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Case Report

Innovative Therapeutic Approaches in Severe Adolescent Depression: Neuroimaging and Pharmacological Insights

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Abstract: Severe depressive disorders with psychotic features in adolescents present diagnostic and therapeutic challenges, often exceeding the limitations of existing guidelines. A 19-year-old patient with four-year history of treatment-resistant severe depression and psychotic features, addressing a broad spectrum of symptoms, including persistent negative symptoms, cognitive impairments, and motor disturbances such as bradykinesia and hypokinesia, was comprehensively assessed. The therapeutic trajectory included multiple pharmacological regimens, neuroimaging evaluations, and standardized scales such as the Positive and Negative Syndrome Scale (PANSS) to monitor clinical outcomes. Initial treatments yielded limited improvements. However, the final regimen resulted in significant symptomatic relief, reflected by marked reductions in PANSS scores (from 105 to 65 over six months). Neuroimaging revealed structural anomalies, including a medial temporal dysplastic lesion and pituitary microadenoma, which contributed to the psychopathology. Symptoms such as anhedonia, avolition, alogia, bradykinesia, episodic derealization, and cognitive impairments showed substantial improvement following tailored interventions. This case underscores the importance of personalized treatment strategies that integrate advanced neuroimaging and innovative pharmacological approaches to address atypical presentations of treatment-resistant psychiatric disorders effectively. Quantifiable improvements in PANSS scores highlight the efficacy of such interventions in managing complex adolescent psychopathologies.

Keywords: Severe Depression, Psychotic Features, Amisulpride, Treatment-Resistant, Neuroimaging, Bradikinesia

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1. Introduction

The incidence of mood disorders among adolescents has been on the rise, reflecting a trend that underscores the need for a deeper understanding and more effective approaches to these conditions. Mood disorders in adolescents, including major depressive disorder and bipolar disorder, present an increasingly varied and heterogeneous clinical picture, emphasizing the complexity of interactions among genetic, biological, and environmental factors [1].

Severe depression in adolescents can be accompanied by psychotic symptoms, which further complicates diagnosis and treatment [2]. A particularly relevant aspect in the early identification of severe depression among adolescents is the recognition of motor symptoms such as bradykinesia and hypokinesia [3]. These are often alarm signs that can be observed by peers and family, signaling a potential psychopathological decline [4]. Bradykinesia, defined as the slowing down of voluntary movements, is a motor symptom commonly found in both neurological and psychiatric

disorders, including depression. Hypokinesia, or the reduction in the amplitude of movement, may also be present and is often more difficult for those around the adolescent to detect [3]. These motor symptoms are not only potential indicators of the severity of the depressive state but also serve as alarm signals that may suggest the need for urgent medical intervention [4,5].

Treatment-resistant depression in adolescents poses a unique challenge, as standard pharmacological regimens often fail to address the full spectrum of symptoms. Advanced neuroimaging techniques have emerged as valuable tools for identifying structural anomalies that may contribute to atypical presentations of mood disorders [6]. For instance, findings such as medial temporal dysplastic lesions or pituitary microadenomas have been associated with persistent depressive and psychotic symptoms [7]. Despite these insights, the integration of neuroimaging into routine psychiatric evaluations remains limited, highlighting a critical gap in current clinical practice [6].

The aim of the present study is to shed light on an intricate instance of severe depressive disorder that defies conventional categorization and responds ambiguously to standard treatment modalities. The patient's onset at 17 years old, marked by non-pathognomonic imaging changes and a blend of depressive and psychotic symptoms, highlights the need for a nuanced approach to psychiatric evaluation and management. This patient's journey underscores the complexity often encountered in psychiatric practice, particularly when faced with symptoms that do not align neatly with recognized diagnostic frameworks. Initial symptoms were overlooked by his family, attributing early motor dysfunctions and mental health decline to adolescent changes rather than recognizing them as early signs of a severe psychopathological condition. This oversight delayed early intervention and could illustrate the role of family and caregivers in recognizing and responding to early mental health symptoms [8].

Further complicating the diagnosis, the patient exhibited symptoms that overlapped with neurological disorders, including episodic memory lapses and impaired motor function, which were initially suspected to be indicative of conditions like epilepsy or multiple sclerosis. However, extensive neurological evaluations, including MRI and EEG, did not confirm these conditions, instead revealing anomalies that required psychiatric interpretation and intervention.

Throughout his treatment, the patient experienced a range of symptoms, including anhedonia, social withdrawal, avolition, alogia, and significant motor impairments such as bradykinesia, which are less commonly associated with depressive disorders in adolescents [4]. These symptoms posed significant challenges in differential diagnosis and highlighted the limitations of existing psychiatric guidelines, which are often inadequate equipped to handle such atypical presentations [9-11]. In response to these challenges, a tailored adjustment framework therapeutic strategy was implemented, which included the use of antipsychotics and antidepressants beyond conventional first-line treatments.

2. Case Report

2.1. Patient History

We present a detailed account of a 19-year-old male patient who was admitted to the psychiatric unit for severe depressive symptoms with psychotic features that began manifesting at age 17. His clinical presentation was marked profound anhedonia, pervasive social withdrawal, avolition, alogia, and apathy, compounded by symptoms of derealization, depersonalization, persistent delusional ideation centered on themes of uselessness and incapacity, and significant cognitive impairments alongside motor disturbances such as bradykinesia, which were initially missed by his family. The patient exhibited a persistently sad mood, high levels of apprehension, and perseverative speech, often commenting on his removal from reality (*"I ob-*

serve things from a third perspective, as a witness to events in which I do not actively participate"). Additionally, he experienced paroxysmal anxiety of varying intensity, spontaneous hypoprosexia, episodic hypomnesia, reduced appetite, decreased sexual drive, and mixed sleep disturbances. His psychiatric condition, which began approximately four years prior, had markedly deteriorated over one month before the described admission.

