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Review article

Movement disorders in cerebrotendinous xanthomatosis

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ABSTRACT

Cerebrotendinous xanthomatosis (CTX) is an inborn error of cholesterol and bile acid metabolism, leading to neuropsychiatric and systemic manifestations. Movement disorders have rarely been reported in CTX, while a detailed appreciation of the full phenotypic spectrum is required in order to prevent underdiagnosis of this disease. This review focuses on the frequency of more unusual, non-ataxia and non-spasticity movement disorders reported in CTX. In total, 39 articles were reviewed, describing 55 CTX patients with a movement disorder. Additionally, we report on seven patients with parkinsonism out of our Dutch cohort of 79 (77 genetically proven) CTX patients. Mean age at onset of the movement disorder was 40 ± 12 years (median 40, range 13–62 years). Movement disorders can be considered a late disease manifestation. Parkinsonism was the most frequently reported movement disorder, followed by dystonia, myoclonus and postural tremor. Movement disorders were found to be mixed in 23% of patients and were usually part of a complex clinical picture, rather than a prominent symptom. Still, in 18% of the cases, a movement disorder was the presenting symptom.

Unusual movement disorders represent a rare clinical feature in CTX, but CTX should be considered in the differential diagnosis of these movement disorders, particularly in case of early onset, and when associated with other neurological features (especially cognitive impairment, pyramidal and cerebellar signs) and/or with systemic features (such as diarrhoea, cataract and tendon xanthomas). CTX is a treatable disorder, stressing the importance of considering CTX as a potential cause of movement disorders.

1. Introduction

Cerebrotendinous xanthomatosis (CTX; OMIM #213700) is an autosomal recessively inherited inborn error of metabolism caused by a deficiency of the mitochondrial enzyme sterol 27-hydroxylase due to mutations in the *CYP27A1* gene [1]. The clinical picture ranges from being nearly asymptomatic in early childhood, up to severe disability at adult age. The classic symptomatology in untreated CTX patients includes infantile-onset diarrhoea, juvenile-onset cataract, young adult-onset tendon xanthomas, and a variety of neurological and psychiatric manifestations. Progressive neurological dysfunction manifests as cognitive impairment, epilepsy, pyramidal and cerebellar signs, peripheral neuropathy and/or movement disorders [2,3]. In the context of inborn errors of metabolism, movement disorders are often mixed and are usually one of the many disease features, rather than a prominent sign [4,5]. Cerebellar signs, especially ataxia, are common and well-known features in CTX patients. This review focuses on the frequency of more unusual, non-ataxia and non-spasticity movement disorders reported in CTX. In 1937, Van Bogaert published the first case of CTX, and a relative of this patient developed palatal and lingual myoclonus during follow-up [6]. Movement disorders in general have rarely been reported in CTX. CTX is a poorly recognized disorder, and a detailed appreciation of the full phenotypic spectrum - including other movement disorders - is required in order to prevent underdiagnosis of this disease. CTX can be treated, which makes it important to consider CTX as a cause of movement disorders [4]. Treatment with chenodeoxycholic acid is effective in normalising the biochemical abnormalities that underlie the pathogenesis in CTX, and positively modifies the natural course of the disease [7]. In this review, we present a comprehensive overview of all movement disorders reported in CTX.

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2. Methods

We systematically reviewed the literature concerning all cases of CTX with movement disorders. The term 'movement disorders' here refers to non-ataxia and non-spasticity motor features that originate from the central nervous system. Pubmed was searched using the following keywords: "cerebrotendinous xanthomatosis" AND "chorea", "dyskinesia", "dystonia", "extrapyramidal signs/syndrome", "movement disorder", "myoclonus", "parkinson", "parkinsonism" and "tremor", up to August 2017. Publications had to be written in English in order to be included. In total, 39 articles [6,8–45] were reviewed, describing 55 CTX patients with a movement disorder. We extracted data on the age of CTX diagnosis, age at onset of the movement disorder, type of movement disorder, classic systemic signs of CTX, as well as other motor manifestations like pyramidal and cerebellar signs. Additionally, we report on seven patients with a movement disorder (parkinsonism) out of our Dutch cohort of 79 (77 genetically proven) CTX patients.

3. Results

In total, 55 CTX patients with a movement disorder were reported in the literature. Demographic and main clinical characteristics of these patients, including seven Dutch CTX patients, are summarized in Table 1 and more extensively in Table e1 (Supplementary Material).

