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Frequency and characteristics of isolated psychiatric episodes in anti-NMDA receptor encephalitis

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Abstract

Importance—Patients with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis often develop prominent psychiatric manifestations. The frequency and type of isolated psychiatric episodes (pure psychiatric symptoms without neurological involvement) either as initial presentation of the disease or as relapse are unknown.

Objective—To determine the frequency, symptoms, and outcome of isolated psychiatric episodes in a cohort of patients with anti-NMDAR encephalitis.

Design—Observational cohort of patients diagnosed over a 5 year period (median follow-up 2 years).

Patients and setting—571 patients with IgG antibodies against the NR1 subunit of the NMDAR were included in the study. Antibody studies were performed at the Universities of Pennsylvania and Barcelona, and clinical information was obtained by the authors or referring physicians.

Main Outcome Measures—Frequency, type of symptoms, and outcome of patients with anti-NMDAR encephalitis and isolated psychiatric manifestations.

Results—23/571 patients (4%) developed isolated psychiatric episodes, 5 at disease onset and 18 during relapses. For all 23 patients, age (median 20 years), gender (91% female), and tumor association (43%, ovarian teratoma) were similar to the population at large. Predominant symptoms included, delusional thinking (74%), mood disturbances (70%, usually manic), and aggression (57%). Brain MRI was abnormal in 10/22 (45%) and CSF showed pleocytosis in 17/22 (77%). Eighty three percent of the patients had full/substantial recovery after immunotherapy and tumor resection when appropriate. After relapse, 17/18 (94%) patients returned to a similar or better pre-relapse functional level.

Conclusions—Isolated psychiatric episodes are rare but can occur as initial onset or relapse of anti-NMDAR encephalitis. Recognition of these episodes is important because they respond to immunotherapy. In patients with new onset psychosis, history of encephalitis, subtle neurological symptoms, and/or abnormal ancillary tests should prompt screening for NMDAR antibodies.

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Introduction

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is an autoimmune disorder in which IgG antibodies are directed against the NR1 subunit of the NMDA receptor (NMDAR). The disorder includes a range of psychotic symptoms early in the course of the disease followed by neurologic involvement, and ultimately protracted cognitive and behavioral symptoms.[1,2] The occurrence of severe behavioral changes reminiscent of a schizophrenia-like illness has fueled speculation that this disorder might define a subset of patients misdiagnosed with a primary psychiatric disease.[3,4] To address this possibility, two major questions need to be answered. First, do some patients diagnosed with primary psychiatric disorders, such as schizophrenia or major depression, harbor IgG NR1 antibodies and respond to immunotherapy? Second, do patients with anti-NMDAR encephalitis commonly have pure psychiatric episodes without neurologic involvement? Several recent studies have addressed the former question, with mixed findings that suggest most patients with well-established primary psychiatric disorders are unlikely to develop IgG NR1 antibodies.[5–8] The current study addresses the second question by determining the frequency and type of isolated psychiatric symptoms either at disease onset or relapse in a large cohort of anti-NMDAR encephalitis. In addition, we provide the clinical clues that led to the diagnosis of anti-NMDAR encephalitis and the response of psychiatric symptoms to immunotherapy.

Methods

Detailed clinical information of the first episode of encephalitis was obtained for 571 patients.[9] Follow-up information was obtained at regular intervals after symptom onset (median follow-up for the entire series, 24 months). Information was obtained by the authors or provided by referring physicians, and has been partially reported for 3 patients in the subset described in this study.[10,11] In all patients the disorder was confirmed by detection of IgG antibodies against the NR1 subunit of the NMDAR in CSF and serum using reported criteria.[1,12] All patients had a detailed work up to rule out other disorders, including brain MRI, and blood and CSF studies. Isolated psychiatric presentations were defined as episodes (either initial presentation or relapse) that occurred in association with NMDAR antibodies in serum or CSF without neurological involvement. Relapse was defined by the new onset or worsening of symptoms at least two months after improvement or stabilization, without any other etiology involved, and persistent detection of NMDAR antibodies. The Mann Whitney U test was used to compare the age at onset. In patients who had psychiatric relapses, the Wilcoxon signed-rank test was used to compare the delay of treatment in the initial episode of the disease with that of the psychiatric relapse. Studies were approved by the Institutional Review Boards of the Universities of Pennsylvania and Barcelona.

