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SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS (AK PANDURANGI, SECTION EDITOR)

Acute and Transient Psychotic Disorders: Newer Understanding

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Abstract

Purpose of Review We review the ongoing research in the area of acute and transient psychotic disorders (ATPDs) with regard to their nosology, epidemiology, clinical description, genetics, and neurobiology, examining evidence for distinctiveness or otherwise of ATPDs. We further highlight the lacuna in research in ATPDs.

Recent Findings Studies on ATPDs as defined in the ICD 10 have been reported from different parts of the world, more so from the developing countries. There is consistent evidence that there exist a group of ATPDs that occur more commonly among females, are often precipitated by stressful life events or exposure to physiological stresses like fever, child birth, are associated with well-adjusted premorbid personality, and show complete recovery in a short period. Although in some cases of ATPDs, there is symptomatic overlap with schizophrenic symptoms in the acute phase, they follow a completely different course and outcome, exhibit genetic distinctiveness, and do not share genetic relationship with schizophrenias or bipolar affective disorder (BPAD). Comparative studies on neurophysiology and neuroimaging in ATPDs and schizophrenias have demonstrated evidence of hyper arousal and hyper metabolism in ATPDs vs hypo arousal and hypo metabolism as noted in the P300 response and on FDG PET studies, respectively. Immune markers such as IL-6, TNF-alpha, and TGF-beta show higher levels in ATPDs as compared to healthy controls. Findings on the neurobiological mechanisms underlying ATPDs, so far, point towards significant differences from those in schizophrenia or BPAD. Although the studies are few and far between, nevertheless, these point towards the possibility of ATPDs as a distinct entity and underscore the need for pursuing alternate hypothesis such as neuro inflammatory or metabolic.

Summary Research on ATPDs is limited due to many reasons including lack of harmony between the ICD and DSM diagnostic systems and clinician biases. Available research data supports the validity of ATPDs as a distinct clinical entity. There is also evidence that ATPDs are different from schizophrenias or BPAD on genetic, neuroimaging, neurophysiological, and immunological markers and require further studies.

Keywords Acute and transient psychotic disorders · Biological studies · Nosology · Schizophrenias · Validity · Genetics · Neuroimaging studies

Introduction

ATPDs have been recognized as a descriptive clinical entity in the ICD-10, as conditions that characteristically have an acute onset in all cases (within 2 weeks); presence of typical symptom clusters which are described as rapidly changing, variable, and polymorphic as well as typical schizophrenic symptoms; there is evidence for associated acute stress in a substantial number of cases and complete recovery in most cases within 2–3 months; this description brings together several concepts described earlier by researchers from several countries in the world under different names such as reactive psychosis [1], cycloid psychosis [2], schizophreniform psychosis [3], hysterical psychosis [4], atypical psychoses [5], acute schizoaffective psychoses [6], acute psychosis of uncertain origin [7] etc. The DSM (The Diagnostic and Statistical Manual of Mental Disorders, Fourth edition DSM-IV) on the other hand has categorized ATPDs as "Brief psychotic disorders (BPD)", and the same has been retained in the

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revised edition of DSM-5 too [8]. However, the ICD-10 [9] also included caution about the nosological status of ATPDs stating 'The limited data and clinical traditions… do not give rise to concepts that can be clearly defined and separated from each other…. The nomenclature of these acute disorders is as uncertain as their nosological status', raising questions about the distinctiveness and validity of these disorders. The issue remains whether even after its official recognition in 1992, ATPDs are in any better understood or better delineated, and to what extent these have been validated further through research. Due to controversies raised by some researchers over its nosological status, ATPD has been in the limelight during revisions of ICD-11 and DSM-5. Yet, after more than 20 years since its uncertain status in the official psychiatric nosological systems, ATPD still remains a relevant disorder in the developing countries like India due to its varied presentation, course, and outcome [10••, 11••].

The validity of the ATPD diagnosis has often been in question, especially in comparison with schizophrenia for various reasons ranging from presentation with schizophrenic symptoms in some patients to the issues related to its diagnostic stability [12–14].

