response to therapy. In general, treatment is typically continued for as long as the patient continues to experience significant improvement in their symptoms with acceptable tolerability of the medication. However, it is important to note that the long-term effects and safety of many of the medications used to treat chorea in *NKX2-1*-RD have not been extensively studied, and there may be potential risks associated with prolonged use of these medications. As such, treatment decisions should be made on a case-by-case basis in consultation with a qualified physician. Regular monitoring of treatment response and adverse effects is also recommended.

The optimal dosage range for drugs used in the treatment of chorea in *NKX2-1*-RD may vary depending on the medication being used, the clinical presentation and response to therapy, and other factors such as age, weight, and comorbidities. For example, the dosing of tetrabenazine, a medication commonly used in the treatment of chorea, is typically initiated at a low dose (12.5 mg/day) and titrated up to a maximum daily dose of 100 mg/day in divided doses, based on the response and tolerance. In general, it is recommended to start at a low dose and titrate up slowly to minimize the risk of adverse effects. Other medications used in the treatment of chorea, such as L-dopa, may also have a wide range of dosages depending on the individual patient and treatment goals. It should be emphasized that in some cases, the doses used were much higher than those typically used, for example, L-dopa up to 33 mg/kg/day [27] or methylphenidate up to 15 mg/kg/day [2]. Based on our personal experience, the standard dosage for methylphenidate is 1 mg/kg/day. Commonly preferred over pellets or spheres are modified-release formulations, such as methylphenidate OROS. The usual starting dose for children aged 6 years and adolescents is 18 mg once daily, with a gradual increase of 18 mg/day at weekly intervals based on clinical response and the presence of adverse effects.

TABLE 4 Pharmacological interventions for chorea at the drug level: summary of treatment used and adverse effects.

Treatment (patients treated with)	Improvement			Adverse effects
	Yes	No	NA	
Alcohol ($n=2$)	1	1	0	NA
Amantadine ($n=1$)	1	0	0	NA
Benztropine ($n=1$)	1	0	0	NA
Beta-blockers ($n=1$)	0	0	1	Yes, not explained
Carbamazepine ($n=3$)	0	2	1	NA
Clobazam ($n=1$)	0	0	1	NA
Clonazepam ($n=7$)	4	3	0	Dizziness and fatigue ($n=1$); No ($n=3$); NA ($n=3$)
Diazepam ($n=1$)	1	0	0	N
L3-4-Dihydroxyphenylaalanine ($n=2$)	0	2	0	NA
L-Thyroxine ($n=1$)	1	0	0	Longstanding euthyroidisim
Fluphenazine ($n=1$)	1	0	0	N
Haloperidol ($n=2$)	1	1	0	Worsening of chorea ($n=1$); somnolence and drooling ($n=1$)
Levodopa/Carbidopa-Levodopa ($n=36$)	9	15	12	Dyskinesias of lower limbs with gait worsening (up to 33/mg/kg/day; $n=1$); dyskinesias ($n=1$); nausea ($n=2$); sedation (up to 100 mg; $n=1$); others not specified ($n=2$); No ($n=5$); NA (=24)
Levetiracetam ($n=1$)	0	1	0	Instability
Methylphenidate ($n=8$)	8	0	0	Hyporexia ($n=2$); No ($n=3$); NA ($n=3$)
Olanzapine ($n=1$)	0	1	0	NA
Propanol hydrocholoride ($n=1$)	1	0	0	Induction of asthma attack
Risperidone ($n=2$)	0	2	0	Falls ($n=1$); tics ($n=1$)
Ropinirole hydrochloride ($n=1$)	1	0	0	N
Sodium valproate ($n=2$)	0	2	0	N ($n=1$), NA ($n=1$)
Sulpiride ($n=1$)	0	1	0	N
Tetrabenazine ($n=21$)	11	7	3	Asthenia ($n=2$); instability ($n=1$); tics and chorea ($n=1$); nocturnal bed-wetting ($n=1$); depressive symptoms ($n=1$); gait freezing ($n=1$); insomnia and nervousness; others not specified ($n=3$); No ($n=4$); NA ($n=5$)
Topiramate ($n=4$)	4	0	0	Depression ($n=1$); depressive symptoms and fatigue ($n=2$); No ($n=1$)
Trihexyphenidyl ($n=3$)	2	0	1	No (=2); NA ($n=1$)

Abbreviation: NA, no data.