Results

Of 571 patients with anti-NMDAR encephalitis, we identified 23 (4%) with isolated psychiatric symptoms; 5 (0.9 %) presented as first episode of encephalitis, and 18 as relapse of encephalitis (Table 1). The median age of these 23 patients (21 women) was 20 years, which was similar to the population at large (median age 21 years; $p = 0.45$), and the median clinical follow-up was 25 months (4–72 months). Ten patients (43%) had an identifiable underlying tumor during the disease, which in all cases was an ovarian teratoma. In five patients, the teratoma was identified during relapse of encephalitis; three of these patients had no previous history of teratoma and two had a recurrent teratoma.

CSF cell counts were available in 22 patients; 17 (77%) had lymphocytic pleocytosis with or without elevated protein (Table 1). Brain MRI studies showed abnormal findings in 10 of 22

patients (Table 1). In 8 of them, abnormalities included uni- or bilateral nonspecific FLAIR changes involving temporal, frontal and/or parietal lobes, with transient contrast enhancement in 2 cases. Another patient had mild atrophy in temporal lobes, and another one had a diffusion restricted abnormality in the corpus callosum (examples shown in Figure 1). EEG results were available for 20 patients, with abnormalities in 15 (either epileptic or nonspecific slowing).

In 5 patients, isolated psychiatric symptoms were the only clinical manifestation of the disease on initial presentation, without eventual development of neurological symptoms. The time from symptom onset until treatment ranged from 2 to 60 weeks (median 9 weeks). Each of these 5 patients had an abnormal MRI. In retrospect, the families of 2 of these patients indicated having noted mild transient facial movements described as excessive blinking, and another patient had hypersalivation. Eighteen patients experienced episodes that were purely psychiatric at relapse. These patients had all been previously diagnosed with anti-NMDAR encephalitis during a classic presentation with neurological components. The median time from symptom onset until treatment of their relapses was 14 days (range 3–60 days), compared to 28 days (range 7–154) in the initial episodes ($p = 0.004$). Given that 64 of the 571 patients of the study experienced a relapse of encephalitis,[9] and 18 of them occurred with isolated psychiatric symptoms, our findings indicate that 28% of all relapses were pure psychiatric episodes. Five of the 18 patients had more than one relapse; of these 5, only 2 had more than one relapse with isolated psychiatric symptoms.

In the 23 patients with pure psychiatric episodes, psychotic symptoms with a mood component dominated the clinical picture (Table 2). Seventeen (74%) patients had delusional thinking, 10 (43%) auditory or visual hallucinations, and 13 (57%) aggressive behavior; 11 of 18 (61%) patients showed aggression during relapses. Sixteen (70%) patients had a documented mood component during the purely psychiatric episode: 11 were noted to be “manic”, “labile”, “impulsive”, or “disinhibited”, 4 experienced depressed mood, and 1 had a “change” in mood without further specification. In 3 of 5 patients with initial psychiatric presentations, the neurological examination only suggested memory problems which were difficult to confirm due to the severity of psychiatric symptoms; 3 of 18 with psychiatric relapses had residual cognitive changes from previous episodes of encephalitis (2 of them had a Korsakoff-like syndrome that remained unchanged during the psychiatric relapse).

Overall, 19 of 23 (83%) patients had full or substantial recovery after treatment of the disease with immunotherapy and when applicable, removal of the teratoma. Four of the 5 patients with initial psychiatric presentations had full recovery by 24 months; from the 5th patient we have limited data indicating that she had not recovered 4 months after symptom onset (Table 1). Fifteen of 18 (83%) patients with purely psychiatric relapses had full recovery or substantial improvement, 2 had severe residual deficits, and 1 died of a thromboembolism after complete psychiatric recovery. Table 1 shows the comparison of the level of recovery attained after the initial episode of the disease with that attained after the psychiatric relapse: 15 patients returned to the same pre-relapse functional level, 1 improved partially without reaching the pre-relapse level, and 2 improved to a better functional status. In these two cases, the relapse of encephalitis led to additional immunotherapy, and in one of them a previously unknown teratoma was detected and removed.

Two representative patients seen by the authors are described below. One of the patients had isolated psychiatric symptoms at disease onset and the other at relapse of encephalitis.