The patient described feeling "*limited, mentally reduced*" with a significant emotional numbing and a progressive decline in cognitive processes. He reported, *"I perceive everything more and more in the unconscious, not like before when I perceived them in the conscious. I want my thoughts back!"* These symptoms had developed between the ages of 16 and 19. He recounted a specific incident that coincided with the onset of these symptoms: *"Just when this problem started, I was holding a white quartz. I started to feel a sharp pain in the right side of my head, as if my brain was blocked. That lasted for a couple minutes. I had a seizure of consciousness block, dissociation occurred and I lost all my personality."* He described the sensation as an *"otherworldly sickness."*

The patient's family history is marked by psychiatric pathology, his maternal aunt had a history of psychiatric disorders, and his father's cousin attempted suicide, driven by a psychotic disorder.

The patient's developmental history was marked by a turbulent family life, including domestic violence and ongoing parental conflicts, which only subsided following the divorce of his parents when he was around 12 years old. Before his mental health deteriorated, he had experimented with marijuana starting around the age of 13 and continued its use intermittently until the age of 15. His involvement in extracurricular activities, particularly debates, showcased a previously high level of functional capacity. Since graduating from high school in 2023, the patient has remained unemployed and resides with his mother, dedicating his efforts to manage his health challenges. Recently, he began his university studies, indicating his ongoing effort to maintain academic engagement despite the challenges posed by his psychiatric condition.

2.2. Diagnosis Procedure & Treatment History

His personal history included benign epilepsy diagnosed at age 12 and subsequent mental health issues such as obsessive-compulsive disorder (OCD) and dysthymia identified at age 16. At 18, he was diagnosed with an acute psychotic disorder and a mild rhabdomyolysis syndrome. He underwent further evaluations at 19, confirming a severe depressive episode with psychotic symptoms.

At the age of 12, the patient presented with acute neurological symptoms, including bilateral tonic contracture, stertorous respiration with a deviated gaze, generalized pallor, and post-ictal aphasia, accompanied by facial tremors and lingual paresthesias. Neurological assessments revealed bradyalgesia and an absence of focal neurological signs, with preserved symmetric reflexes and a negative Romberg sign. EEG monitoring detected abnormal background activity consistent with stage II sleep, characterized by asynchronous electrical discharges across bilateral centrotemporal regions. Imaging revealed no focal lesions or hemorrhagic events, but noted the presence of an arachnoid cyst in the paramedian posterior fossa. The absence of other neurological deficits led to a provisional diagnosis of benign rolandic epilepsy, managed with Diazepam as needed for futher rolandic epileptiform acute episodes.

By the age of 16, psychiatric symptoms had become pronounced, with the patient experiencing persistent intrusive thoughts, compulsive behaviors, and severe anxiety symptoms, all impacting social interactions and academic performance. The patient was diagnosed with dysthymia, obsessive-compulsive disorder, and generalized anxiety disorder, initiating a treatment regimen that included 5-hydroxytryptophan and Sertraline for six months. At 17, the patient's condition deteriorated further, exhibiting increased social withdrawal, difficulty concentrating, and a pervasive loss

of interest in daily activities. The symptoms escalated into a sensation of mental dissociation and profound negativism, affecting daily functioning. These developments led to the initiation of small doses of Risperidone, to manage emerging psychotic symptoms. During that time, the patient reported the initial emergence of symptoms characterized by episodic frontal headaches of a compressive nature. Despite these symptoms, he maintained a facade of normalcy, continuing his social and academic engagements with an apparent increase in sociability and confidence. However, he experienced recurrent sensations of derealization, depersonalization, and dissociation, indicating a progressive decline in mental functioning.

By the age of 18, the patient voluntarily admitted himself during a psychiatric crisis characterized by profound social withdrawal, reduced affective response, and suicidal ideations. Clinical observations included hypomobile mimicry, monotone and incoherent speech, and general behavioral disorganization, suggestive of deepening psychosis. A complex regimen of antipsychotics (Haloperidol, Aripiprazole, Olanzapine, Flupentixol) and benzodiazepines was administered, adjusted throughout a 29-day hospitalization. The discharge plan continued with Aripiprazole, Olanzapine, and Haloperidol oral solution to manage symptoms of psychosis compounded with depressive features [12]. The given diagnosis at that time was *Acute Psychotic Disorder*. During the same year, the patient sought psychiatric care, experiencing a constellation of symptoms - profound depressive mood, abulia, anhedonia, alogia, avolition, extensive social withdrawal, and a stark reduction in overall functionality. Notably, his expressive behaviors were diminished, characterized by an apathetic demeanor and a vague, searching gaze that conveyed his detachment from the immediate environment. Throughout this hospital stay, the patient exhibited significant resistance to verbal communication, which was delayed and minimalistic, hinting at his deeper cognitive disarray. The monotonous and subdued tone of his voice, alongside fragmented and often incoherent speech, suggested disorganized thought processes. Episodic derealization episodes and a semicatatonic state further complicated his clinical picture, accompanied by severe impairments in executive functions and marked global amnesia. Despite a partial awareness of his mental health condition, his behaviors were predominantly characterized by negativism and a reluctance to engage in routine activities or social interactions. The diagnostic conclusion was a *Severe Depressive Episode with Psychotic Features* and a mixed personality disorder – schizoid personality with dependent personality elements, influencing a tailored pharmacological approach. The initial regimen included Cariprazine, Sertraline at 100 mg daily, and Pregabalin at 75 mg daily. This was complemented by a gradual reduction of benzodiazepines to manage insomnia and anxiety without fostering dependency.