[a]Sixty-eight patients were included, although some were treated with more than one drug, so the data are for more than 68 patients.

According to the product information, the maximum daily dosage is 54 mg (some guidelines suggest higher doses for patients >12 years and 50 kg, up to 72 mg/day without exceeding 2 mg/kg/day, and for patients aged 6 years and weighing >50 kg, up to 108 mg/day) [39].

The definition of "good response" varies greatly across studies and is incompletely defined. Regrettably, the majority of studies did not employ specific scales for movement disorders, relying instead on empirical assessments to determine improvement. This is an area that requires improvement in future studies, therefore, we suggested using the UHDRS to ensure that all measures are standardized in future studies and facilitate, for example, meta-analyses of individual patients. However, the very good overall response of symptoms and the low incidence of adverse effects with methylphenidate warrant a methylphenidate trial in every patient with *NKX2-1*-RD [2, 15, 26, 28, 31, 32].

In the treatment of chorea in *NKX2-1*-RD, the adverse effects associated with the drugs used can be influenced by various factors, including medication type, dosage, and individual patient response. It is important to note that a significant proportion of the articles did not provide information on adverse effects, and the potential risk and severity of adverse effects may differ based on the specific medication and individual patient characteristics. The study showed that L-dopa, tetrabenazine, and clonazepam were associated with adverse effects such as dyskinesia, nausea, sedation, asthenia, depression, instability, nocturnal bed-wetting, gait freezing, eye itching, and dizziness or fatigue [2, 12, 17–19, 21–23, 27, 30–33]. However, none of these adverse effects were severe.

In the treatment of chorea in *NKX2-1*-RD, the order of drug administration can vary depending on clinical presentation, medical history, and response to therapy. Treatment plans are customized to the individual patient and may involve a combination of medications. However, the order in which these medications are prescribed may vary depending on clinical response and potential adverse effects. In some cases, multiple drugs were combined or administered

TABLE 5 Methodological quality of the included studies.

Domain	Selection	Ascertainment		Causality				Reporting	Final score
Author, year/Item	1	2	3	4	5	6	7	8	
Asmus et al., 2005	0	1	1	0	0	1	0	0	3
Asmus et al., 2007	0	0	1	0	0	0	0	0	1
Asmus et al., 2009	1	0	1	0	0	0	0	0	2
Balicza et al., 2018	0	1	1	0	0	1	0	0	3
Barreiro et al.,2011	0	0	0	0	0	0	0	0	0
Blumkin et al., 2018	1	1	1	0	0	1	0	0	4
de Gusmao et al., 2016	0	1	1	0	0	0	1	1	4
Devos et al., 2006	0	0	1	0	0	0	0	0	1
Ferrara et al., 2012	1	1	1	0	0	1	0	0	4
Fons et al., 2012	0	1	1	0	0	1	1	1	5
Gauquelin et al., 2017	0	1	1	0	0	0	1	0	3
Gras et al., 2012	1	1	1	0	0	0	1	1	5
Koht et al., 2016	0	1	1	0	0	1	0	0	3
Konishi et al., 2013	0	1	1	0	1	1	1	1	6
Nakamura et al., 2012	0	1	1	0	0	1	0	0	3
Parnes et al., 2019	1	0	1	0	0	0	0	0	2
Peall et al., 2013	1	1	1	0	0	1	0	0	4
Provenzano et al., 2016	0	1	1	0	0	0	1	1	4
Rosati et al., 2015	0	1	1	0	0	0	0	0	2
Salvado et al., 2013	0	1	1	0	0	0	0	0	2
Salvatore et al., 2010	0	1	1	0	1	0	0	0	3
Santos-Silva et al., 2019	1	1	1	0	0	0	0	0	3
Sempere et al., 2013	0	1	1	0	0	0	0	0	2
Shiohama et al., 2018	0	1	1	0	1	1	0	0	4
Tübing et al, 2018	0	1	1	0	0	1	0	0	3
Uematsu et al., 2012	0	1	1	0	0	0	0	0	2
Veneziano et al, 2014	0	0	1	0	0	0	0	0	1
Williamson et al., 2014	0	0	1	0	0	0	0	0	1