Patient 1

This 19 year old male with no past psychiatric or medical history was initially admitted for behavioral changes in the setting of a non-specific left frontotemporal abnormality found on brain MRI after a motor vehicle collision. The patient drove off the road but was unable to recall the circumstances. His parents described that he had been “acting strangely” over the preceding few months, often not remembering events and repeating words. He was discharged following the MRI at an outside hospital, but brought to the University of Pennsylvania emergency room after becoming acutely agitated prior to a scheduled EEG, with yelling, crying, and combative behaviors. There were no preceding fevers, headaches, or substance use. Aside from subacute cognitive symptoms described above, there were no neurological abnormalities noted, though in retrospect the parents described excessive eye blinking that they thought was due to anxiety.

Psychiatry consult observed the patient to be manic during hospitalization. He was routinely observed to be speed walking in the halls of the hospital, with decreased sleep, pressured speech, and inappropriate laughing. He exhibited grandiosity and delusional thinking. He was started on valproic acid for management of symptoms, as well as IV methylprednisolone for concern of a demyelinating disease. Because of the abnormal MRI findings, a more extensive work up was pursued. EEG was normal, but CSF revealed lymphocytic pleocytosis, and anti-NMDAR antibodies were detected. No other CSF abnormalities were found. Tumor screening was negative. After behavioral stabilization, the patient was discharged on valproic acid, prednisone, and azathioprine. Over the next 9 months, the patient returned to near behavioral baseline, and both prednisone and valproic acid were tapered off. He remained on immunosuppression with azathioprine. No further complications or relapses have arisen.

Patient 2

This 28 year old female with no past psychiatric or medical history initially presented with bizarre behaviors and visual hallucinations. She appeared delusional and grandiose at this time. The patient was treated for bacterial and suspected HSV encephalitis without improvement after admission. Brain MRI, CSF studies, and EEG were normal. She was transferred to an inpatient psychiatric facility where a psychiatrist noted rhythmic right upper extremity movements, leading to admission to the University of Pennsylvania neurology service for suspected encephalitis. Three weeks after symptom presentation the patient had witnessed seizures and was intubated. CSF studies revealed anti-NMDAR antibodies and she was started on intravenous immunoglobulin and steroids, with gradual improvement though a prolonged hospital course. Tumor screening was negative. She was transferred to inpatient psychiatry prior to discharge, and ultimately made a full recovery, maintained on oxcarbazepine for ~1 year and then no medication.

Thirty-three months after the first episode, the patient began demonstrating increasingly bizarre behavior in the context of tetrahydrocannabinol use and poor sleep. She was preoccupied with religion, and became anxious, labile, and disinhibited. Hypersexuality, paranoia, and mania were prominent. She was admitted to the University of Pennsylvania Neurology service, and was extremely agitated and violent, requiring prolonged restraints. CSF analysis revealed an increase of NMDAR antibody titers compared with those obtained during the phase of recovery of the initial episode, 29 months earlier (1:64 at relapse versus 1:8). No neurologic symptoms were noted throughout the hospitalization and no tumor was found. She was treated with intravenous immunoglobulin and steroids, followed by rituximab and cyclophosphamide. Psychiatric symptoms were managed with valproic acid, quetiapine, and chlorpromazine. The patient was transferred to inpatient psychiatry and

discharged 10 days later. She remained stable from a neurological and psychiatric perspective at multiple outpatient visits for at least 4 months since.

Discussion

We report 23 patients with anti-NMDAR encephalitis who developed isolated psychiatric symptoms either as initial episode of the disease (5 patients) or as relapse of encephalitis (18 patients). Predominant symptoms included delusional thinking, auditory or visual hallucinations, and manic and aggressive behavior. The fact that 5 patients had initial psychiatric presentations without neurologic symptoms or past history of encephalitis suggests that some cases of anti-NMDAR encephalitis can be mistaken for a primary psychiatric disorder. These 5 patients were identified because they had abnormal brain MRI findings, explaining why a more comprehensive investigation including CSF analysis was pursued, and implying some degree of underdiagnosis in those without abnormal ancillary tests. This possibility is discussed in further detail below. Eighty three percent of patients with isolated psychiatric episodes of anti-NMDAR encephalitis had good outcome due to immunotherapy and tumor removal when applicable, supporting the autoimmune origin of the psychiatric symptoms. Remarkably, 15 of 18 patients who had suffered previous episodes of encephalitis improved to a similar pre-relapse functional status and 2 patients recovered to a better functional status, likely as a result of the detection and removal of a previously unnoted ovarian teratoma in one patient and additional immunotherapy in the other.