At the age of 19, 90 days before the current admission, the patient presented for reevaluation with an improved but still concerning symptomatology including persistent depressive mood, abulia, repeated alogia, and avolition. While there was no evidence of delusional or hallucinatory activity, the overall reduction in his global functionality remained significant. The primary diagnosis at this presentation was obsessive-compulsive disorder (OCD), with secondary issues including a moderate depressive episode and other acute psychotic disturbances. The adjusted treatment plan included Vortioxetine at 10 mg daily and Amisulpride at 200 mg daily to better target depressive and obsessive-compulsive symptoms. During the same year, continued challenges with social withdrawal, anhedonia, and episodes of derealization prompted another reassessment. The patient's self-report and clinical indicators reflected ongoing depressive states and reduced tolerance to frustration. To address these, his medication regimen was further refined to include Clomipramine (starting at 25 mg, adjusted to 50 mg daily), Escitalopram (10 mg daily), Paliperidone (6 mg daily), and Trihexyphenidyl (2 mg daily). Despite ongoing adjustments to the treatment regimen, there have been no notable changes in the patient's condition.

2.3. Paraclinical Investigations

The proposed methodology for treatment adjustments in patients diagnosed with psychiatric disorders, with a particular emphasis on the Positive and Negative Syndrome Scale (PANSS) application, necessitates a multi-model approach encompassing clinical assessment, neuroimaging findings, and physiological changes observable through neurophysiological measures such as EEG. Notably, we delineate a structured approach that emphasizes both quantitative evaluation and individualized treatment planning, which aligns with contemporary psychiatric insights emphasizing the need for precision-based care strategies.

To begin, the identification of key clinical symptoms must precede any treatment modifications [11]. The PANSS is instrumental in systematically assessing symptom severity in patients presenting with psychotic features and depressive disorders. This structured assessment tool comprises three subscales: Positive Symptoms, Negative Symptoms, and General Psychopathology. Regular administration of the PANSS will provide insights into the symptomatology, thus dictating potential pharmacological interventions or adjustments during treatment [13,14]. In parallel, neuroimaging techniques, particularly Magnetic Resonance Imaging (MRI), should be employed to visualize structural and functional changes within the brain that may correlate with specific symptomatology. For instance, findings have demonstrated reductions in gray matter volume within critical regions such as the medial temporal cortex which can be indicative of the disease's severity [15].

Moreover, EEG assessments could be instrumental in identifying abnormal electrical activity in the brain, potentially serving as a marker for specific neuropsychiatric disorders. Research underscores the importance of linking neurophysiological data with symptoms to form more informed and dynamic treatment strategies [16,17]. For instance, atypical patterns on EEG may correlate with specific symptom clusters within the PANSS, propelling timely adjustments to treatment protocols or dosage.

2.3.1. MRI studies

At the age of 19, during the current hospitalization, the patient underwent a series of detailed paraclinical investigations to support the clinical assessments and provide an overview of his neurological and psychiatric health.

A native magnetic resonance imaging (MRI) revealed no acute intracranial changes, no expansive or mass-effect lesions, and maintained normal ventricular and sulcal architecture, suggesting no significant atrophy or hydrocephalus. A pellucid septum deduplication (Figure 1 &2) and a posterocerebellar arachnoid cyst (Figure 3) were highlighted by the MRI investigation.

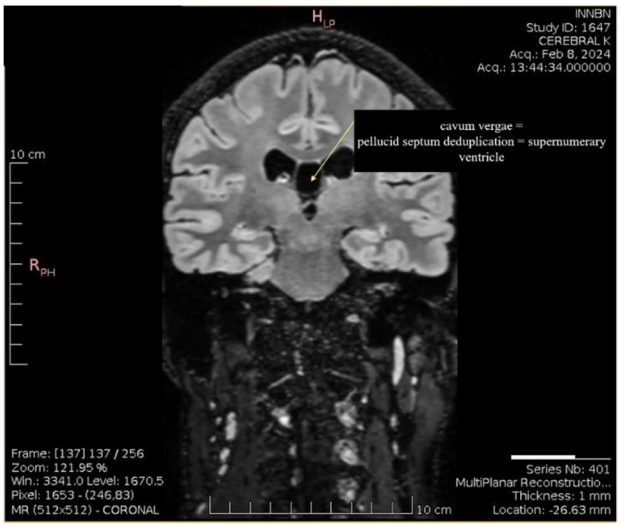

Figure 1. Cavum vergae/ Pellucid septum deduplication/ Supernumerary ventricle.

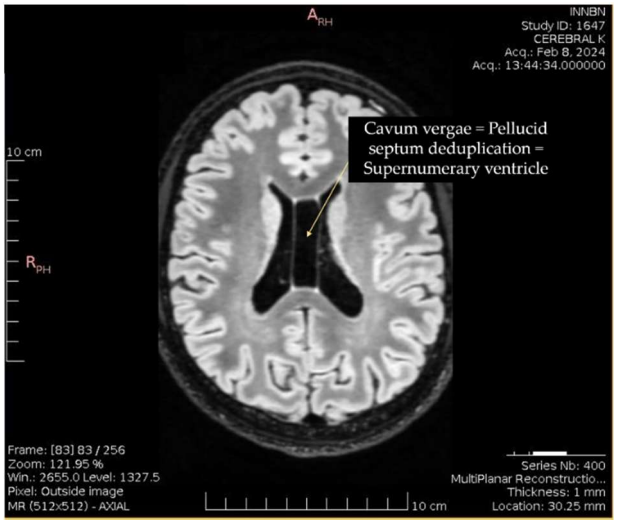

Figure 2. Cavum vergae/ Pellucid septum deduplication/ Supernumerary ventricle.

