Movement Disorders
CLINICAL PRACTICE
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's disease and other choreic disorders. In Tourette's syndrome, paranoid delusions as well as 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, and ATX-ATXN3, whereas 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, whereas 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's disease, late-onset Tays-Sachs, and Niemann-Pick.

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

During the past decade, more attention has been directed toward the nonmotor symptoms of movement disorders, a group of diseases and conditions classically recognized as mainly motor. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* stresses the common cooccurrence of psychotic symptoms in neurocognitive disorders, and information on the neurobiology of hallucinations and delusions associated with neurological conditions has expanded rapidly over the past decade.[1] Whereas an overwhelming number of studies have been published on psychosis in dementia with Lewy bodies (DLB) 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 International Classification of Diseases, Tenth Revision (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

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Keywords: psychosis, psychotic, delusions, hallucinations, psychiatry.
Dr. Rossi and Farcy contributed equally to this work.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 5 August 2019; revised 2 November 2019; accepted 1 December 2019.
Published online 7 January 2020 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.12882

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, or 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 belief 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 (M.R. and N.F.) 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 DLB- or DRT-associated psychosis in idiopathic PD were excluded because these entities were extensively reviewed in other publications. However, patients with mutations in PD-related genes were included because 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, given that other clinical features may predominate over movement disorders.

Results

Results of the systematic literature search are shown in Figure 1. In total, 11,635 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. 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. Table 2 illustrates the phenomenology of psychosis in different movement disorders, as well as 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 PD-Related Genes

PARK-GBA

Presence of visual hallucinations unrelated to DRT was reported in 45% (14 of 31) of PARK-GBA patients.[2] This frequency was surprisingly similar to the estimated 50% of lifetime prevalence of

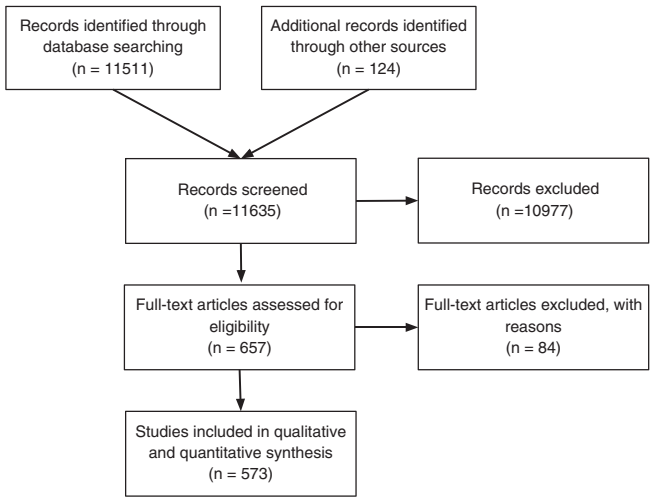

FIG. 1. Flow diagram of the study selection process.

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% confidence interval: 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's disease types II and III.[8,9] To date, delusions have not been reported in PARK-GBA patients.

TABLE 1 *Frequency of psychotic patients reported in different movement disorders*

Movement Disorders	n = Patients/n = Articles
Monogenic parkinsonisms	At least[1] 431/11[S1–S562]
Atypical parkinsonisms	At least[1] 157/46[S57–S103b]
Choreas	At least 1,149/59[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]
NBIA	22/19[S261–S278]
Others	
WD	At least 69/33[S279–S310]
NP disease	At least 106/27[S85, S311–S337]
LOTS	At least 40/15[S338–S355]

[1] "At least" indicates that some minor inaccuracy exists given that some publications do not clearly report the total number of patients with psychosis for a specific condition.
[2] "S" means Supporting Information references.