Mean age at CTX diagnosis was 35 ± 11 years (median 36, range 14–67 years). Mean age at onset of the movement disorder was 40 ± 12 years (median 40, range 13–62 years), which was 43 ± 10 years (median 41, range 26–62 years) in case of parkinsonian symptoms or parkinsonism, and 38 ± 15 years (median 37, range 13–62 years) in case of the other movement disorders.

Fig. 1 shows the classical systemic and neurological features of CTX at time of diagnosis of the movement disorder. Classical systemic features were cataract (82%), diarrhoea (31%) and tendon xanthomas (76%). Associated neurological features were cognitive impairment (87%), pyramidal signs (74%), cerebellar signs (68%), polyneuropathy (45%), psychiatric signs (37%), and epilepsy (29%). Ataxia is one of the most common motor abnormality in CTX, and the cerebellar involvement is also partly responsible for other movement disorders seen in CTX. Fig. 2 shows an overview of the other movement disorders reported in CTX. There were no reports of chorea or tics in CTX in the literature. In 10 patients, "extrapyramidal signs" were not further specified. Dystonia was seen in 19 patients (31%), mostly (multi)focal (blepharospasm, oromandibular, cervical and limb dystonia) [23,24,27–30,33–35,37,39,41,43]. Myoclonus was seen in 11 patients (18%) [6,9,25,27,34,35,42]. Lagarde et al. [34] described the co-occurrence of dystonia and myoclonus in six patients. Their phenotype differed from that of the classic myoclonus dystonia syndrome, because of the involvement of the distal parts of the upper limbs. Five patients were diagnosed with a palatal myoclonus, with also pharyngeal, laryngeal or lingual involvement. In six patients (10%), a postural tremor was reported, which was part of another movement disorder in three patients [8,25–27]. In total 32 patients, including seven patients of our own cohort of 79 (77 genetically proven) Dutch CTX patients, were identified with parkinsonian symptoms or parkinsonism [10–23,25,29–33,36,38,44,45]. The distribution of the parkinsonism was mostly asymmetric, and characterized by rest tremor (n = 11), bradykinesia/hypokinesia/akinesia (n = 26), rigidity (n = 23), hypomimia (n = 15), hypophonia (n = 9) and postural instability (n = 7). In 14 patients (23%), the movement disorder was mixed. Movement disorders reported in CTX patients were usually part of a complex clinical picture, rather than predominant features. However, in 11 patients (18%), the movement disorder was the presenting symptom, although all patients had one or more systemic features of CTX (diarrhoea, cataract, and/or tendon xanthomas) [17,18,23,24,29,33,34,36,38,44]. These patients reported symptoms only related to their movement disorder, but examination also showed other neurological features in seven patients (pyramidal signs, cerebellar signs, and/or polyneuropathy), and cognitive impairment in seven patients. Gait disturbances and falls were reported in 45 and 18% of patients, respectively. Not only movement disorders, but also pyramidal and cerebellar signs can contribute to gait disturbances and falls. The exact nature of the gait disorder could not be distuinguished because of lack of specific data in the literature.

Table 1
Main demographic and clinical characteristics in 62 CTX patients, including seven Dutch CTX patients, with a movement disorder.

Demographic characteristics	
M/F/unknown	30/29/3
Mean age CTX diagnosis	35 ± 11 years (median 36, range 14–67 years)
Mean age diagnosis movement disorder	40 ± 12 years (median 40, range 13–62 years)
Classic systemic CTX features	
Cataract	51 (82%)
Diarrhoea	19 (31%)
Tendon xanthomas	47 (76%)
Classic neurological CTX features	
Cognitive impairment	54 (87%)
Pyramidal signs	46 (74%)
Cerebellar signs	42 (68%)
Polyneuropathy	28 (45%)
Psychiatric signs	23 (37%)
Epilepsy	18 (29%)
Movement disorders	
Dystonia	19 (31%)
Cervical	1
Blepharospasm	2
Oromandibular	5
Limb	15
Myoclonus	11 (18%)
Palatal	5
Limb	6
Postural tremor	6 (10%)
Parkinsonism/Parkinsonian symptoms	32 (52%)
Symmetric/Asymmetric	6/16
Rigidity	23
Bradykinesia/Hypokinesia/Akinesia	26
Hypophonia	9
Hypomimia	15
Rest tremor	11
Postural instability	7
Extrapyramidal signs, not specified	10 (16%)
Gait disturbances	28 (45%)
Falls	11 (18%)