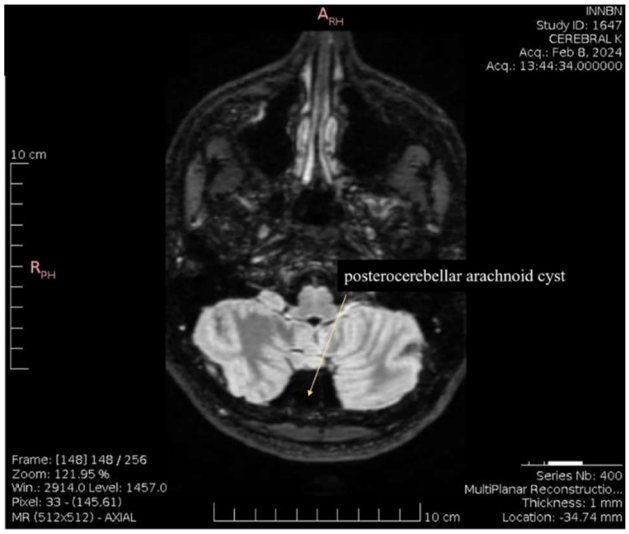

Figure 3. Posterocerebellar arachnoid cyst.

Additionally, the examination showed a mega cisterna magna without significant alterations in cortical relief (Figure 4). Notably, a small lesion measuring 6 by 3 mm was observed in the deep medial temporal cortex at the level of the uncus. This lesion exhibited a hyperintense signal on FLAIR sequences and a hypointense signal on T1-weighted images, without diffusion restriction, suggesting a potential cortical dysplastic lesion (Figure 5).

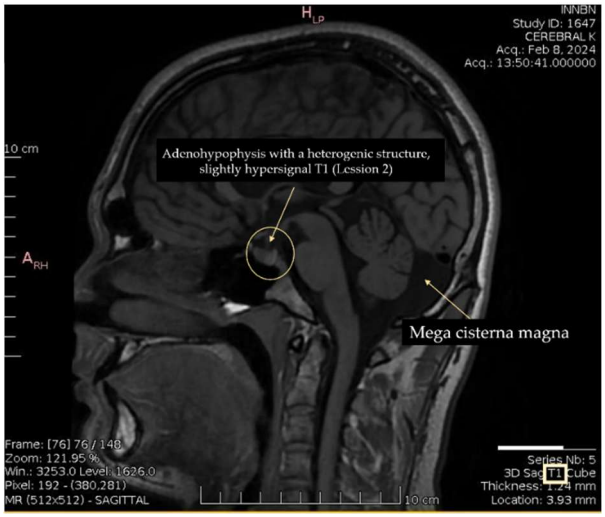

Figure 4. Mega cisterna magna and the adenohypophysis with a heterogenic structure, slightly hypersignal T1.

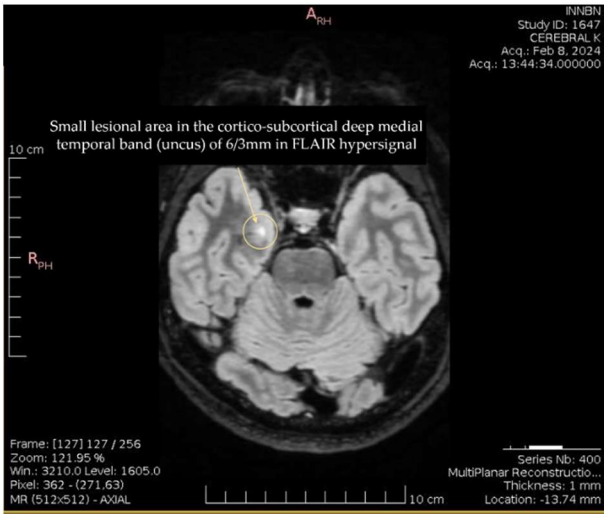

Figure 5. A small lesion measuring 6/3 mm observed in the deep medial temporal cortex at the level of the uncus, hyperintense signal on FLAIR.

Another MRI examination, performed natively and post-contrast, centered on the cerebral floor and specifically the sellar region, revealed a pituitary gland with normal dimensions (15.2/11.5/7.3 mm in transverse, anteroposterior, and craniocaudal dimensions, respectively) with a planoconcave upper contour. The neurohypophysis displayed a typical lenticular shape with a physiological T1 hypointensity located posteriorly within the gland, showing no abnormalities (Figure 4). The adenohypophysis demonstrated a heterogeneous structure due to the presence of a pseudonodular accumulation measuring approximately 6/4/6.9 mm. This lesion exhibited a low signal on T2, a slightly hyperintense signal on T1, and a hypointense signal on FLAIR (Figure 6). It showed poor enhancement in post-contrast images and was located intraglandularly, midline and slightly right of apramedian, anterior to the neurohypophysis. Both the pituitary stalk and the surrounding hypothalamic infundibular regions appeared normal in thickness, with no pathologic signal or structural abnormalities. The cortical relief was symmetrical with normal gray-white matter differentiation and overall brain trophicity preserved. No signal abnormalities were noted in the cerebellar white matter. A right infratentorial paramedian posterior fossa arachnoid cyst was observed, measuring 21/17 mm in its maximum axial dimensions.

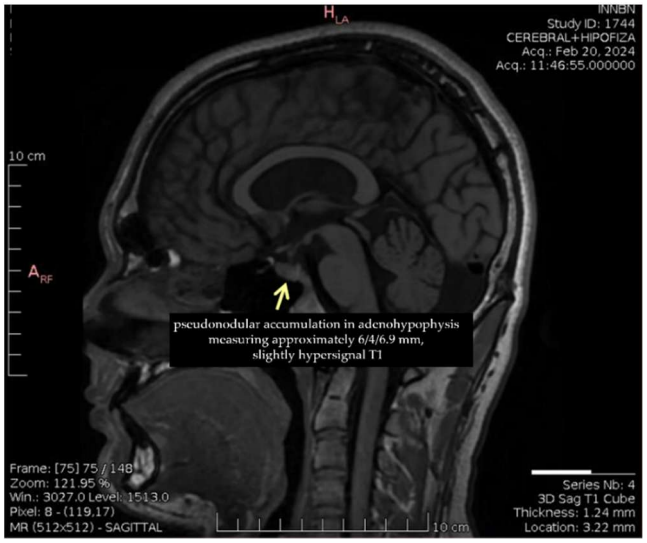

Figure 6. A pseudonodular accumulation in adenohypophysis measuring approximately 6.4/6.9 mm, slightly hypersignal T1.

