Educational Review

Nosology and Phenomenology of Psychosis in Movement Disorders

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ABSTRACT

Background: Psychotic symptoms such as delusions and hallucinations are part of the clinical picture of several conditions presenting movement disorders. Phenomenology and epidemiology of psychosis in Parkinson's disease have received wide attention; however, the presence of psychosis in other movement disorders is, comparatively, less-well-known.

Objectives: To review psychotic symptoms present in different movement disorders.

Methods: A comprehensive and structured literature search was performed to identify and analyze data on patients with movement disorders and comorbid psychosis.

Results: In monogenic parkinsonisms, such as PARK-GBA, PARK-LRRK2, and PARK-SNCA, visual hallucinations related to dopamine replacement therapy are frequent as well as are delusions in PARK-LRRK2, and PARK-SNCA, but not in PARK-GBA. Different types of delusions and hallucinations are found in Huntington disease and other choreic disorders. In Tourette syndrome, paranoid delusions, visual, olfactory and auditory hallucinations have been described, which usually develop after an average of 10 years of disease. Delusions in ataxias are more frequent in ATX-TBP, ATX-ATN1, ATX-ATXN3, while it is rare in Friedreich's ataxia. Psychosis is also a prominent and frequent clinical feature in Fahr's disease, Wilson's disease, Neurodegeneration with brain iron accumulation, and some lysosomal storage disorders, while it is uncommon in atypical parkinsonisms and dystonia. Psychosis usually occurs at late disease stages,

but may appear as onset symptoms of the disease, especially in Wilson's disease, Huntington disease, Late-onset Tays Sachs and Niemann-Pick.

Conclusion: Psychosis is a frequent comorbidity in most hyperkinetic and hypokinetic movement disorders. Appropriate recognition is relevant both in the early and late disease stages.

During the last decade more attention has been directed towards the nonmotor symptoms of movement disorders, a group of diseases and conditions classically recognized as mainly motor. The DSM-5 stresses the common co-occurrence of psychotic symptoms in neurocognitive disorders, and information on the neurobiology of hallucinations and delusions associated with neurologic conditions has expanded rapidly over the last decade[1]. Whereas an overwhelming number of studies have been published on psychosis in Dementia with Lewy Bodies and on dopamine replacement therapy (DRT)-associated psychosis in idiopathic Parkinson's disease (PD), phenomenology, epidemiology, and putative mechanisms of psychotic disorders in other movement disorders have received much less attention. The objective of the current educational review was to systematically search for and analyze clinical features of psychosis associated with movement disorders.

According to the American Psychiatric Association and the World Health Organization, current conceptualization of psychosis requires the presence of prominent hallucinations or delusions[1]. The ICD-10 (F06.0) describes Organic Hallucinosis as persistent or recurrent hallucinations occurring in clear consciousness, with or without preserved insight. Delusions may be present but are less prominent. The Organic Delusional Disorder (F06.2) consists of persistent or recurrent delusions which

dominate the clinical picture and may be accompanied by hallucinations or a thought disorder.

Hallucinations are defined as sensory perceptions in the absence of a corresponding external or somatic stimulus, and are described according to the sensory domain in which it occurs. Hallucinations may occur with or without insight into their hallucinatory nature. Hallucinations are distinguished from illusions, which are misperceptions of a sensory stimulus. These perceptual phenomena occur in many neuropsychiatric conditions, including movement disorders.

Delusions are false beliefs based on false inferences about external reality or about, oneself and maintained firmly despite conflicting evidence that contradicts the belief. Delusions are commonly present in patients with dementia and patients under DRT. Delusions may consist of different themes such as persecutory, grandiose, erotomanic, nihilistic, and somatic content, or bizarre content such as though control or withdrawal. Different and varied phenomenology may include the belief that one is being intentionally harmed, tricked, followed, spied on, poisoned or drugged, tormented, ridiculed, cheated, conspired against (persecutory delusions), the conviction that one possesses special powers, talents or abilities; or is famous or God, an angel, a devil or a saint (grandiose delusions). Less frequent are beliefs that one's thoughts, feelings, or

behaviors are being controlled by an external force (thought control) or that thoughts are being inserted into one's mind (thought insertion), that a person or group is removing or extracting one's thoughts (thought withdrawal), that one's mind can be or is being read by another person, the belief that a spouse or lover is unfaithful (delusion of infidelity), the belief that one is loved by another person of higher status (erotomania), the belief that one is infested with insects, spiders, worms, or other organisms (Ekbom syndrome) or the belief that one's body is abnormal, diseased, or changed in some manner.

Delusional misidentification includes various themes, such as the belief that a spouse, family member, or other familiar individual has been replaced by an impostor who is physically, but not psychologically, identical to the replaced person (Capgras delusional belief), or the believe that different people are in fact a single person (Fregoli delusion), or that a double of oneself exists (Doppelgänger), and the belief that one or more of one's organs or body parts are missing or no longer exist (Cotard delusion).