PARK-SNCA

Psychotic features in PARK-SNCA have been reported among individuals with heterozygous mutations (e.g., p.A53T) and among those attributable 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 on a single case with SNCA duplication that developed delusions and auditory hallucinations and was clinically diagnosed with schizophrenia 10 years before 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 23 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 noncarriers (odds ratio [OR] = 8.4).[16] However, in a different sample of 27 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 given that they are induced by DRT, visual and auditory hallucinations as well as paranoid delusions unrelated to DRT have also been reported in PARK-

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
PD-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			
HD	++	+++	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			
WD	+++	++	NS
NP disease	++	++	NS
LOTS	+++	+	NS
CTX	−	+	NS

+: isolated cases (low frequency); ++: some cases (intermediate frequency); +++: many cases (high frequency); −: not reported.
NS, not specified; 22qDS, 22q11.2 deletion syndrome; CBS, corticobasal syndrome; ADCY5, adenylyl cyclase 5; CTX, cerebrotendinous xanthomatosis.

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, and 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 before 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 hyper-religiosity.[26–30] Visual hallucinations were usually associated to DRT[22–25] and were 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

This multisystem condition is associated with an increased risk of early-onset PD.[38] The prevalence of psychosis in this condition ranged between 10% and 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 PD

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 PD-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 around 10% to 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 with this condition were reported, with patients presenting visual and auditory hallucinations as well as paranoid delusions.[51–55] Visual hallucinations commonly occur several years after 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 3 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 10 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] has been rarely reported.

PARK-DCTN1 and PARK-SYNJ1

No patients with psychosis have been reported on in these conditions.

MSA

Hallucinations related to DRT have been rarely reported in 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]

PSP

Psychosis in 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 given that they persisted after L-dopa 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 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's Disease

Patients with Huntington's 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 preceding 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 1 of 24 (4%) premanifest mutation carriers close to motor-based disease onset and in 3 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 Othello syndrome (delusional jealousy), Ekbom syndrome (delusional parasitosis), *folie à deux* (a type of psychosis occurring simultaneously in 2 intimately related persons who share some elements of the illness), as well as somatic, auditory, and visual hallucinations.[80,82,84] 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 CAG expansion, age at disease onset, or sex remains inconclusive, with some studies failing to find a significant link[78,86,90] and 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 have been reported in some studies, suggesting that there may be modifying genes interacting with the HD gene to increase 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 OR 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 1 patient revealed nonspecific 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 before neurological symptom 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 because of risk of severe parkinsonism.[103]

McLeod syndrome (CHOR-XK)

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

Adenylyl Cyclase 5–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's Syndrome

Prevalence of psychosis in Tourette's 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 before 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 as 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 5 patients with psychotic symptoms revealed severe loss of Purkinje cells and also loss of neurons in the dentate nucleus, inferior olives, and SN, 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), 7 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 attributed 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 attributed 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–N-methyl-D-aspartate receptor encephalitis, has been excluded from this review). Psychosis has been reported in myoclonus-dystonia attributed 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, and 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, as well as visual and auditory hallucinations, have been reported.[149–151] The association of psychosis with dementia is common,[147,149,152] and a propensity toward 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 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 (aged <40 years) 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 given that 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, given that 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 2 of 12 patients.[178] Even though psychiatric disturbances have been reported in 50% to 70% of Wilson's disease (WD) patients,[179,180] < 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) types 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.[174,200–202,204,205] 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[203,204,208] 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 because of 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 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 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 given that 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, given that 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 HD, 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 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 because of 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 awareness about the comorbidity of psychosis with different movement disorders.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

M.R.: 1A, 1B, 1C, 2A
N.F.: 1A, 1B, 1C, 2A
S.E.S.: 1A, 1B, 2B
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Disclosures

Ethical Compliance Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The authors confirm that the approval of an institutional review board and informed consent was not required for this work.

Funding Sources and Conflicts of Interest: The authors report no sources of funding and no conflicts of interest.

Financial Disclosures for previous 12 months: The authors declare that there are no disclosures to report.

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Supporting Information

Supporting information may be found in the online version of this article.

Appendix S1: Supporting Information