sequentially, resulting in the number of drugs exceeding the number of patients. The most frequent drug combinations were tetrabenazine and L-dopa, L-dopa and methylphenidate, and L-dopa and carbamazepine.

There are limited data on the temporal variation in the use of specific drugs for the treatment of chorea in *NKX2-1*-RD. The choice of medication and the timing of its initiation may vary depending on a number of factors, including the age of the patient, the clinical presentation, comorbidities, and response to previous treatments. Ultimately, the specific timing and sequence of medication initiation should be individualized.

There are also limited data on the use of deep brain stimulation (DBS) and *NKX2-1*-RD. The only reference in the literature to a case of *NKX2-1* undergoing DBS was a 2013 poster presentation describing an unsuccessful attempt [40]. This patient is not mentioned in the subsequent article published by the same group, nor have any additional articles been published regarding *NKX2-1* and DBS [38]. Unpublished data from a London, UK-based group revealed a

successful treatment for a girl with *NKX2-1*-RD. The patient, who was initially misdiagnosed with cerebral palsy, underwent scoliosis surgery and subsequently received DBS at the age of 18 years. The intervention yielded excellent results, leading to significant improvements. Subsequently, she was able to go to university.

One of the significant strengths of our study is that it is the first to systematically analyse individual genetic, clinical, and treatment response data. This comprehensive approach has allowed us to gain new insights into the pathogenesis of *NKX2-1*-RD and identify potential avenues for future research. Our review provides a valuable resource for clinicians and researchers interested in this field, and we hope that it will serve as a foundation for further investigation and progress in the development of targeted therapies for these complex conditions.

One constraint for data interpretation arises from the substantial number of missing data points present in numerous variables, thereby necessitating prudence in forming definitive conclusions. Despite the existence of well-defined reporting protocols for clinical cases, such as the CARE guidelines, which emphasize the importance of detailing intervention specifics (e.g., drugs used), administration particulars (e.g., dosage, strength, duration), changes made to the intervention (with rationale), and outcomes (including adverse and unforeseen events), most of the studies examined in this review exhibited poor methodological quality [41]. Another limitation of this study is the lack of information on quality of life and treatment adherence, which should be considered in future research.

In summary, we provided a comprehensive literature review of the treatment of chorea in 68 patients with *NKX2-1*-RD. It is our sincere hope that this work will inspire clinicians and scientists to furnish more elaborate reports of treatment protocols, thereby providing an impetus for the advancement and refinement of current therapeutic approaches.

Methodological considerations and key findings in studies of drug treatment in chorea in *NKX2-1*-RD