Methods

We conducted a comprehensive and structured search in PubMed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (http://www.prisma-statement.org) using a list of keywords, namely: atypical parkinsonism, progressive supranuclear palsy, PSP, multiple system atrophy, MSA,

corticobasal, CBS, CBD, genetic parkinsonism, SNCA, VPS35, LRRK2, Parkin, PINK1 , PARK2, Kufor-Rakeb, ATP13A2, DJ-1, PARK9, GBA, glucocerebrosidase, Niemann-Pick, chorea, Huntington disease, neuroacanthocytosis, Huntington-like, Tourette syndrome, tic disorders, myoclonus, myoclonic, dystonia, tremor, ataxia, Wilson's disease, Fahr, PLA2G6, PANK2, NBIA, pallido-pyramidal, hypokinetic, hyperkinetic, and basal ganglia in combination with psychosis, psychotic, hallucination, delusion, delusional, thought disorder and illusion. Publications written in English and published up to December 31, 2018 were screened. Types of publications screened included case reports, case series or case-controlled studies, literature reviews, and any other type of publication that could contain clinical information on psychosis in movement disorders. Abstracts and titles were screened and cross-checked for relevance by two authors (MR and NF) working separately. Full-texts containing clinical data of patients with movement disorders and comorbid psychosis were analyzed. Back-searching of retrieved publication reference lists was conducted to identify gray literature. Publications based on Dementia with Lewy Bodies or DRT-associated psychosis in idiopathic PD were excluded as these entities were extensively reviewed in other publications. However, patients with mutations in PD-related genes were included as traditionally they have received less attention and may present unique differential features, such as psychosis unrelated to DRT. In order to compare findings on monogenic parkinsonisms with idiopathic PD, data available on systematic reviews on

psychosis in idiopathic PD were analyzed. Diseases classified as dementia, such as Frontotemporal Dementia and Creutzfeldt Jakob Disease or conditions eliciting movement disorders, such as myoclonus in the context of metabolic diseases were excluded, as other clinical features may predominate over movement disorders.

Results

Results of the systematic literature search are shown in Figure 1. In total, 11635 publications were initially identified, of which 567 were included in qualitative and quantitative synthesis after excluding those publications without individual data or percentages of patients with movement disorders and psychotic symptoms. The frequency of psychotic patients reported in the selected movement disorders are shown in Table 1. The most relevant clinical features of each disorder are described below. In most cases, psychotic features were most frequent during the disease course or at advanced disease stages. However, in a few disorders, psychosis preceded all other clinical features and presented as a first symptom of the disease. Figures 2 and 3 illustrate the phenomenology of psychosis in different movement disorders, and its relation to both the disease course and to DRT. Psychosis was considered as related to DRT if there was either a clear temporal association between onset or resolution of psychosis and starting or stopping of DRT, or if explicitly stated by the authors.

Patients with mutations in Parkinson's disease-related genes

PARK-GBA

The presence of visual hallucinations unrelated to DRT was reported in 45% (14 out of 31) of PARK-GBA patients[2]. This frequency was surprisingly similar to the estimated 50% of lifetime prevalence of DRT-related visual hallucinations found in idiopathic PD, and is considered to be a consequence of Lewy body pathology spreading into the temporal lobe[2,3]. However, a high frequency (78%) of visual hallucinations developing under DRT was also reported in PARK-GBA, a greater frequency than in PARK-LRRK2 (38%) or in idiopathic PD (53%)[4]. Similar figures have been found in other studies, with rates of psychosis in PARK-GBA patients receiving DRT ranging between 46%[5] and 53%[6]. Finally, a recent meta-analysis found that PARK-GBA was associated with a 1.83-fold increased risk for psychosis (95%CI: 1.23–2.74, p = 0.003)[7]. Visual hallucinations developed in PARK-GBA after disease onset and were commonly associated with cognitive decline or dementia[2,6] as well as with the presence of deleterious or severe GBA variants causing Gaucher disease types II and III[8,9]. To date, delusions have not been reported in PARK-GBA patients.

PARK-SNCA

Psychotic features in PARK-SNCA have been reported among individuals with heterozygous mutations (e.g p.A53T) and among those due to gene duplications,

although the exact prevalence is not known. Psychotic symptoms, mostly consist of multimodal hallucinations (visual, auditory and olfactory), often combined with paranoid delusions that may be persistent and refractory to treatment, eventually dominating the clinical picture[10-12]. Psychotic symptoms presenting at disease onset are rare[12,13]. Takamura and colleagues reported a single case with SNCA duplication that developed delusions and auditory hallucinations and was clinically diagnosed with schizophrenia ten years prior to developing parkinsonian motor signs[13]. Psychosis in PARK-SNCA developed in most cases after several years of disease[10-12]. Visual hallucinations were commonly related to DRT, cognitive decline or dementia[10-12,14,15].

PARK-LRRK2

In a cohort of twenty-three PD patients carrying the G2019S mutation in the LRRK2 gene, delusions were found in 13% of cases and visual hallucinations in 26%, which was significantly more frequent than in non-carriers (OR = 8.4)[16]. However, in a different sample of twenty-seven PARK-LRRK2 patients, no hallucinations or delusions were observed[14]. Although psychotic symptoms of most PARK-LRRK2 patients resemble those of patients with typical idiopathic PD as they are induced by DRT, visual and auditory hallucinations as well as paranoid delusions unrelated to DRT have also been reported in PARK-LRRK2[17,18]. In some cases, psychosis was associated with dementia and depression[17,18].

PARK-PRKN

Psychosis has been rarely reported in PARK-PRKN. Delusional jealousy, delusion of self-persecution, paranoid delusions, visual and third person auditory hallucinations have been reported in these patients, usually after several years of disease[19,20]. In only a few cases psychosis occurred prior to motor symptom onset[19]. Psychotic symptoms were usually related to DRT[19-21] and persisted even after antiparkinsonian drug reduction and treatment with antipsychotics[21]. Some cases were associated with depression, but not related to cognitive impairment[19].