Patients in this cohort were followed closely so that new behavioral abnormalities may have led to prompt diagnosis and treatment of relapses. It is possible that some isolated psychiatric episodes observed at relapse might have progressed to neurologic involvement if not treated early in the course. However, comprehensive analysis of the 571 patients revealed that those with other monosymptomatic or milder forms of the disease (e.g., isolated movement disorders or brainstem dysfunction) did not necessarily progress to multi-symptom disease despite prolonged periods without treatment.[9,13] Similar observations were previously made in a smaller series of 6 patients with relapses of anti-NMDAR encephalitis, which showed in 4 patients that symptoms were more limited than during the initial episode (e.g., 2 patients had speech problems, 1 ataxia, and 1 psychiatric symptoms).[11] Moreover, in the current study 3 of the 5 patients with pure psychiatric symptoms on initial presentation did not receive appropriate treatment until 9, 17, and 60 weeks after symptom onset, which is well beyond the expected window of neurologic deterioration (neurologic decline often occurs within 2–3 weeks of psychiatric symptoms).

While the current work focuses on the frequency and type of isolated psychiatric symptoms in patients with anti-NMDAR encephalitis, several recent studies have explored whether patients with well-defined psychiatric disorders (e.g. schizophrenia, major depression, borderline personality disorder [BLPD]) had NMDAR antibodies. These studies help to address the bias towards patients with abnormal ancillary findings identified here. One study reported the presence of NMDAR antibodies in serum of 3 of 46 (6%) patients with first onset schizophrenia; the target subunit (e.g., NR2 versus NR1) was not determined and only one of the patients appeared to improve after immunotherapy.[8] In contrast, another series examined serum from 80 patients with first onset psychosis who one year later met DSM-IV-TR criteria for schizophrenia-spectrum illness, along with 40 control patients.[5] None in either group had NR1 IgG antibodies, consistent with the findings of another smaller series of patients with schizophrenia.[6] More recently Steiner and colleagues[7] examined the prevalence of NMDAR antibodies in serum from 121 patients with initial diagnosis of schizophrenia, 70 with major depression, 38 with BLPD, and 230 normal individuals. NR1 IgG antibodies were only identified in 2 patients who in retrospect had a classical picture of

anti-NMDAR encephalitis. IgA, IgM or IgG antibodies reacting with NR2 were identified in 10/119 (8%) patients with schizophrenia and 2/70 (3%) with major depression. However, the causative antibodies in anti-NMDAR encephalitis are not IgA or IgM subtypes, but NR1 IgG antibodies. The clinical significance of NMDAR IgA and IgM antibodies in these disorders deserve further study given that similar antibodies have been reported in dementia[14] and viral encephalitis.[15] Considering the large number of patients studied with well-defined psychiatric disorders such as schizophrenia, depression, or borderline personality disorder,[7] it is highly unlikely that NR1 IgG antibodies are present or involved in these diseases. However, there are no systematic analyses of patients with new onset psychosis without neurological symptoms seen in psychiatric centers. Many of these patients are not studied with MRI or EEG, and only a small minority may have CSF evaluations. In this setting, the possibility of anti-NMDAR encephalitis is still rarely considered and most patients are not tested for NR1 IgG antibodies.

Findings from this study have several practical implications. For patients with past history of anti-NMDAR encephalitis, any behavioral change might represent relapse. In these patients, serum and CSF antibody testing should be obtained if possible, and patients treated aggressively with immunotherapy and symptomatic management of psychiatric symptoms.[1,3] No specific guidelines exist for treatment of psychiatric symptoms in this setting, but clinical experience and anecdotal evidence suggest use of highly sedating medications available in multiple formulations such as quetiapine, chlorpromazine, valproic acid, and benzodiazepines;[3] high potency antipsychotics like haloperidol have been observed to exacerbate motor symptoms in patients with anti-NMDAR encephalitis. In this series most patients received steroids, but in general for a short period of time.[3] Most importantly, an interdisciplinary approach to management is needed. Given that relapses may represent the presence of a not previously identified or recurrent tumor, patients should have tumor screening, mainly focusing on a teratoma of the ovary. In patients presenting to a psychiatrist with new onset psychosis or mania, history of illness and other clinical data should serve as a guide as to whether CSF and serum analysis is necessary (keeping in mind that in 15% of patients, antibodies are only detected in CSF).[9] Past history of encephalitis or encephalopathy of unclear etiology, mild neurological abnormalities such as transient facial twitching, and abnormal, albeit non-specific, EEG or MRI are all examples of findings that might prompt antibody studies.

