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HOW TO CITE THIS ARTICLE: Nayak A and Math SB. Unavailability of Screening Tool for Adults with Autism Spectrum Disorder: Indian Context. *Indian J Psychol Med*. 2024;46(4):366–367.

ACCESS THIS ARTICLE ONLINE
Website: journals.sagepub.com/home/szj
DOI: 10.1177/02537176231226120

Leucine-rich Glioma Inactivated 1 (LGI-1) Limbic Encephalitis Presenting with Psychotic Symptoms without Seizures: A Case Report with Five-year Follow-up and Review of Literature

To the editor,

Antibodies against Leucine-rich Glioma Inactivated 1 (LGI-1) protein are the second most common cause of Autoimmune Encephalitis (AIE).[1] Seizures, classically Faciobrachial Dystonic Seizures (FBDS), are the commonest symptoms of LGI-1 limbic encephalitis (LGI-1 LE) (incidence: 87.5%–100%); cognitive impairment, psychiatric symptoms, sleep disturbances, and hyponatremia are also frequently seen.[2–5]

Confusion, memory impairment, personality change, depression, and anxiety are common neuropsychiatric symptoms of LGI-LE.[6] Psychosis has been described with LGI-1 LE, but always in association with seizures (**Table 1**). We report a case of LGI-1 LE, presenting with psychotic symptoms without co-occurring seizures, which has not been reported earlier. A written informed consent was taken from the patient.

A 48-year-old male presented to psychiatry services in 2018 with five months of irritability, memory deficits, impaired attention and concentration, panic attacks, sleep disturbances, anxious and depressive ruminations, fleeting referential delusions, fleeting elementary auditory hallucinations, vague fearfulness, and visual hallucinations. He was diagnosed with schizoaffective disorder at another center. On examination, the patient was disoriented to time and place, and had brisk reflexes in lower limbs, bilateral postural tremors and rigidity in upper limbs (right > left), and bradykinesia on the right side. He was prescribed risperidone 2 mg, with which his extrapyramidal symptoms worsened. Considering the atypical presentation, the neurology team advised investigations for neurological etiology. The patient was found to have LGI-1 antibodies in serum and cerebrospinal fluid. Electroencephalogram (EEG) revealed brush delta waves. A single pulse of intravenous methylprednisolone (IVMP) and five cycles of large-volume plasmapheresis (LVPP) were administered, following which, nearly 80% improvement was observed in the presenting symptoms, with residual mild cognitive deficits. He was prescribed mycophenolate mofetil 1,000 mg/day, memantine 20 mg/day, and clonazepam 1 mg/day on discharge.

The patient was maintaining well during his next visit after six months for the sixth cycle of LVPP. However, there were depressive and anxiety symptoms during this follow-up, for which escitalopram 10 mg/day was prescribed, with the continuation of other medicines advised previously.

In 2021, the patient complained of irritability and cognitive disturbances for two to three months, despite good adherence to medications. Addenbrooke's cognitive

TABLE 1.

Summary of Cases of Leucine-rich Glioma Inactivated 1 Autoimmune Encephalitis Presenting with Psychosis.