2.3.2. EEG studies

The EEG studies performed across different sessions with the patient, at the age of 19, provided a detailed evaluation of the patient's brain electrical activity. The first EEG was conducted overnight for 12 hours. The recording captured a stable alpha rhythm at 10 Hz, reactive to eye-opening with physiologic sleep spindles during N1 and N2 sleep stages. The study reported no spontaneous epileptiform activities, ictal events, or cardiac arrhythmias, indicating an absence of acute neurological disturbances during sleep. The second EEG, a 45-minute awake EEG study, displayed a dominant alpha rhythm, slightly hypervolted, ranging between 10-11 cycles per second, primarily modulated in the temporo-occipital and centro-parietal regions, and attenuating upon eye-opening. Beta rhythms were noted in central and anterior regions. Despite several artifacts due to blinking, muscle movements, and intermittent swallowing, the recording was primarily clear of significant epileptiform activity, with only rare sharp waves and no ictal events.

The EEG findings over time indicate a background of cortical dysplasia, likely dating back to the patient's diagnosis of rolandic epilepsy around age 12, with no significant progression into more severe epileptic conditions.

2.4. Clinical observation

Since the patient has been under clinical observation, other investigative assessments including electrocardiograms (EKGs) and comprehensive bio-humoral blood analyses have consistently remained within normal limits. These tests have been instrumental in monitoring the patient's overall physical health and ensuring that no underlying physiological disturbances contribute to his psychiatric condition. Notably, the only minor deviation observed has been a slight hyperprolactinemia, with a level of 63.7 ng/mL. This elevation is modest and requires monitoring due to its potential effects on endocrine function, though it did not necessitate immediate clinical intervention.

3. Management and treatment

3.1. Diagnosis

At the age of 19, the patient's therapeutic regimen was methodically adjusted in response to the evolving psychopathological profile, with continuous monitoring employed to rigorously evaluate the efficacy of each intervention and guide subsequent modifications in the treatment strategy. This section of the results will discuss the adjustments, the monitoring process, and the evaluations that shaped the current treatment approach.

After two years of rigorous treatment and diagnostic assessments, the diagnostic committee convened to finalize the patient's diagnosis. Following extensive evaluations, the consensus was to diagnose the patient with **a severe depressive episode with psychotic symptoms.** This diagnosis was reached after careful consideration of the patient's clinical presentation, response to treatment, and comprehensive assessment results.

In the process of establishing a definitive diagnosis, the committee also deliberated on several differential diagnoses. The possibility of simple schizophrenia was considered due to the persistent negative symptoms and episodic exacerbations of psychotic features. Obsessive-compulsive disorder (OCD) was another potential diagnosis, particularly given the patient's intense preoccupation with a perceived internal void, which manifested as persistent obsessive thoughts significantly impacting his daily functioning. Additionally, the committee evaluated the likelihood of depersonalization-derealization syndrome, suggested by the patient's recurrent experiences of feeling detached from reality and self, which were prominently present in the symptomatology but varied in intensity over the course of treatment. Each potential diagnosis was scrutinized against the backdrop of the patient's longitudinal clinical data, therapeutic responses, and the evolution of his symptomatology under carefully monitored treatment regimens.

However, the diagnostic process was significantly complicated by the limitations of DSM-5 criteria and other standardized classification frameworks. The patient’s presentation did not align neatly with existing diagnostic categories, as his symptoms spanned affective, psychotic, cognitive, and motor domains, challenging the rigid boundaries set by conventional nosological systems.

Given these diagnostic complexities, a purely categorical approach proved inadequate, necessitating a dimensional and integrative evaluation. The incorporation of neuroimaging findings, which revealed structural anomalies such as a medial temporal dysplastic lesion and a pituitary microadenoma, further guided the diagnostic process by providing objective neurobiological correlates of the patient's psychopathology.

3.2. Assessment Protocol and PANSS Application

The treatment trajectory for the patient was structured into four distinct phases, each characterized by specific pharmacological interventions and systematically evaluated using the Positive and Negative Syndrome Scale (PANSS) to ascertain the efficacy of the treatments and to guide subsequent modifications. PANSS served as the primary quantitative measure for symptom assessment and treatment response monitoring throughout the patient's clinical course.

During the baseline assessment and follow-up monitoring, trained psychiatrists conducted PANSS evaluations at the initiation of each treatment phase to establish severity across three domains: positive symptoms (delusions, conceptual disorganization, hallucinatory behavior), negative symptoms (blunted affect, emotional withdrawal, poor rapport, avolition), and general psychopathology (anxiety, depression, disorientation).

Follow-up PANSS assessments were administered at four-week intervals throughout each treatment phase to track symptom trajectories and determine treatment efficacy. The assessments were conducted in standardized clinical environments to minimize variability, with two independent raters conducting the evaluations to ensure reliability.

3.3. Treatment Adjustment Framework

The methodology implemented a phase-based approach to treatment adjustments, with each phase characterized by specific therapeutic strategies and PANSS thresholds for progression. Progression to subsequent treatment phases was triggered when PANSS improvement fell below 25% for Phase T0, 35% for Phase T1, and

45% for Phase T2, with assessments conducted at predetermined intervals (8, 12, and 16 weeks respectively).

Phase T0 (Initial Stabilization): This phase emphasized the implementation of conventional first-line treatments according to standard guidelines for adolescent depression with psychotic features. The pharmacological regimen included Cariprazine initiated at 3 mg and escalated to 6 mg daily, alongside Sertraline progressively increased from 50 mg to 100 mg daily. PANSS assessments during this phase established baseline severity with initial values of 18 for positive subscale, 20 for negative subscale, and 45 for general psychopathology.