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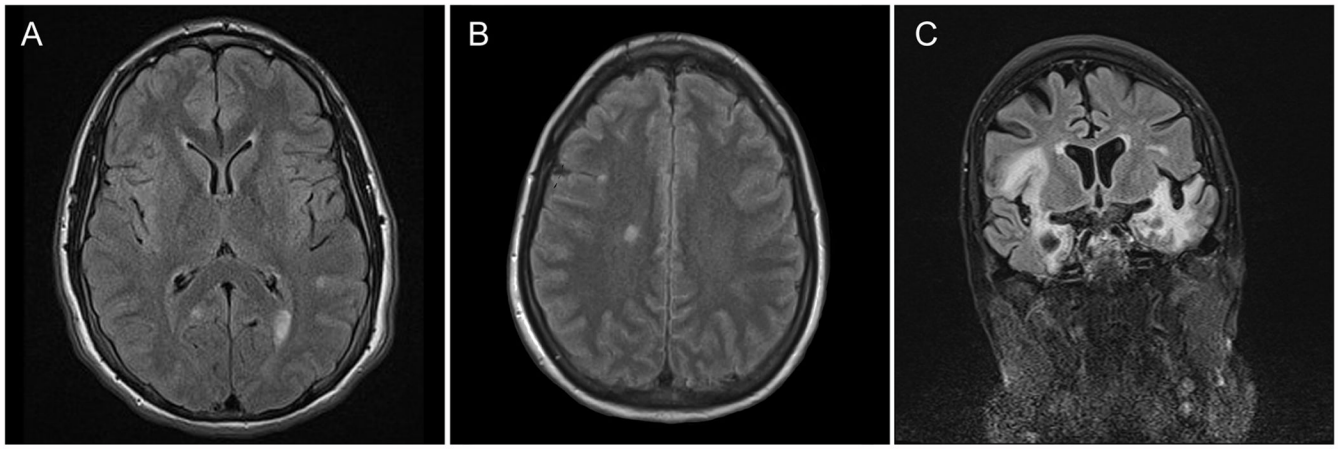

Figure 1.
Brain MRI of three patients with isolated psychiatric symptoms: (A) MRI of patient # 3 obtained at initial episode of encephalitis with pure psychiatric symptoms; note the FLAIR signal abnormalities in the left parietal lobe and adjacent to the splenium of the corpus callosum; (B) patient # 17, the MRI shows cortical and subcortical FLAIR changes in the right frontal lobe identified during a relapse of encephalitis manifesting with isolated psychiatric symptoms; (C) patient # 23, bilateral, extensive cortical and subcortical FLAIR changes identified during a relapse of encephalitis manifesting with isolated psychiatric symptoms.