PARK-PINK1

Psychosis in this condition was reported in isolated cases and included visual hallucinations[22-25], paranoid and grandiose delusions as well as hyperreligiosity[26-30]. Visual hallucinations were usually associated to DRT[22-25], and also observed in the context of grandiose delusions and impulse control[31,32]. In a few cases, visual hallucinations were associated with dementia[23,24,29]. Treatment with high doses of quetiapine or clozapine showed good efficacy in some cases[31,32].

PARK-DJ-1

Psychotic episodes in PD patients with the DJ-1 gene mutation have been rarely described and include visual hallucinations and paranoid delusions. Some patients were on DRT and psychosis developed most often after several years of disease[33-37].

22q11.2 deletion syndrome (22q11.2DS)

This multisystem condition is associated with an increased risk of early-onset Parkinson's disease[38]. The prevalence of psychosis in this condition ranged between 10% to 30% and developed usually during childhood or early adulthood[39-41]. Psychotic symptoms included auditory and visual hallucinations, as well as paranoid delusions[39,40,42]. Psychosis was frequently associated with mental retardation[41,42] as well as increased caudate head volume, principally on the left side[43]. Psychotic symptoms sometimes improved with clozapine, quetiapine and valproic acid[39,44]. Special attention should be paid to the risk of clozapine-associated seizures[38].

PARK-VPS35

No reports of psychosis associated with mutations in this gene were found.

Idiopathic Parkinson's disease

Systematic reviews revealed that he most common psychotic symptom in Idiopathic Parkinson's disease (IPD) is visual hallucination with an estimated pooled prevalence of

28.2% (±19.1 to 39.5)[45] followed by isolated delusions (mostly paranoid)[46]. DRT-induced visual hallucinations are more frequent in IPD than in patients with mutations in Parkinson's disease-related genes (except for PARK-GBA that shows similar figures) and are also commonly associated with dementia[45,47]. In IPD, the content of hallucinations is often stereotyped with frequent descriptions of animals[48]. Unlike genetic parkinsonisms where multimodal hallucinations combined with delusions are the most frequent psychotic features, minor hallucinations including passage, feeling of presence or illusions are one of the most common early psychiatric symptoms in IPD[49]. Auditory hallucinations, like verbal hallucinations perceived as originating outside the head are also more frequent in IPD (estimated pooled prevalence of 8.9%) compared to monogenic parkinsonisms, in which a few cases were reported[50]. Psychosis, especially minor hallucinations, can affect about 10-42% of untreated IPD individuals at early disease stages[51], but is considerably more infrequent in monogenic parkinsonisms, in which psychosis is commonly associated with disease progression.

Atypical Parkinsonisms

PARK-ATP13A2

Some cases with psychosis associated to this condition were reported, with patients presenting visual and auditory hallucinations as well as paranoid delusions51-55. Visual hallucinations commonly occur several years after the disease onset and are often

associated with DRT and dementia[52,54-56]. Response to antipsychotic treatment has been only partial[47].

PARK-DNAJC6.

Levodopa-induced visual hallucinations have been reported in three patients with this genetic condition[57]. One presented psychotic disturbances at disease onset at the age of 21 years. Another patient exhibited psychosis unrelated to DRT, with symptoms beginning at the age of ten years, with vivid and terrifying visual hallucinations which increased in frequency, followed within a few months by parkinsonism and cognitive decline[58].

PARK-FBXO7.

In this type of genetic parkinsonism, DRT-induced psychosis characterized by delusions[59] and hallucinations[60,61] have been rarely reported.

PARK-DCTN1 and PARK-SYNJ1.

No patients with psychosis have been reported in these conditions.

Multiple system atrophy.

Hallucinations related to DRT have been rarely reported in multiple system atrophy (MSA)[62]. However, some patients with MSA did present psychotic features unrelated to DRT, such as religious, persecutory, and somatic delusions, as well as auditory and visual hallucinations (usually of small animals)[63-66]. Psychotic manifestations were not related to dementia[63,64,66].

Progressive supranuclear palsy.

Psychosis in progressive supranuclear palsy (PSP) is rare. Visual and auditory hallucinations, as well as paranoid delusions, bizarre delusions and an unusual schizophrenia- like syndrome have all been described[67-70]. In some cases, auditory hallucinations occurred during DRT; however, they were not considered related to treatment since they persisted after levodopa discontinuation, or, in other cases, hallucinations remitted spontaneously, before discontinuation of therapy[71]. Unlike classical PSP, in the Guadeloupean population of PSP-like parkinsonism, visual and auditory hallucinations unrelated to DRT have been reported in 59% of the cases, some of them with comorbid delusions[72].

Corticobasal syndrome

Presence of psychotic symptoms is uncommon and consists of auditory and visual hallucinations as well as persecutory delusions[73-75]. Psychosis, which has been usually

associated with dementia, responds to antipsychotic treatment in some patients[73]. Patients with alien limb syndrome may experience the delusion of external control[76].

Choreas

Diagnosis of the underlying cause of chorea is challenging in cases in which psychosis develops before the onset of chorea. In fact, chorea may be misdiagnosed as tardive dyskinesia in psychotic patients receiving neuroleptics[77].