Brain magnetic resonance imaging (MRI) was done in 47 patients, and was abnormal in 44 patients (94%). Cerebral and cerebellar atrophy was seen in 24 (51%) and 29 (62%) patients, respectively. The most frequent features were cerebellar white matter changes with dentate nuclei involvement in 38 patients (81%), followed by white matters changes of the cerebral peduncles (n = 11, 23%) and internal capsule (n = 7, 15%). Fig. 3 shows characteristic MRI findings in two Ducth CTX patients. Beside the typical T2 hyperintense brain MRI signal changes in the dentate nuclei, involvement of the basal ganglia and/or substantia nigra is also described in CTX patients with parkinsonism [10,11,13,15,29,30,33,36,38]. Hyperintensities on T2-weighted images of substantia nigra (n = 7, 15%), globus pallidus (n = 5, 11%), or striatum (n = 2, 4%) have been described on brain MRI. There were

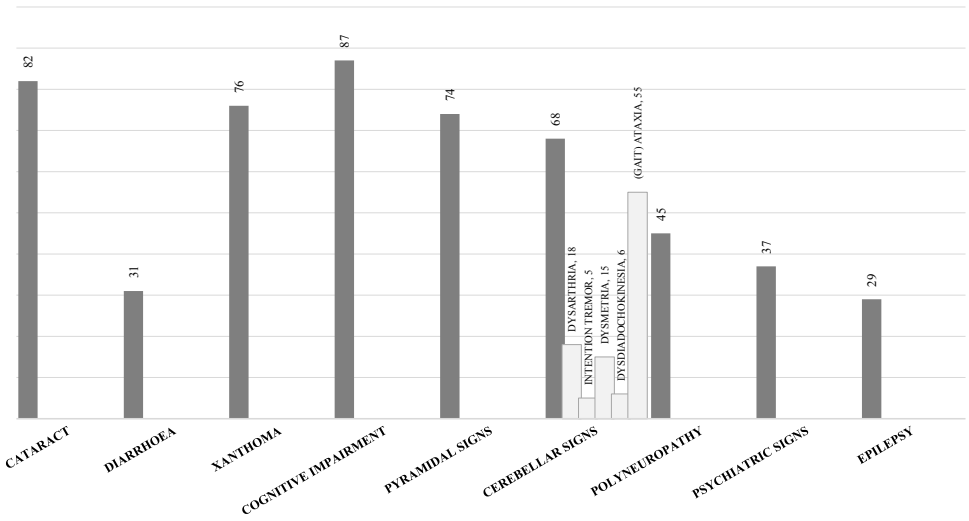

Fig. 1. Classical systemic and neurological features (%) at time of diagnosis of the movement disorder in 62 CTX patients, including seven Dutch CTX patients.

no reports of involvement of the basal ganglia on brain MRI in CTX patients with one of the other movement disorders. Functional dopaminergic imaging has revealed a clear presynaptic dopaminergic deficit in 9 of 10 patients with CTX and parkinsonism [15,17,18,29,30,33,36,38]. Post-synaptic functional studies were normal in 2 patients, and abnormal in 1 patient [18,38].

4. Discussion

CTX is a poorly recognized disorder, and a detailed appreciation of the full phenotypic spectrum is required in order to prevent underdiagnosis of this disease. Pyramidal and cerebellar signs are frequent and well-known features of CTX [2]. Ataxia is one of the most common motor abnormality in CTX, and the cerebellar involvement is also partly responsible for other movement disorders seen in CTX. In this review, we presented an overview of all other movement disorders reported in CTX.

In the literature, the reported incidence of 'extrapyramidal signs' in CTX is 21%–33% [31,40]. Because of other neurologic features, which mostly dominate the clinical picture, movement disorders in CTX patients may also be overlooked and underestimated [15]. Movement disorders were found to be mixed in 23% of patients and were usually part of a complex clinical picture, rather than a predominant symptom. Still, in 18% of the cases the movement disorder was the presenting symptom. Mean age at onset of the movement disorder was 40 ± 12 years. Although there is a wide range in age at onset, movement disorders can be considered as a late disease manifestation, as shown earlier by Mignarri et al. [46] Our literature study shows that at time of diagnosis of the movement disorder, most patients already had systemic or other neurological disease manifestations.