Table 1

Characteristics of patients with discrete psychiatric episodes

Gender	Age	Abnormal tests			α-NMDAR Ab		Tumor	Predominate psychiatric symptoms	Immunotherapy (order of treatment)	Pre- vs post-relapse clinical status	Recovery at last follow up
Initial episode		**MRI**	**EEG**	**CSF**	**CSF**	**serum**					
F	13	X		NA	+	NA	X	delusions, mania, suicidal	1. steroids, 2. IVIg	--	full, 24 months
F	18	X		X	+	+	X	delusions, AVH, hyperphagia	1. steroids, IVIg	--	full, 34 months
M	19	X	X	X	+	NA		aggression, delusions, mania	1. steroids, 2. AZA	--	full, 25 months
F	20	X	NA	X	+	+		delusions, depression	1. steroids, IVIg, 2. RTX, 3. MMF	--	full, 37 months
F	46	X	X	X	+	NA		aggression, AVH, delusions	unknown	--	no improvement, 4 months
Relapse											
F	12		X		+	−		aggression, delusions, disinhibited, echolalia	1. steroids, IVIg (initial); 2. plasmapheresis, CTX, RTX, MMF (relapses)	Equal	full, 46 months
F	13		X		+	+		aggression, AVH, delusions, suicidal	1. steroids (initial); 2. steroids, 3. IVIG, 4. RTX, CTX, 5. MMF (relapses)	Worse	substantial (>75%), 72 months
F	13		NA	X	+	+		aggression, delusions, lability	1. steroids, 2. IVIg (initial); 3. MMF, 4. RTX, 5. plasmapheresis (relapses)	Equal	full, 47 months
F	14	NA			+	+	X[a]	delusions, labile	1. steroids, IVIg	Equal	full, 35 months
F	15		X	X	NA	+	X[b]	aggression, AVH, delusions	1. steroids, IVIg	Better	full, 47 months
F	16			X	+	+		aggression, catatonic mania	1. steroids, IVIg	Equal	substantial (>75%), 39 months
F	17		X	X	+	+		depression	1. steroids, 2. IVIg, 3. plasmapheresis initial); 4. IVIg, steroids, 5. MMF (relapses)	Equal	full, 22 months
F	18		X	X	+	+	X[c]	mania	1. steroids, 2. IVIg (initial); 4. IVIg (relapse)	Equal	full, 13 months
F	24		X	X	+	−	X	aggression, delusions, mania	1. IVIg, 2. steroids, RTX	Equal	full, 20 months
F	24		X	X	+	+	X	delusions, AVH	1. plasmapheresis, 2. steroids, 3. IVIg, 4. AZA	Equal	substantial (>75%), 16 months
F	26	X	X	X	+	+	X[b]	aggression, mania	1. plasmapheresis, 2. IVIg, 3. RTX	Equal	substantial (>75%), 28 months

Gender	Age	Abnormal tests			α-NMDAR Ab		Tumor	Predominate psychiatric symptoms	Immunotherapy (order of treatment)	Pre- vs post-relapse clinical status	Recovery at last follow up
Initial episode		**MRI**	**EEG**	**CSF**	**CSF**	**serum**					
F	28	X	X	X	+	+		aggression, AVH, delusions, mania	1. steroids, IVIg, 2. CTX, RTX	Equal	full, 36 months
F	30		X	X	+	NA	X[b]	aggression, AVH, delusions	1. steroids, 2. RTX, CTX	Equal	died (PE) 25 months
F	30	X	X	X	+	−		aggression, AVH, delusions, depression	1. steroids, 2. IVIg, 3. plasmapheresis, 4. CTX	Equal	severe deficits, 80 months
F	34		X	X	+	−	X[d]	aggression	1. steroids (initial); 2. IVIg (relapse)	Better	substantial (>75%), 22 months
F	34		NA		+	NA		AVH, delusions	1. steroids, 2. IVIg (initial); 3. steroids, IVIg (relapse)	Equal	full, 23 months
M	34	X			+	−		AVH, delusions, mood changes	1. steroids (initial); 2. steroids (relapse)	Equal	substantial (>75%), 44 months
F	62	X	X	X	+	NA		disinhibited	1. steroids, IVIg, 2. CTX (initial); 3. steroids, CTX, 4. RTX (relapse)	Equal	severe deficits, 20 months

NA: not available; empty cell indicates normal;

(a) Recurrence of ovarian teratoma (OT) at relapse;

(b) Tumor only found at relapse, earlier screening negative;

(c) New OT (other site) at relapse;

(d) OT seen at initial episode, but only removed at relapse;

AVH: auditory/visual hallucinations; AZA: Azathioprine; CTX: Cyclophosphamide; IVIg: intravenous immunglobulin; MMF: Mycophenolate Mofetil; ; PE: pulmonary embolism; RTX: Rituximab

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Table 2

Symptoms in patients with isolated psychiatric episodes

	Timing of isolated psychiatric episode		
Symptoms	**All [n (%)]**	**Initial**	**Relapse**
Aggression	**All [n (%)]**	2 (40%)	11 (61%)
Auditory-visual hallucinations	13 (57%)	2 (40%)	8 (44%)
Delusions	10 (43%)	5 (100%)	12 (67%)
Mood	17 (74%)	3 (60%)	13 (72%)
Manic	16 (70%)	2 (40%)	5 (28%)
Depressed	7 (30%)	1 (20%)	3 (17%)
Labile, disinhibited, impulsive	4 (17%)	0	4 (22%)
other	4 (17%)	0	1 (6%)
Insomnia	1 (4%)	1 (20%)	6 (33%)
Memory	7 (30%)	3 (60%)	3 (17%)