- Based on the available evidence, methylphenidate may be considered a potential first-line treatment for chorea in NKX2-1-RD, given its relatively low incidence of adverse effects and overall good response rate. However, due to the limited information and the need for further research, we suggest that caution be exercised before establishing a formal recommendation for its use. Future studies with larger sample sizes and more rigorous designs are required to provide stronger evidence and support more definitive treatment recommendations.
- The optimal age for initiation of drug treatment for chorea in *NKX2-1*-RD is not well established and may vary depending on the clinical presentation and disease course.
- The dosage of drugs used in the treatment of chorea in *NKX2-1*-RD should be tailored to the individual patient and titrated slowly to minimize the risk of adverse effects.
- Regular monitoring of treatment response and adverse effects is recommended.
- It is recommended to use objective and validated questionnaires to assess patients' quality of life and adherence to treatment.
- Treatment plans for chorea in *NKX2-1*-RD are typically tailored to the individual patient and may involve a combination of medications, physical therapy, botulinum toxin (for focal dystonia), and L-thyroxine (for drop attacks), depending on the clinical presentation and response to therapy.
- It is recommended that the reporting of drug treatments for *NKX2-1*-RD follow the CARE guidelines.
- Further studies are warranted to evaluate the use of DBS in patients with *NKX2-1*-RD.

AUTHOR CONTRIBUTIONS

Laia Nou-Fontanet: Writing—original draft; writing—review and editing; investigation. **Carmen Martín-Gómez:** Methodology; writing—original draft; writing—review and editing; validation; formal analysis. **Rebeca Isabel-Gómez:** Methodology; validation; formal analysis. **Anne-Catherine Bachoud-Lévi:** Supervision. **Giovanna Zorzi:** Supervision. **Alessandro Capuano:** Supervision. **Juan Antonio Blasco-Amaro:** Methodology; supervision. **Juan Darío Ortigoza-Escobar:** Investigation; writing—original draft; writing—review and editing; validation; supervision.

FUNDING INFORMATION

This study is supported by the European Commission within the contract SANTE/2018/B3/030-SI2.813822 under which the European Reference Networks (ERNs) Guidelines programme is being developed. This work is produced within the framework of the European Reference Network for Rare Neurological Diseases, Project ID 739510.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no other conflicts of interest relevant to this work.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

Due to the nature of the study, it did not need to be approved by an ethics committee.

ORCID

Laia Nou-Fontanet https://orcid.org/0000-0001-7381-3983
Carmen Martín-Gómez https://orcid.org/0000-0003-0748-2762
Anne-Catherine Bachoud-Lévi https://orcid.org/0000-0003-3000-2210
Giovanna Zorzi https://orcid.org/0000-0001-7041-5365
Alessandro Capuano https://orcid.org/0000-0002-7729-7952

Juan Antonio Blasco-Amaro https://orcid.org/0000-0002-5500-8187
Juan Darío Ortigoza-Escobar https://orcid.org/0000-0002-6320-2641