Huntington disease.

Patients with Huntington disease (HD) frequently show depression, anxiety, irritability, aggression, apathy and obsessive compulsive behaviors[78]. Psychosis in HD disease is rare and its prevalence is estimated to range between 3% and 30%, with most recent studies reporting a prevalence of 10%[78-86]. It may manifest as a prodromal symptom, months or years prior to motor or cognitive dysfunction[84,87,88]. Kirkwood and collaborators reported psychosis developing in 5.2% of the patients during the first year of disease, and in 18.3% during the first 10 years of disease[80]. More recently, a large prospective study failed to find psychosis in 34 premanifest mutation carriers, even late after motor-based disease onset, whereas it was present in only one out of 24 (4%) premanifest mutation carriers close-to motor-based disease onset and in three out of 70 (4%) early-symptomatic patients, suggesting that psychosis rarely occurs during the

prodromal or early symptomatic HD stages[81]. Psychosis in HD is characterized by different types of delusions, such as persecutory, grandiose and nihilistic. However, other psychotic symptoms have also been reported, such as the Othello syndrome (delusional jealousy), the Ekbom syndrome (delusional parasitosis), *folie à deux* (a type of psychosis occurring simultaneously in two intimately related persons who share some elements of the illness), as well as somatic, auditory, and visual hallucinations[80,82,844]. Psychosis is commonly associated with depression and cognitive decline, but the frequency of psychosis declines as cognitive impairment becomes more severe[78,84,85,89]. The association between psychosis and size of the CAG expansion, age at disease onset or gender remains inconclusive, with some studies failing to find a significant link[78,86,90], while others, finding lower number of CAG repeats and younger age at time of HD clinical diagnosis in individuals presenting with psychosis[85]. Familial aggregation and predisposition to psychosis has been reported in some studies, suggesting there may be modifying genes interacting with the HD gene to increase the susceptibility to psychosis[88,89]. Psychosis in HD is one of the major predictors of nursing home placement[91]. Severe or frequent visual and auditory hallucinations were more than twice as common in skilled nursing facility residents compared to patients living at home (4.9% vs. 2%, p=0.007)[91]. Response to antipsychotics was variable, with partial response observed in several cases[92]. Typical antipsychotics, such as haloperidol may exert a dual effect, by controlling both psychotic symptoms and choreic movements;

however, in more advanced stages of disease, atypical antipsychotics, such as risperidone, olanzapine or quetiapine are also effective, and better tolerated than typical antipsychotics[92].

Sydenham's chorea.

A large study examined the association of Sydenham's chorea and psychosis and estimated odds ratio was 13.8[93]. Delusions of persecution and auditory hallucinations, mimicking schizophrenia may develop[93-97] and may frequently occur after chorea has subsided[94]. Autopsy examination of one patient revealed non-specific mineral deposits in the basal ganglia, similar to those found in schizophrenia and normal aging[94]. Treatment usually shows good response to atypical antipsychotics[95-98].

TITF-1 related benign hereditary chorea.

Psychosis in this condition was reported in isolated cases and included delusions and visual and auditory hallucinations[99], which were usually well controlled with atypical antipsychotics[100].

Chorea-acanthocytosis (CHOR-VPS13A1).

Delusions and hallucinations have been reported in some cases[77,101,102], of which a schizophrenia-like syndrome was sometimes the first clinical manifestation, occurring

months to years prior to neurological symptoms onset[77,102,103]. Psychosis in this condition was unrelated to seizures, albeit hallucinations such as an epileptic aura were occasionally reported[101]. Response to antipsychotics was usually partial or ineffective[77,102]. Typical antipsychotics should be used with caution due to risk of severe parkinsonism[103].

McLeod syndrome (CHOR-XK).

Psychosis was reported in several patients[104-106], including a schizophrenia-like presentation preceding the onset of chorea by several years[107,108], responding to both typical and atypical antipsychotics[105,106].

Adenylyl cyclase 5 (ADCY5)-related dyskinesia.

In this autosomal dominant disease, in which patients usually have chorea, including facial dyskinesia, and dystonia; psychosis (mainly auditory hallucinations, and grandiose, religious and persecutory delusions, thought insertion and thought broadcasting) was reported in a few cases[109,110].

Tourette syndrome

The prevalence of psychosis in Tourette syndrome ranged between 2.5% and 14.6%[111-114]. The most frequent psychotic symptoms were visual, olfactory and auditory

hallucinations, and paranoid delusions, which usually developed after an average of 10 years of disease[115-118]. Even though some of the patients reported psychotic symptoms during childhood, many had already developed tics prior to the onset of psychosis[113]. Interestingly, some patients received antipsychotics as a treatment for tics before developing psychosis[113]. Psychotic symptoms were effectively treated with haloperidol[113,119].

Ataxias

Psychosis has been reported in several conditions that include ataxia as a predominant or consistent clinical feature, such dominant [120,121] recessive cerebellar ataxias[122,123] .