Phase T1 (Optimization): When improvement fell below the expected threshold (less than 25% reduction in PANSS scores after 8 weeks), treatment optimization was initiated. The psychopathological profile was characterized by lingering negative symptoms such as affective flattening, anhedonia, and avolition, as well as cognitive disruptions manifesting as impaired executive functions and episodic memory deficits. These symptoms continued to significantly hinder the patient's social interactions and aca-demic performance. This phase involved adjusting medication dosages and introducing Aripiprazole at 10 mg daily alongside Escitalopram at 10 mg daily to replace Sertraline. PANSS scores were monitored for improvements, with modest reductions observed (positive subscale: 16, negative subscale: 19, general psychopathology: 42).

Phase T2 (Augmentation): Due to continued suboptimal response (less than 35% reduction from baseline PANSS scores) and the lack of substantial or measurable improvement in the patient's condition—a sentiment echoed by the patient himself—the therapeutic strategy was revised to gradually reduce the previous medication dosages and transition to alternative pharmacological options. Paliperidone was introduced at 6 mg daily, complemented by Clomipramine at 50 mg daily and Trihexyphenidyl at 2 mg daily. This phase was characterized by systematic PANSS evaluations showing marginal improvements (positive subscale: 15, negative subscale: 18, general psychopathology: 40).

Phase T3 (Innovative Approaches): When conventional treatments failed to produce sufficient clinical improvement, the methodology prescribed evidence-informed but non-standard therapeutic strategies. This final phase implemented high-dose Amisulpride (600 mg daily) in combination with Vortioxetine (20 mg daily). Regular PANSS assessments documented significant clinical improvements, with final scores demonstrating substantial reductions across all domains (positive subscale: 12, negative subscale: 14, general psychopathology: 35). Implementation of high-dose strategies in this phase was accompanied by systematic safety monitoring, including monthly electrocardiograms, comprehensive metabolic panels, and prolactin level assessments to detect potential adverse effects early.

3.4. Integration of Neuroimaging and EEG Data into Treatment Protocol

A novel aspect of this case was the systematic integration of neuroimaging findings into the treatment decision-making process. This approach was guided by the neurodevelopmental hypothesis of treatment-resistant psychiatric disorders, which postulates that structural brain anomalies may predict treatment response patterns.

The identification of a 6×3 mm hyperintense lesion on FLAIR sequences in the deep medial temporal cortex prompted consideration of medications with enhanced blood-brain barrier penetration. This guided the decision to employ higher doses of Amisulpride, which demonstrates favorable penetration characteristics compared to other antipsychotics in this neuroanatomical context.

The detection of a pseudonodular accumulation (6×4×6.9 mm) in the adenohypophysis necessitated a dual consideration: optimizing dopaminergic modulation while implementing vigilant monitoring for endocrine disruption. This finding informed both the selection of Amisulpride, which has selective D2/D3 receptor affinity, and the implementation of prolactin monitoring protocols during treatment.

Also, the EEG findings were systematically incorporated into treatment decisions through a structured protocol: the documentation of a stable alpha rhythm at 10 Hz with physiologic sleep spindles during N1 and N2 sleep stages was interpreted as a positive prognostic indicator for response to serotonergic and dopaminergic agents. This finding supported the escalation to high-dose Amisulpride in Phase T3. The absence of spontaneous epileptiform activities on longitudinal EEG monitoring provided reassurance for safely implementing higher medication doses without increased seizure risk. This was particularly relevant given the patient's history of rolandic epilepsy diagnosed at age 12.

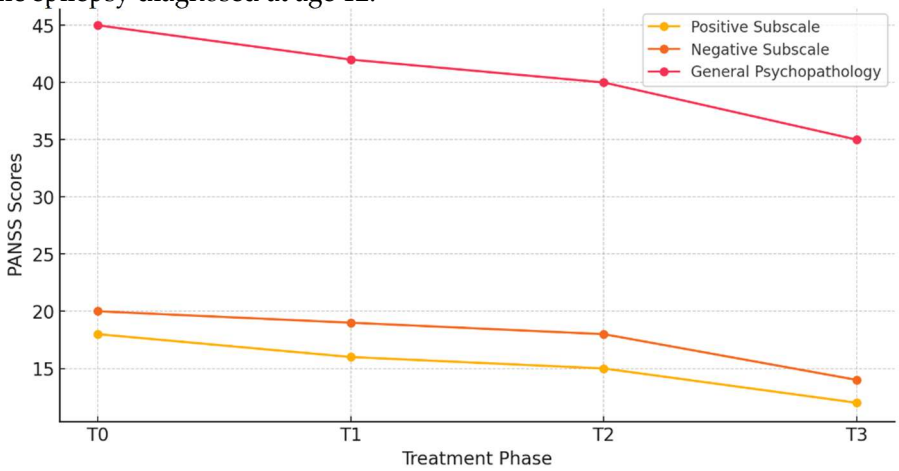

Figure 7. PANSS Score progression over treatment phases (T)

The new treatment approach yielded significant clinical improvements, as evidenced by notable reductions in PANSS scores and enhanced dispositional outcomes (Figure 7). The patient exhibited marked reductions in symptoms across all subscales—positive, negative, and general psychopathology—signaling substantial relief from the pervasive symptoms that had previously dominated his psychiatric profile. Notably, the patient reported a profound alleviation in the feeling of internal void, which had been a persistent source of distress.

4. Discussion

The case exemplifies the intricate and multifaceted nature of psychiatric disorders in adolescents, particularly illustrating the diagnostic and therapeutic challenges posed by severe depression accompanied by atypical psychotic symptoms. This patient's clinical journey highlights the nuanced complexities of early symptom identification, the adaptation of treatment protocols beyond adhering to DSM-V criteria, the diagnostic process in this case was meticulous, taking into account the broad spectrum of symptoms exhibited by the patient. The final diagnosis of a severe depressive episode with psychotic features was carefully considered against potential differential diagnoses, including simple schizophrenia and obsessive-compulsive disorder (OCD), driven by the patient's profound internal void and obsessive thoughts. d standard guidelines, and the critical importance of a tailored diagnostic approach.