Parkinsonism is the most frequently reported type of movement disorder in CTX patients, followed by dystonia, myoclonus and postural tremor. Parkinsonism in the context of CTX is rarely isolated, and often accompanied by cognitive impairment, pyramidal and/or cerebellar

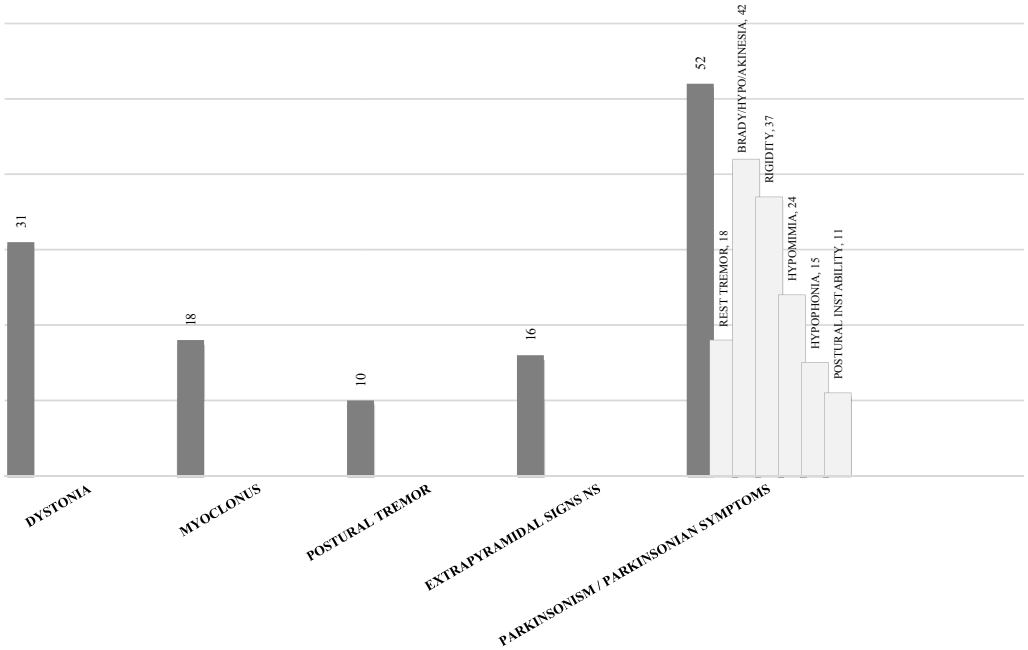

Fig. 2. Type of movement disorder (%) in 62 CTX patients, including seven Dutch CTX patients.

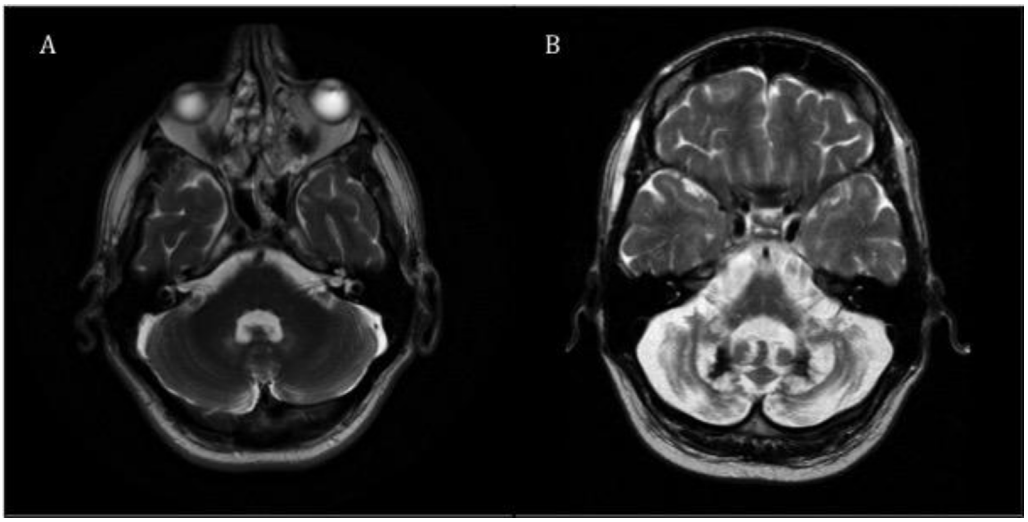

Fig. 3. Axial T2-weighted images of two adult Dutch CTX patients with advanced disease stage (A: CTX 1, B: CTX 4) show symmetric hyperintensities of dentate nuclei (A, B). Also symmetric hyperintensities of the surrounding white matter, and cerebellar atrophy is shown (B). The hypointense lesions are due to the deposition of hemosiderin and calcifications.