Dominant cerebellar ataxias

In autosomal dominant cerebellar ataxias, psychosis was reported in different genetic subtypes, such as ATX-ATXN2 (SCA2), ATX-ATXN3 (SCA3), ATX-ATXN7 (SCA7), ATX-ATXN8 (SCA8), ATX-ATXN10 (SCA10), ATX-PPP2R2B (SCA12), ATX-TBP (SCA17) and ATX-ATN1 (Dentatorubral-pallidoluysian atrophy), most often after several years of disease course[120,121,124,125]. Among these genetic subtypes, psychosis is more frequent in ATX-ATXN3, ATX-TBP and ATX-ATN1 in comparison to other subtypes, such as ATX-ATXN2, ATX-ATXN8, ATX-PPP2R2B or ATX-ATXN10, in which the presence of psychosis was reported in a few cases[120,124-130]. In ATX-ATXN3 or

Machado–Joseph Disease, the most common spinocerebellar ataxia worldwide, a frequency of psychosis of 4.5% was found in a large cohort of 112 patients[120]. Patients with psychotic symptoms were older and presented later onset than those without psychosis[120]. Anatomopathological studies in five patients with psychotic symptoms revealed severe loss of Purkinje cells and also loss of neurons in the dentate nucleus, inferior olives and substantia nigra, but usually with preserved frontal, temporal and parietal cortex. These findings are similar to those found in patients with autosomal dominant cerebellar ataxias without psychosis[120,121]. Patients with psychosis did not differ significantly in midbrain tyrosine hydroxylase activity staining[121]. In Fragile X tremor/ataxia syndrome, an X-linked dominant ataxia, psychosis is uncommon[121].

Recessive cerebellar ataxias

In Friedreich's ataxia, the most common autosomal recessive cerebellar ataxia worldwide, psychosis is rare, usually occurring after years or during the final stages of disease and responding in most cases to antipsychotics, such as risperidone, quetiapine and aripiprazole[131,132]. In cerebrotendinous xanthomatosis (ATX-CYP27A1), seven patients developed delusions and hallucinations during the disease, responding partially to antipsychotics and chenodeoxycholic acid[133-135]. In some patients, psychosis was associated with cognitive decline[133]. Other recessive ataxias can show psychosis as part of a broader clinical picture, such as Maple syrup urine disease (ATX-BCKDHB),

succinic semialdehyde dehydrogenase deficiency (ATX-ALDH5A1), the hepatocerebral type of Mitochondrial DNA depletion syndrome (ATX-C10orf2), mitochondrial complex III deficiency nuclear type 2 (ATX-TTC19), spastic paraplegia type 15 (HSP-ZFYVE26), X-linked mental retardation syndrome due to mutations in the MECP2 gene, and Hartnup disease (SLC6A19)[123].

In summary, psychosis in different neurodegenerative ataxias occur commonly after several years of disease and included auditory or visual and somatic hallucinations, paranoid delusions and delusions of reference[120,125-128]. Taking into consideration that psychosis as the initial symptom has rarely been reported, the presence of psychosis in early disease stages should point to ATX-ATXN3, ATX-TBP, ATX-ATN1 or cerebrotendinous xanthomatosis. Dementia[121,136] or depression[121,125] have been occasionally associated with psychosis. Treatment with atypical antipsychotics is usually effective in controlling psychotic symptoms[125,137].

Dystonia

Psychosis was reported in some genetic dystonias, like myoclonus-dystonia due to heterozygous mutations or deletions in the epsilon-sarcoglycan gene (MYC/DYT-SGCE). In this condition, both hallucinations and paranoid delusions have been reported, usually associated with other psychiatric conditions, such as depression, panic

disorder, social phobia, obsessive-compulsive disorder, and alcohol dependence or abuse, but not with cognitive decline[138-141]. In rapid-onset dystonia-parkinsonism caused by mutations in the ATP1A3 gene (DYT/PARK-ATP1A3), psychotic symptoms may present before or concurrently with motor symptom onset[142] or even in the absence of dystonia or parkinsonism[143]. In other conditions, like secondary dystonia, dystonic features may be comorbid with the exacerbation or onset of psychotic symptoms[144].

Myoclonus

Psychosis is extremely rare in conditions that feature myoclonus as a predominant, or long-standing clinical manifestation (myoclonus related to multisystemic general medical conditions, such as anti-NMDA receptor encephalitis has been excluded from this review). Psychosis has been reported in myoclonus-dystonia due to heterozygous mutations or deletions in the epsilon-sarcoglycan gene (MYC/DYT-SGCE)[139], in patients with myoclonic epilepsy of Lafora (MYC/ATX-EPM2A and MYC/ATX-NHLRC1)[145], in which prolonged complex visual hallucinations are mostly of epileptic origin and may respond to antiepileptic drugs, rather than antipsychotics[145], and in some types of neuronal ceroid-lipofuscinoses (NCLs) with myoclonus as a prominent and consistent associated movement disorder (MYC-CLN6, MYC-DNAJC5, MYC-CLN3, MYC/ATX-KCTD7)[146-147]. NCLs presents with psychosis in up to 20% of patients, although some of them combine psychosis with myoclonus or myoclonic epilepsy[148]. Delusions, visual

and auditory hallucinations have been reported[149-151]. The association of psychosis with dementia is common[147,149,152] and a propensity towards neuroleptic malignant syndrome has been reported[153,154].

Tremor

Psychosis is absent in disorders that include tremor as a predominant or frequent clinical manifestation in the absence of other signs of parkinsonism.