The management of this patient required a departure from conventional treatment guidelines, necessitated by the patient’s lack of response to standard therapeutic regimes. The decision to employ a higher dosage of amisulpride and introduce Vortioxetine was based on a evidence-informed approach but ventured beyond typical clinical protocols.

Early symptoms in complex psychiatric cases, such as the motor symptoms initially observed in this patient, are often subtle and can be easily overlooked or misinterpreted. This case underscores the necessity for clinicians to maintain a high degree of vigilance and to consider a wide differential diagnosis when faced with atypical presentations [3].

Motor symptoms in psychiatric disorders are not uncommon but are often underrecognized. The presence of motor symptoms can significantly complicate the clinical picture, as they may be misinterpreted as primary neurological disorders rather than manifestations of an underlying psychiatric condition. As noted by Peralta and Cuesta (2017), motor abnormalities are frequently observed in patients with severe mental illnesses, especially schizophrenia and related psychotic disorders, and are suggestive of more widespread neurological disruption [18]. In this patient's case, the early motor symptoms prompted a more comprehensive neurological and psychiatric evaluation, leading to an understanding that these were part of a broader psychopathological profile. Research indicates that motor symptoms in psychiatric patients may be indicative of more severe psychopathology and a poorer prognosis. Recent studies highlight that motor abnormalities in young psychiatric patients could predict a more severe illness trajectory and greater disability, which emphasizes the need for early recognition and treatment of these symptoms [19]. Furthermore, the integration of physical therapies or targeted medications to alleviate motor symptoms, such as trihexyphenidyl, could be crucial for improving patient outcomes [20,21]. Physical therapies have also shown promise in supporting individuals with neurodevelopmental conditions, including autism, by enhancing motor coordination and sensory integration, as suggested by the success seen in movement disorder treatments within neurology [22].

The diagnostic process in this case adhered to the DSM-V criteria for major depressive disorder (MDD) with psychotic features, which requires the presence of a major depressive episode accompanied by delusions or hallucinations, typically mood-congruent, that are not better explained by another psychotic disorder [23]. While the patient's presentation fulfilled these criteria—marked by persistent low mood, anhedonia, psychomotor disturbances, and psychotic symptoms—several atypical features complicated the diagnostic process. The DSM-V provides a structured framework for diagnosing MDD with psychotic features, emphasizing the importance of ruling out differential diagnoses such as schizophrenia, schizoaffective disorder, and bipolar disorder with psychotic features [24]. However, the limitations of the DSM-V become evident in cases like this, where overlapping symptomatology and atypical presentations challenge the rigid categorical boundaries of psychiatric diagnoses. The presence of motor symptoms, derealization-depersonalization phenomena, and an obsessive preoccupation with an "internal void" added layers of complexity that required careful longitudinal assessment and consideration of alternative diagnoses.

The possibility of simple schizophrenia was considered due to the persistence of negative symptoms, such as affective flattening and avolition, which are characteristic of this subtype [25]. However, the lack of sustained positive symptoms (e.g., hallucinations, delusions) distinct from depressive episodes and the absence of significant functional decline not associated with mood episodes argued against this diagnosis. Also. diagnosing simple schizophrenia requires a clear trajectory of negative symptoms independent of mood disorders [26]. The patient's intense preoccupation with a perceived internal void and recurring obsessive thoughts suggested a possible diagnosis of OCD. While OCD shares some cognitive features with depressive disorders, the absence of compulsive behaviors and the predominant role of mood symptoms differentiated this case from classic OCD presentations. Research indicates that while obsessive thoughts can manifest in depression, the compulsive rituals typical of OCD are absent in MDD with psychotic features [27,28]. The patient's recurrent experiences of detachment from reality and self were suggestive of *depersonalization-derealization syndrome*. However, these symptoms were more episodic and appeared secondary to mood disturbances, consistent with the DSM-V's criteria for mood disorders with associated dissociative features [29].

The DSM-V criteria, while comprehensive, face significant limitations in addressing atypical presentations and overlapping symptomatology. In this case, the categorical approach of the DSM-V proved insufficient for capturing the interplay of motor, cognitive, and mood symptoms [30]. Research highlights the need for a dimensional diagnostic framework that integrates neurobiological markers and symptom spectra rather than relying solely on rigid categorical distinctions [31]. Current clinical guidelines also emphasize treating symptoms rather than understanding their underlying mechanisms, often leading to fragmented care. The reliance on symptomatology-based classification systems, may overlook the neurodevelopmental and psychosocial factors contributing to complex psychiatric disorders like this one [32].

The transition from child to adult psychiatry presents inherent challenges that were particularly evident in this case. Adolescents with severe and complex psychopathology often experience significant difficulties during this critical transition, which can compromise continuity of care and exacerbate existing symptoms. One of the key challenges lies in the differing diagnostic frameworks and clinical priorities between child and adult psychiatry [33]. In child psychiatry, the focus is often on developmental psychopathology and behavioral issues, while adult psychiatry places greater emphasis on mood disorders, psychotic features, and long-term management of chronic conditions. This divergence can lead to inconsistencies in diagnostic approaches, as seen in this case, where the patient's symptoms initially aligned with obsessive-compulsive tendencies and developmental disturbances, but later evolved into a clearer picture of severe depression with psychotic features [34].

Standard guidelines for treating major depressive disorder (MDD) with psychotic features emphasize a combination of antidepressants and antipsychotics, complemented by psychotherapy. The American Psychiatric Association (APA) guidelines recommend starting with first-line selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) for depressive symptoms, while second-generation antipsychotics, such as olanzapine or risperidone, are suggested for psychotic features [35]. Similarly, the National Institute for Health and Care Excellence (NICE) guidelines highlight the importance of combined therapy in severe cases but caution against exceeding recommended dosages without clear evidence [36]. In this case, the patient’s resistance to standard treatment necessitated a deviation from these guidelines, particularly during the latter phases of treatment. While guidelines serve as critical starting points for treatment, their applicability diminishes in cases of treatment resistance. The reliance on standardized approaches often fails to address the nuances of individual symptomatology and the dynamic nature of complex psychiatric disorders.