S. No.	Author	Age/ Gender	Psychotic Symptoms	Other Features	Treatment	Outcome
1	Endres et al. (2020)[12]	50 years/ male	Delusion of inability to urinate	Severe insomnia, cognitive decline, reduced energy and interest, hyponatremia, single status epilepticus	Pulse therapy with 500 mg IVMP, with oral tapering, followed by a second pulse three months later	Partial improvement in mood and cognitive symptoms after first pulse. No relevant improvement after a second pulse
2	Pollak et al. (2017)[13]	57 years/ male	Visual hallucinations, persecutory delusions, grandiose delusions, tangentiality (worsening of psychosis after recovery from AIE)	Cognitive complaints, personality change, generalized tonic-clonic seizures, chanting in sleep, nocturnal involuntary movements, Déjà vu, Hyponatremia, Apathy	Three days of IVMP, plasma exchange, five days of IVIG, and antiseizure medications. Seven months later, three days of IVMP, plasma exchange, and pulsed intravenous cyclophosphamide. Later given risperidone up to 4 mg and fluoxetine 20 mg/day, and benzodiazepines	Residual cognitive difficulties, apathy, nightmares, and anxiety
3	Janas-Kozik et al. (2017)[14]	14 years/ female	Delusions of persecution, reference, and misinterpretation	Agitation, seizures, neuroleptic malignant syndrome with antipsychotics	Acyclovir up to 1,500 mg/ day, haloperidol up to 9 mg/day, risperidone up to 3 mg/day, olanzapine up to 5 mg/day, goprinosine, valproic acid, buspirone, methylprednisolone 1 g for five days, 20 g IVIG for five days	Residual sensory aphasia, labile affect, and retrograde amnesia after three months
4	Wang et al. (2018)[15]	18 years/ male	Persecutory delusions	Personality change, short-term memory impairment, FBDS, hyponatremia	Risperidone 0.5 mg/day, antiseizure medications, IVMP 1 g/day for five days, IVIG 0.4 g/kg/day for five days	Complete clinical recovery after five weeks
5	Reyazuddin et al. (2020)[16]	43 years/ male	Visual hallucinations	FBDS, ataxic gait, cognitive impairment, steroid-induced hypomania	Brief pulse therapy with IVMP 1 g for seven days, four sessions of plasma exchange	Relapse of symptoms after one month, followed by patient's demise (cause of death unclear)
6	Notturno et al. (2021)[17]	71 years/ female	Paranoid ideations	Aimless wandering, confusion, agitation, anxiety, impulsivity, rigidity, bradykinesia, FBDS, raised creatinine phosphokinase levels	IVIG 0.4 g/kg/day for five days, haloperidol 1.5 mg/ day, levetiracetam, 500 mg IVMP for five days	Infrequent facial twitches, poor verbal communication, and apathy after three weeks. Died after two months due to a cardiac ailment
7	Wu et al. (2021)[18]	69 years/ male	Delusions, hallucinations	Cognitive decline, anxiety, depression, agitation, irritability, sleep disorder, FBDS, hyponatremia	Memantine, duloxetine, IVMP, carbamazepine	Complete improvement of seizures, near complete recovery of cognition after eight days, significant improvement of psychiatric symptoms
8	Kim et al. (2020)[19]	47 years/ female	Manuscript in Korean language, details could not be obtained			

IVMP: intravenous methylprednisolone; IVIG: intravenous immunoglobulins; AIE: Autoimmune Encephalitis; FBDS: Faciobrachial Dystonic Seizures.

examination-3 score was 85/100 (deficits in delayed recall, visuospatial domain, and fluency). Serum testing revealed strong positivity for the LGI-1 antibody. IVMP 1 g and five cycles of LVPP were administered for five days. There was an improvement in the presenting symptoms, and the patient was discharged on clonazepam 2.5 mg/day, memantine 20 mg/day, and mycophenolate mofetil 1,000 mg/day. Escitalopram was tapered and stopped, as depressive symptoms had remitted.

The patient next presented in 2022, with recent memory disturbances,

non-pervasive low mood, anhedonia, easy fatiguability, decreased attention and concentration, sleep and appetite disturbances, depressive ruminations, panic attacks, along with irritability over trivial issues for seven months. Serum testing showed strong positivity for the LGI-1 antibody. IVMP for five days and five cycles of LVPP were administered. Considering a relapse despite immunomodulation, a whole-body PET MRI was done, where no evidence of a tumor was found. One g rituximab injection was given. He was discharged on escitalopram 15 mg/day, clonazepam 1 mg/day, tapering doses of prednisolone, and advised a second dose of rituximab after two weeks. In 2023, a telephonic follow-up with the patient and attenders revealed that the patient was adherent to the treatment and was maintaining well.

All the past reported cases of LGI-1 LE with psychosis also had seizures; FBDS was the commonest semiology (**Table 1**). Our patient never had seizures, which might have caused his misdiagnosis of schizoaffective disorder. Our patient had fleeting referential delusions and hallucinations. Delusions, hallucinations, and formal thought disorder are the psychotic symptoms described with LGI-1 LE (**Table 1**).

The onset of primary psychosis, particularly in men, is around 20 years of age.[7] However, our patient's psychotic symptoms started at 47 years. In the earlier reported LGI-1 LE patients with psychotic symptoms, the age of onset was either early (14–18 years) or late (43–71 years) (**Table 1**).

In addition, cognitive complaints, focal neurological deficits, and sensitivity to neuroleptic medications prompted us to investigate for AIE.

Rituximab was chosen during the last relapse for our patient, because of relapses despite regular adherence to mycophenolate mofetil. Rituximab appears to have a role in the management of LGI-1 LE.[8,9] LGI-1 LE is a B-cell mediated AIE,[10] with the antibody targeting a synaptic antigen,[11] which might explain the effectiveness of rituximab in LGI-LE.