Fahr's disease or idiopathic basal ganglia calcification

Mutations in the SLC20A2, PDGFB, PDGFRB and the XPR1 genes have been identified in several idiopathic basal ganglia calcification (IBGC) families with autosomal dominant inheritance, some of which reported hallucinations and delusions[155-158]. Psychotic symptoms that were commonly reported include auditory and visual hallucinations as well as paranoid, reference and grandiose delusions[159-162]. Age at presentation seems to influence the type of psychiatric symptom. Young individuals (under 40 years of age) usually present psychosis without neurological features; whereas after the fifth decade of life, patients present movement disorders and dementia at disease onset[159-161,163,164]. Imaging studies indicated that presence of psychosis was proportional to the extent of cerebral calcifications[163]. Treatment with atypical antipsychotics is usually effective to alleviate psychotic symptoms[158,165];

however, caution is advised as patients with basal ganglia calcifications may be more vulnerable to developing parkinsonism[159].

Neurodegeneration with brain iron accumulation

Psychosis in neurodegeneration with brain iron accumulation (NBIA) has been reported in several cases, although the exact prevalence is unknown. Psychotic symptoms include visual and auditory hallucinations, as well as delusions[166-170]. Psychosis has occasionally been associated with dementia or mental retardation[166-170] and may frequently occur at disease presentation as the only symptom, especially in patients with PLA2G6 mutations, or years before the onset of neurological manifestations[171-175]. In such cases, abnormal brain MRI findings, such as the 'the eye of the tiger' sign can help avoid misdiagnosis of schizophrenia. Psychotic symptoms are generally unrelated to DRT[167,169,170,176], although some DRT-related psychosis cases have been reported[168]. Psychotic symptoms in NBIA usually respond to neuroleptic treatment[166,168,171,173]. Use of typical antipsychotics requires special caution, since these drugs may induce parkinsonism or dystonia[177]. Though rare, increased sensitivity to neuroleptics (a paradoxical worsening of psychosis) has been reported[167].

Wilson's disease

In the first description of the disease, S. A. Kinnier Wilson described psychotic symptoms in two of twelve patients[178]. Even though psychiatric disturbances have been reported in 50% to 70% of Wilson's disease (WD) patients[179,180], less than 10% showed psychosis, suggesting that this manifestation is not a hallmark of the disease[179,181-183]. On the other hand, psychotic symptoms at disease onset may be present in 35% of patients[180,184] with an interval between onset of psychosis and diagnosis of WD of 2.4 years[185]. This poses an important differential diagnosis with schizophrenia. In most cases in which psychotic symptoms were the first manifestation of WD, these were paranoid delusions and hallucinations[180,186,187]. Psychotic symptoms during the course of WD are similar to those appearing at disease onset[188,189]. Psychosis may be related to discontinuation of penicillamine treatment[190,191], which usually reverts after treatment is restored or antipsychotics prescribed[192] or after liver transplantation[193]. Psychotic symptoms may also be related to an ineffective zinc treatment[194]. Treatment of psychotic symptoms in WD includes penicillamine monotherapy, which resolves psychosis indirectly by improving copper metabolism. However, redistribution of copper from the liver to other organs, including the brain, after penicillamine treatment may paradoxically cause or aggravate psychosis in some patients[195]. Most studies show poor or lack of response to antipsychotics, except for high doses of clozapine or risperidone[189,196]. In some cases of psychosis refractory to antipsychotics, electroconvulsive therapy reverted hallucinations and delusions[197,198].

Niemann-Pick disease

Psychotic manifestations are prominent and frequent in Niemann-Pick disease (NP) type C, A and B. A recent systematic review of psychiatric signs in NP type C found a prevalence of psychosis of 62%[199]. Psychosis may present as paranoid delusions, thought disorder, and visual, auditory or somatic hallucinations[200-203]. Psychosis as the initial presentation was reported in several cases and may be the only symptom for several years resulting in misdiagnosis of schizophrenia[1744,200-202,204,205]. In these cases, diagnosis of NP disease may be delayed, especially when patients develop dyskinesias after neuroleptic use, which can be mistakenly interpreted as a drug-induced movement disorder rather than clinical manifestation of NP disease[201,206]. The presence of neurological manifestations, (e.g. vertical supranuclear gaze palsy, gelastic cataplexia, ataxia, dystonia and seizures), treatment-resistant psychosis or paradoxical worsening of psychosis with neuroleptics suggest an organic cause like NP disease[205,207,208]. Psychosis is frequently associated with other psychiatric symptoms, such as depression[2044,203,208] and cognitive decline[200,202,205,208]. Postictal psychosis was also reported in NP disease type C, generally limited to a psychotic disorder that follows complex partial or generalized seizure activity, or a cluster of seizures[209]. Frontal lobe atrophy may be prominent in NP disease type C, and might be associated with psychosis[174]. Psychosis usually responds to antipsychotic medications, but paradoxical

worsening and resistance to antipsychotics can be observed, which might be ameliorated in some cases by using miglustat, a drug that inhibits glycosphingolipid synthesis and the only approved targeted therapy for the disease[210,211]. Antipsychotics should be used carefully due to the high frequency of dystonia, which worsens with these types of medications. Risk of a neuroleptic-induced lipidosis has also been reported[212].