signs. Still, parkinsonism can be the presenting neurological symptom. The reported incidence of parkinsonism in CTX is 9% in a study done by Mignarri et al. [46] The incidence of parkinsonism in our Dutch patient cohort is also 9%. Although mostly asymmetrical, the clinical presentation of parkinsonism in CTX is that of a atypical parkinsonian syndrome, with early age of onset, early onset of gait disturbances and/or cognitive abnormalities, and/or co-existent other neurological signs [22]. Rubio-Agusti et al. [30] described a case of corticobasal syndrome in a patient who showed no other neurological signs suggestive of classic CTX, like ataxia. The mechanism causing parkinsonism in CTX is poorly understood, although nuclear imaging indicates an important contribution of nigra degeneration.

Beside the typical T2 hyperintense brain MRI signal changes in the dentate nuclei, also involvement of the basal ganglia and/or substantia nigra is described in CTX patients with clinical parkinsonism. Still, signal changes of the basal ganglia and substantia nigra have not been consistently reported in CTX patients with parkinsonism. In our own cohort of Dutch CTX patients, none of the patients with parkinsonism had involvement of the basal ganglia and/or substantia nigra on MRI. Histological studies in CTX show a combination of xanthomatous lesions, lipid crystal clefts, fibrosis, and hemosiderin deposition, in selective areas within the central nervous system, pathognomic for this disease [47]. There are no specific data on brain pathology in CTX patients with parkinsonism or other movement disorders. The second most reported movement disorder in CTX is dystonia. Abnormal cerebellar output could play a role in the pathogenesis of dystonia in CTX [48]. Dystonia has been seen as a basal ganglia disorder, but alterations in activity, connectivity and structure of the cerebellum are also associated with dystonia. In CTX, cerebellar involvement typically starts in the dentate nuclei, extending into the surrounding white matter of the cerebellar hemispheres. Also, hyperintense signal abnormalities are seen of the inferior olive of CTX patients on brain MRI [47]. The occurrence of dystonia in CTX is probably due to dysfunction of networks that connect different structures involved in sensorimotor integration. Dysfunction in the dentato-rubro-olivary pathway could play a role in the occurrence of palatal myoclonus in CTX [49]. Postural tremor, seen in only a minor part of the patients, is likely part of a parkinsonian, dystonic or cerebellar syndrome.

While there is evidence that treatment with chenodeoxycholic acid normally arrests and even can prevent the development of new neurological symptoms, the effect on movement disorders in CTX seems to be limited. One of the reasons could be that movement disorders can be considered as a late disease manifestation. The mean age at diagnosis of CTX of the patients reviewed was 35 years. After significant pathology has occurred, the effect of chenodeoxycholic acid treatment is limited and deterioration may continue [50]. Parkinsonism seems to be a treatment-resistent feature in CTX patients. Not only treatment with CDCA seems to have no effect on parkinsonism, but also six out of seven patients with parkinsonism in our Dutch cohort of 79 (77 genetically proven) CTX patients, developed parkinsonism during follow-up while on treatment with CDCA. The effect of L-dopa is controversial, with a mild or temporary effect in most patients, suggesting a more extensive nigrostriatal dysfunction rather than a 'pure' presynaptic dopaminergic deficit [13,15,17–19,22,23,29,30,33,36,38]. Also early motor fluctuations were reported in literature [23]. Ohno et al. [18] suggested that Diphenylpyraline hydrochloride (DPP), a dopamine reuptake inhibitor, is the therapeutic choice for treating parkinsonism in CTX. They describe three patients who showed a better response to DPP than to levodopa, but as yet there are no other cases supporting this hypothesis or confirming this observation. A positive effect of Botulinum toxin is reported in two patients with jaw-opening dystonia and one patient with blepharospasm [28,33,34].

In conclusion, movement disorders represent a rare clinical feature in CTX - a treatable inborn error of metabolism. Still, CTX should be considered in the differential diagnosis of movement disorders, particularly in case of an early onset and when associated with other neurological features (especially cognitive impairment, pyramidal and cerebellar signs) and/or with systemic features (such as diarrhoea, cataract and tendon xanthomas).

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Author contributions

Bianca M.L. Stelten: design of the study, writing of the manuscript, final approval.

Bart P.C. van de Warrenburg: critical reading of the manuscript, final approval.

Ron A. Wevers: critical reading of the manuscript, final approval.

Aad Verrips: design of the study, critical reading of the manuscript, final approval.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.07.006.

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