REFERENCES

1. Thorwarth A, Sarah SH, Schrumpf P, et al. Comprehensive genotyping and clinical characterisation reveal 27 novel NKX2-1 mutations and expand the phenotypic spectrum. *J Med Genet*. 2014;51(6):375-387.
2. Gras D, Jonard L, Roze E, et al. Benign hereditary chorea: phenotype, prognosis, therapeutic outcome and long term follow-up in a large series with new mutations in the TITF1/NKX2-1 gene. *J Neurol Neurosurg Psychiatry*. 2012;83(10):956-962.
3. Hamvas A, Deterding RR, Wert SE, et al. Heterogeneous pulmonary phenotypes associated with mutations in the thyroid transcription factor gene NKX2-1. *Chest*. 2013;144(3):794-804.
4. Nattes E, Lejeune S, Carsin A, et al. Heterogeneity of lung disease associated with NK2 homeobox 1 mutations. *Respir Med*. 2017;129:16-23.
5. Moher D, Altman DG, Liberati A, Tetzlaff J. PRISMA statement. *Epidemiology*. 2011;22(1):128.
6. Breedveld GJ, van Dongen JWF, Danesino C, et al. Mutations in TITF-1 are associated with benign hereditary chorea. *Hum Mol Genet*. 2002;11(8):971-979.
7. Veritas Health Innovation. *Covidence Systematic Review Software*. Veritas Health Innovation; 2023.
8. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *Evid Based Med*. 2018;23(2):60-63.
9. Moura-Coelho N, Cunha JP, Papa-Vettorazzi R, Gris Ó, Güell JL. Acute corneal allograft rejection following SARS-CoV-2 vaccination—a systematic review. *Acta Ophthalmol*. 2022;101(1):e1-e13.
10. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64(4):401-406.
11. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the *Journal of Clinical Epidemiology*. *J Clin Epidemiol*. 2011;64(4):380-382.
12. Barreiro J, Alonso-Fernández JR, Castro-Feijoo L, et al. Congenital hypothyroidism with neurological and respiratory alterations: a case detected using a variable diagnostic threshold for Tsh. *J Clin Res Pediatr Endocrinol*. 2011;3(4):208-211.
13. Fons C, Rizzu P, Garcia-Cazorla A, et al. TITF-1 gene mutation in a case of sporadic non-progressive chorea. Response to levodopa treatment. *Brain Dev*. 2012;34(3):255-257. doi:10.1016/j.braindev.2011.04.007
14. Provenzano C, Zamboni M, Veneziano L, et al. Functional characterization of two novel mutations in TTF-1/NKX2.1 homeodomain in patients with benign hereditary chorea. *J Neurol Sci*. 2016;360:78-83. doi:10.1016/j.jns.2015.11.050
15. Salvado Figueras M, Boronat Guerrero S, Hernández Vara J, Álvarez SJ. Corea por mutación de TITF1/NKX2-1: descripción fenotípica y respuesta terapéutica en una familia. *Rev Neurol*. 2013;56(10):515-520.
16. Sempere AP, Aparicio S, Mola S, Pérez-Tur J. Benign hereditary chorea: clinical features and long-term follow-up in a Spanish family. *Park Relat Disord*. 2013;19(3):394-396.
17. Konishi T, Kono S, Fujimoto M, et al. Benign hereditary chorea: dopaminergic brain imaging in patients with a novel intronic NKX2.1 gene mutation. *J Neurol*. 2013;260(1):207-213.
18. Nakamura K, Sekijima Y, Nagamatsu K, Yoshida K, Ikeda SI. A novel nonsense mutation in the TITF-1 gene in a Japanese family with benign hereditary chorea. *J Neurol Sci*. 2012;313(1–2):189-192.
19. Shiohama T, Ohashi H, Shimizu K, et al. L-Thyroxine-responsive drop attacks in childhood benign hereditary chorea: a case report. *Brain Dev*. 2018;40(4):353-356.
20. Uematsu M, Haginoya K, Kikuchi A, et al. Hypoperfusion in caudate nuclei in patients with brain–lung–thyroid syndrome. *J Neurol Sci*. 2012;315(1–2):77-81.
21. de Gusmao CM, Kok F, Casella EB, Waugh JL. Benign hereditary chorea related to NKX2-1 with ataxia and dystonia. *Neurol Genet*. 2016;2(1):1-2.
22. Ferrara JM, Adam OR, Kirwin SM, et al. Brain-lung-thyroid disease: clinical features of a kindred with a novel thyroid transcription factor 1 mutation. *J Child Neurol*. 2012;27(1):68-73.
23. Parnes M, Bashir H, Jankovic J. Is benign hereditary chorea really benign? Brain–lung–thyroid syndrome caused by NKX2-1 mutations. *Mov Disord Clin Pract*. 2019;6(1):34-39.
24. Rosati A, Berti B, Melani F, Cellini E, Procopio E, Guerrini R. Recurrent drop attacks in early childhood as presenting symptom of benign hereditary chorea caused by TITF1 gene mutations. *Dev Med Child Neurol*. 2015;57(8):777-779.
25. Salvatore E, Di Maio L, Filla A, et al. Benign hereditary chorea: clinical and neuroimaging features in an Italian family. *Mov Disord*. 2010;25(10):1491-1495.
26. Devos D, Vuillaume I, de Becdelievre A, et al. New syndromic form of benign hereditary chorea is associated with a deletion of TITF-1 and PAX-9 contigous genes. *Mov Disord*. 2006;21(12):2237-2240.
27. Asmus F, Horber V, Pohlenz J, et al. A novel TITF-1 mutation causes benign hereditary chorea with response to levodopa. *Neurology*. 2005;64(11):1952-1954.
28. Tübing J, Bohnenpoll J, Spiegler J, et al. Methylphenidate can improve chorea in NKX2.1 and ADCY5 mutation-positive patients—a report of two children. *Mov Disord Clin Pract*. 2018;5(3):343-345.
29. Santos-Silva R, Rosário M, Grangeia A, et al. Genetic analyses in a cohort of Portuguese pediatric patients with congenital hypothyroidism. *J Pediatr Endocrinol Metab*. 2019;32(11):1265-1273.
30. Koht J, Løstegaard SO, Wedding I, Vidailhet M, Louha M, Tallaksen CME. Benign hereditary chorea, not only chorea: a family case presentation. *Cerebellum Ataxias*. 2016;3(1):1-7.
31. Gauquelin L, Tran LT, Chouinard S, Bernard G. The movement disorder of brain–lung–thyroid syndrome can be responsive to methylphenidate. *Tremor Other Hyperkinet Mov (N Y)*. 2017;7:508.
32. Blumkin L, Lerman-Sagie T, Westenberger A, et al. Multiple causes of pediatric early onset chorea-clinical and genetic approach. *Neuropediatrics*. 2018;49(4):246-255.
33. Balicza P, Grosz Z, Molnár V, et al. NKX2-1 new mutation associated with myoclonus, dystonia, and pituitary involvement. *Front Genet*. 2018;9:1-5.
34. Asmus F, Devlin A, Munz M, Zimprich A, Gasser T, Chinnery PF. Clinical differentiation of genetically proven benign hereditary chorea and myoclonus-dystonia. *Mov Disord*. 2007;22(14):2104-2109.
35. Veneziano L, Parkinson MH, Mantuano E, Frontali M, Bhatia KP, Giunti P. A novel de novo mutation of the TITF1/NKX2-1 gene causing ataxia, benign hereditary chorea, hypothyroidism and a pituitary mass in a UK family and review of the literature. *Cerebellum*. 2014;13(5):588-595.
36. Williamson S, Kirkpatrick M, Greene S, Goudie D. A novel mutation of NKX2-1 affecting 2 generations with hypothyroidism and choreoathetosis: part of the spectrum of brain–thyroid–lung syndrome. *J Child Neurol*. 2014;29(5):666-669.