In cases where standard treatments are ineffective, alternative pharmacological strategies may be considered. Amisulpride, an atypical antipsychotic, has been explored as an augmentation agent in treatment-resistant depression. A study published by Rittmannsberger reported that low-dose amisulpride (50 mg) added to existing antidepressant therapy resulted in clinical improvement in patients with resistant depression [37]. Additionally, Vortioxetine, a multimodal antidepressant, has been evaluated for its efficacy in treatment-resistant cases. A recent study indicated that vortioxetine at doses up to 40 mg/day was effective and well-tolerated in patients with treatment-resistant depression [38].

Amisulpride’s pharmacodynamic properties, including its selective antagonism of dopamine D2 and D3 receptors, make it particularly effective in addressing both positive and negative symptoms of psychotic disorders. Higher doses of Amisulpride have been successfully used in severe cases of schizophrenia, with evidence suggesting its effectiveness in resistant psychosis and depressive episodes associated with significant negative symptoms [39]. This approach aligns with findings from studies suggesting that augmentation with atypical antipsychotics like Amisulpride can enhance antidepressant efficacy in treatment-resistant depression [36]. Furthermore, the use of Vortioxetine, known for its multimodal action on serotonin receptors, may

offer benefits in addressing both depressive and cognitive symptoms in complex cases [40].

Magnetic Resonance Imaging (MRI) studies have identified structural and functional brain abnormalities in individuals with Major Depressive Disorder with Psychotic Features (MDDP). Notably, reductions in gray matter volume have been observed in regions such as the subgenual cingulate cortex, which is implicated in mood regulation [41]. In this case, the MRI findings provided insights into the neurobiological underpinnings of the patient's psychopathology. The identification of a hyperintense lesion on FLAIR imaging in the medial temporal cortex at the level of the uncus, alongside a hypointense signal on T1-weighted images, suggests the presence of a cortical dysplastic lesion. This anomaly, though not pathognomonic, aligns with findings in studies linking structural brain abnormalities with treatment-resistant psychiatric disorders [42]. The absence of acute diffusion-restricted lesions or significant cortical atrophy further supports the chronic and developmental nature of the condition. The observed dysplastic lesion may play a role in the patient's persistent cognitive impairments and feelings of derealization, as the medial temporal lobe is implicated in memory and emotional processing [43]. Moreover, the presence of the arachnoid cyst in the posterior fossa, while typically incidental, cannot be entirely excluded as a contributing factor to the patient's episodic neurological symptoms, including derealization and sensorimotor disturbances [44]. The pituitary microadenoma identified in a subsequent MRI raises additional questions about the interaction between neuroendocrine dysregulation and the patient's psychiatric presentation. Pituitary abnormalities have been associated with hyperprolactinemia and hypothalamic-pituitary axis dysregulation, which could contribute to mood instability and cognitive decline, as suggested by studies in psychotic depression [45, 46].

Similar MRI findings have been documented in cases of severe depression with psychotic features [47]. One study identified reduced gray matter volume in the medial temporal cortex as a hallmark of severe depressive disorders, particularly in treatment-resistant cases [48]. An additional study reported that hyperintensities in subcortical and cortical regions on FLAIR sequences were more prevalent in patients with psychotic depression, further linking these neuroanatomical features with symptom severity and persistence [49]. Additionally, the arachnoid cyst observed in this case is consistent with documented findings on the potential impact of such cysts on cognitive and psychiatric functions, particularly when located in regions associated with cerebrospinal fluid dynamics and cortical connectivity [50,51].

5. Conclusions

This case underscores the complexity of treatment-resistant severe adolescent depression with psychotic features and highlights the necessity of an integrative, precision-based approach in psychiatric management. The patient's atypical presentation—characterized by a constellation of persistent negative symptoms, cognitive dysfunction, and motor abnormalities such as bradykinesia—complicated the diagnostic process and necessitated a deviation from standard treatment algorithms. The presence of structural anomalies, including a medial temporal dysplastic lesion and a pituitary microadenoma, further reinforces the underutilized potential of neuroimaging in elucidating the neurobiological underpinnings of atypical and treatment-resistant psychiatric disorders. These findings advocate for the systematic incorporation of neurobiological assessments into psychiatric practice to refine differential diagnoses and inform targeted interventions.

The transition to a high-dose amisulpride and vortioxetine regimen, guided by systematic Positive and Negative Syndrome Scale (PANSS) assessments, resulted in significant symptomatic amelioration, particularly within the negative and cognitive symptom domains. This therapeutic response underscores the efficacy of pharmacological strategies extending beyond conventional treatment algorithms, advocating for a more adaptable, patient-specific approach in cases exhibiting non-canonical

psychiatric symptomatology. The case further challenges rigid adherence to standardized clinical guidelines, emphasizing the necessity for dynamically tailored interventions that account for neurodevelopmental and neurobiological heterogeneity in psychiatric disorders.

Beyond the scope of this case, these findings underscore broader implications for the refinement of psychiatric care. Future research should focus on enhancing predictive models for treatment-resistant psychiatric disorders through the integration of neuroanatomical, neurophysiological, and genetic markers, thereby advancing precision psychiatry.

In conclusion, this case reinforces the imperative for a paradigm shift toward multimodal, precision-based psychiatric interventions, particularly for patients exhibiting atypical symptom constellations. By advancing the role of neuroimaging, optimizing pharmacological strategies, and advocating for a more dynamic, individualized treatment framework, psychiatric practice can move toward a more robust, evidence-driven model, ultimately improving patient outcomes in treatment-resistant affective and psychotic disorders.

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