Late-onset Tay-Sachs (LOTS) or chronic GM2 gangliosidosis

Hexosaminidase A deficiency in adults or Late-onset Tay-Sachs (LOTS) is a common cause of recurrent psychotic syndrome[213]. The prevalence of psychosis ranges from 30% to 50% among adult-onset cases, and many patients are misdiagnosed with paranoid schizophrenia[214]. Other psychotic features include visual and auditory hallucinations and the Capgras syndrome[215-217]. Psychosis precedes all other clinical features in most cases[213,217-219]. Nevertheless in some patients, psychosis develops late after many years of neurological symptoms[213]. Psychosis is frequently associated with depression[213,215,217], catatonia[216,218] and in some cases with dementia[213]. Postpartum psychosis, with affective and bizarre delusions was also reported in LOTS, and may resolve with lithium[220]. Treatment of psychotic patients with LOTS should not include phenothiazines or tricyclic antidepressants since they may worsen neurological manifestations by inhibiting the activity of lysosomal enzymes[214,221]. Psychosis

refractory to neuroleptics as well as neuroleptic malignant syndrome[116,218] have been described in several cases[215,216,218]. Lithium and electroconvulsive therapy have frequently proven successful to treat psychotic symptoms in this condition[215,216,219].

Neurobiology of psychosis in movement disorders

The pathophysiology of psychosis and the role of motor circuits in the development of psychosis is complex and will be summarized here only briefly, as it is beyond the scope of this review. It has been shown that lesions of the right lateral prefrontal cortex or its efferent projections, such as the basal ganglia and limbic system are associated with delusions[222]. Likewise, frontostriatal circuitry disruption after loss of neurons, as in caudate atrophy observed in patients with Huntington disease, may alter relevant processing of striatal-limbic information and favor the development of psychosis[223]. Cerebellar dysfunction has also been described in both schizophrenia and in populations at risk for psychosis, suggesting that the cerebellum may play a role in the development of psychosis[224]. In addition to structural alterations, faulty dopamine signaling, including altered dopamine receptor modulation has been proposed as a possible pathway for the genesis of delusions[225]. [18F] Fluoro-2-deoxy-D-glucose (FDG) hypometabolism of the striatal and temporal lobes was found in some IBGC patients with psychosis[161,226], suggesting a disruption of cortico-subcortical neural circuits. In tauopathies, the abnormal tissue burden distribution, more than the disease type, may

trigger psychosis[74]. In summary, brain mechanisms underlying delusional symptoms may be similar in both primary and secondary psychosis but this requires further study.

Conclusion

Psychosis is a common symptom in many conditions in which the primary manifestation is a movement disorder, making it important to evaluate the presence of psychosis during patient monitoring. The most frequent types of psychotic manifestations reported among patients with movement disorders include visual hallucinations and delusions, which occur most often after several years of disease duration and are sometimes associated with cognitive decline or depression. In cases in which psychosis is the presenting clinical manifestation, the diagnosis of secondary psychosis may often be delayed.

Comprehensive neuropsychiatric assessment of psychosis in movement disorder conditions as well as the association with cognitive or other psychiatric manifestations is lacking in most reports. Although typical and atypical antipsychotics may be useful to treat psychosis among patients with movement disorders, no structured or class-I evidence studies have been published to date. DRT discontinuation and use of neuroleptics have been the main treatment strategies reported in the literature. Psychosocial interventions, which are also important tools for the treatment of patients

with primary psychosis, were not mentioned in any of the high-quality studies analyzed for this review.

Psychotic manifestations in the absence of signs and symptoms of a movement disorder should motivate clinicians to a close follow-up of these patients. Treatment with neuroleptics may confuse the clinical picture due to the development, in some cases, of secondary movement disorders, stressing the challenge to identify a specific movement disorder as a comorbid condition of psychosis in clinical practice. We hope this review will provide the clinician with useful guidelines to improve the awareness about the comorbidity of psychosis with different movement disorders.

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Legends to figures.

Figure 1. Flow diagram of the study selection process.

Table 1. Frequency of psychotic patients reported in different movement disorders.

Movement disorders	n=patients/n=articles
Monogenic parkinsonisms	At least* 431/11[S1-S56**]
Atypical parkinsonisms	At least* 157/46[S57-S103**]
Choreas	At least 1149/59[S104-S163]
Tic disorders	70/22[S164-S180]
Ataxias	At least 63/29[S181-S209]
Dystonia	17/8[S210-S217]
Myoclonus	14/8[S212,S218-224]
Basal ganglia calcification	At least 113/37[S225-S260]
Neurodegeneration with brain iron accumulation	22/19[S261-S278]
Others	
Wilson's disease	At least 69/33[S279-S310]
Niemann-Pick disease	At least 106/27[S85, S311-S337]
Late-onset Tay-Sachs	At least 40/15[S338-S355]

* 'At least' indicates that some minor inaccuracy exists as some publications do not clearly report the total number of patients with psychosis for a specific condition.