37. Asmus F, Langseth A, Doherty E, et al. "Jerky" dystonia in children: spectrum of phenotypes and genetic testing. *Mov Disord*. 2009;24(5):702-709.
38. Peall KJ, Lumsden D, Kneen R, et al. Benign hereditary chorea related to NKX2.1: expansion of the genotypic and phenotypic spectrum. *Dev Med Child Neurol*. 2013;56(7):642-648.
39. Adler LA, Zimmerman B, Starr HL, et al. Efficacy and safety of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, double-blind, parallel group, dose-escalation study. *J Clin Psychopharmacol*. 2009;29(3):239-247.
40. Peall KJ, Lumsden D, Kneen R, et al. NKX2.1 case series: novel mutations and additional clinical characteristics. *Mov Disord*. 2013;28(S1):S256-S257.
41. Riley DS, Barber MS, Kienle GS, et al. CARE guidelines for case reports: explanation and elaboration document. *J Clin Epidemiol*. 2017;89:218-235.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Nou-Fontanet L, Martín-Gómez C, Isabel-Gómez R, et al. Systematic review of drug therapy for chorea in *NXK2*-1-related disorders: Efficacy and safety evidence from case studies and series. *Eur J Neurol*. 2023;30:3928-3948. doi:10.1111/ene.16038