Literature suggests improvement of psychotic symptoms in LGI-1 LE with treatment; residual deficits and relapses are common, except for two patients who had a complete recovery, but there was no information on their follow-up (**Table 1**). The five-year follow-up data in our case is probably the longest follow-up reported in an LGI-1 LE patient presenting with psychotic symptoms.

Atypical age of onset, fleeting nature of psychotic symptoms, cognitive deficits, sensitivity to antipsychotics, presence of focal neurological deficits, prominent sleep disturbances, and EEG abnormalities should be considered as pointers toward possible neurological etiology for patients presenting with psychotic symptoms.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Submitted: 29 Oct. 2023
Accepted: 23 Dec. 2023
Published Online: 11 Feb. 2024

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HOW TO CITE THIS ARTICLE: Mamtani H, Mailankody P, Thippeswamy H, Mathuranath PS, Mahadevan A, Chandra SR and Thirthalli J. Leucine-rich Glioma Inactivated 1 (LGI-1) Limbic Encephalitis Presenting with Psychotic Symptoms without Seizures: A Case Report with Five-year Follow-up and Review of Literature. *Indian J Psychol Med*. 2024;46(4):367–370.

ACCESS THIS ARTICLE ONLINE
Website: journals.sagepub.com/home/szj
DOI: 10.1177/02537176231226191

Technology-based Interventions to Reduce the Treatment Gap for Common Perinatal Mental Disorders in Low- and Middle-income Countries (LMICs): Challenges and the Way Forward

To the editor,

Low- and middle-income countries (LMICs) bear a high burden of common Perinatal Mental Disorders (PMDs) among parents.[1,2] These non-psychotic mental health conditions, including depression and anxiety, adversely affect day-to-day functioning and can be identified in primary care settings.[3] Untreated PMDs are associated with adverse obstetric and infant outcomes, such as abortion and stillbirth, which in turn lead to further negative mental health consequences for parents.[4,5] These outcomes are also associated with an increased risk of complicated grief, suicidal ideation, and marital disruption.[5] In LMICs, these prevalent PMDs remain largely undiagnosed and untreated, with low treatment contact coverage compared to high-income countries.[2,6,7] Moreover, a significant proportion of parents in LMICs are not routinely screened for the need for psychological support.[8] This is primarily the case due to a lack of evidence-based interventions and service models addressing the mental health needs of parents during the perinatal period.

Approaches to Reduce the Treatment Gap

To address this gap, the brief interventions and stepped care approach for screening, referral, and management of perinatal depression in resource-limited settings are promising approaches.[9,10] They may be adopted under existing healthcare settings, including Reproductive, Maternal, Newborn, Child, and Adolescent Health (RMNCH+A) programs and National Mental Health Programs.[9] Brief interventions, including complementary health practices (CHPs) such as psycho-education, relaxation exercise, and health promotion techniques (e.g., sleep hygiene, dietary advice), can be delivered by primary health care workers (HCWs) (e.g., auxiliary nurse midwifes or Accredited Social Health Activists in India, and Thai village health volunteers in Thailand) or non-specialist HCWs in approximately 10–15 minutes with minimal training.[9,11] CHPs have shown effectiveness in reducing perinatal anxiety and grief among parents after stillbirth and fear of childbirth.[12] Additionally, primary HCWs-based models are effective, feasible, and scalable for integrative care, including screening, monitoring, and referral care. These models effectively improve the screening of perinatal women for depression using the Patient Health Questionnaire (PHQ-2 or PHQ-9) in tertiary care settings[13] and can be included as community-based assessments (e.g., Community Based Assessment Checklist in India) and part of national programs.[14] However, there are various challenges for the implementation of these interventions/models in resource-limited settings, including limited training resources, overburdened primary HCWs with multiple responsibilities under different programs, and difficulty maintaining records and arranging follow-ups. Most of these issues, however, can be addressed by innovative technology-based interventions.

Technology-based Interventions—Promising Solution

Innovative technology-based interventions, such as clinical decision support systems, mobile applications, and chatbots, can improve access to healthcare services.[15,16] They can support training and screening, surveillance, and monitoring.[17] They can also help in developing a comprehensive surveillance system at the primary level for detecting PMDs and providing digital brief psycho-social interventions. Innovative technology-based interventions can empower primary health care settings