** ‘S’ means Supplementary References

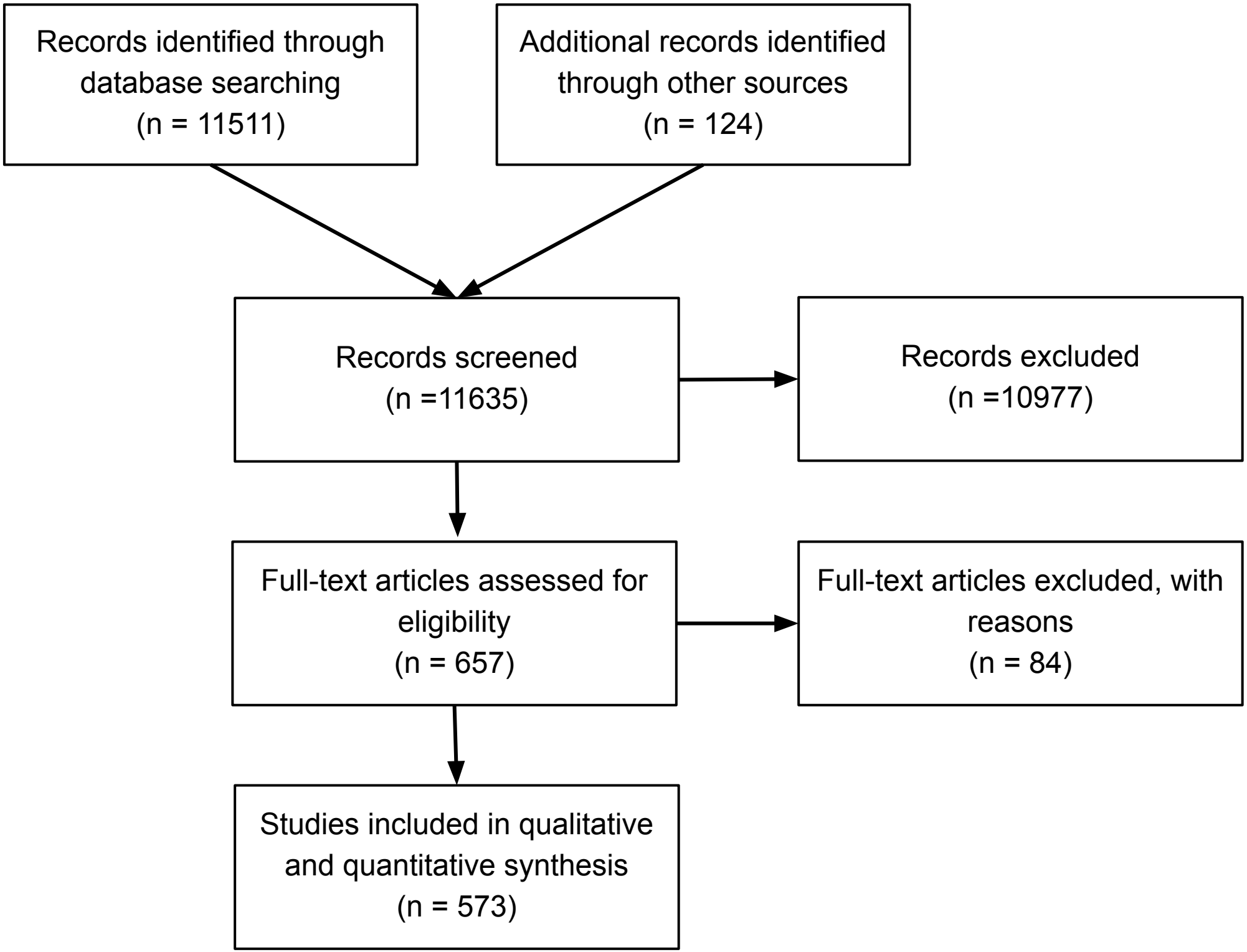
Table 2. Phenomenology of psychosis in different movement disorders

Movement disorders	Psychosis at disease onset or in the early stages	Psychosis in intermediate or late disease stages	Psychosis related to dopamine-replacement therapy
Parkinson's disease-related genes			
PARK-GBA	-	+++	++
PARK-SNCA	+	+++	+++
PARK-LRRK2	+	+++	+++
PARK-PRKN	+	++	+
PARK-PINK1	-	++	++
PARK-DJ-1	-	++	++
22qDS	+	++	NS
Atypical parkinsonisms			
PARK-ATP13A2	+	+++	+++
PARK-DNAJC6	+	+	+
PARK-FBXO7	+	+	+
MSA	-	+	++
PSP	-	+	+

CBS	-	+	+
Choreas			
Huntington disease	++	+++	NS
Sydenham's chorea	-	++	NS
Benign hereditary chorea	-	+	NS
Chorea-acanthocytosis	+	+	NS
McLeod syndrome	++	++	NS
ADCY5-related dyskinesia	-	+	NS
Tic disorders	+	++	NS
Ataxias	+	++	NS
Dystonia	+	+	NS
Myoclonus	+	++	NS
Basal ganglia calcification	++	++	NS
NBIAs	++	++	NS
Others			
Wilson’s disease	+++	++	NS

Niemann-Pick disease	++	++	NS
Late-onset Tay-Sachs	+++	+	NS
CTX	-	+	NS

+: isolated cases (low frequency), ++: some cases (intermediate frequency), +++: many cases (high frequency), -: not reported, NS: not specified. 22qDS: 22q11.2 deletion síndrome, MSA: multiple system atrophy, PSP: progressive supranuclear palsy, CBS: corticobasal síndrome, NBIAs: neurodegeneration with brain iron accumulation, CTX: cerebrotendinous xanthomatosis


Records identified through database searching (n = 11511)
Additional records identified through other sources (n = 124)
Records screened (n =11635)
Records excluded (n =10977)
Full-text articles assessed for eligibility (n = 657)
Full-text articles excluded, with reasons (n = 84)
Studies included in qualitative and quantitative synthesis (n = 573)