Research on ATPDs has been limited for several reasons, mainly due to lack of consensus on a clear definition especially in settings where most such conditions would be commonly seen, for example the emergency rooms where they are given an alternative diagnosis, and also due to the fact that such conditions are more frequently described from developing countries and have not found a place in research publications. ATPDs therefore have been a victim of exclusion from research; while uncertainty of its nomenclature and nosological status should have propelled further systematic research into the condition, it was taken as evidence for not worthy of any scholarly attention.

In this paper, we present a review focusing on most recent research on the different domains of ATPD ranging from clinical, neurobiological, neuroimaging, neurophysiological, biochemical, and family studies and discuss further the evidence supporting the validity of this diagnosis, about its relationship with the known psychotic disorders, i.e., schizophrenia and manic depressive psychosis (BPAD). Our discussion also raises a debate on the vexing question of the phenomenon of psychosis as seen outside the lens of diagnostic biases.

Current Nosological Status

The ICD-10 had included four subtypes of ATPD, which include polymorphic with or without symptoms of schizophrenia, non-polymorphic variants that are schizophrenia-like or predominantly delusional. The duration criteria required that there must be a complete remission of symptoms within 3 months, except in the presence of schizophrenic symptoms in which case it is limited to 1 month. Due to the lack of clinical validity for such subtypes from the field trials [15], the ICD-11 has done away with the non-polymorphic variants and simply subtypes ATPD as either single-episode or recurrent. The ICD-11 continues to advocate the duration criterion of remission within 3 months [16].

There is difference in how DSM approaches this condition. In the Diagnostic and Statistical Manual, 5th Edition (DSM-5), functional acute, short-lasting psychotic episodes are either subsumed under Brief Psychotic Disorder (BPD) or Schizophreniform Disorder. The clinical description of ATPD fits more closely with that of BPD. However, the duration criterion for BPD requires complete remission within 1 month of onset. For those patients in whom psychosis persists beyond 1 month but remits completely within 6-month duration, there is another label called schizophreniform psychosis. Thus, there is recognition in DSM 5 of an acute psychotic condition, which completely remits within 6 months, which are not considered as schizophrenias. Thus, a patient with an acute psychosis of, say 6 weeks but without classic schizophrenic symptoms would be called ATPD in ICD-11, but Psychosis Not Otherwise Specified in DSM-5, and a patient with an acute psychosis of 6-week duration with schizophrenia like symptoms but without the 6-month behavioral change would be diagnosed as schizophrenia in ICD-11 and schizophreniform in DSM-5.

These inconsistencies in nosology of ATPD and lack of harmonization within the two classificatory systems are one of the reasons for a limited research attention.

Epidemiology and Clinical Features

Studies estimating the epidemiology of ATPD are very sparse. Few nationwide studies from UK and Denmark suggest its annual incidence per 1,00,000 population to be in the range of 3.9 to 9.6 [17–19], while prevalence studies report an estimated prevalence ranging from 5.8 to 20% in hospital based/clinic samples [17, 19–22]. With regard to gender differences, several studies have demonstrated similar findings for ATPD being more frequently encountered in females [23••] or with equal prevalence in both genders [17–19, 24] and with higher rates of increased age in females than males [18, 24]. However, an earlier age of onset has been more frequently reported from low- and middle-income developing countries [25, 26, 27•, 28]. Mortality risk in ATPD has been found to be quite high and an almost similar standardized mortality ratio for all causes (natural and unnatural) with schizophrenia and bipolar disorder [29, 30]. Suicidal behavior has also been found to be quite high (36–55%) in the acute polymorphic phase usually associated with mood instability and agitation [31–33].

Many studies have explored for predisposing and precipitating factors for ATPD and have come up with varied risk factors and precipitating factors. Most common factors are social and cultural factors, which have mostly been reported from developing countries [34, 35•, 36]. Higher prevalence in migrant populations has also been reported [37–39]. Stressful life events [40••, 41••], child birth [23••], marital dispute, etc. have been clearly linked to precipitate an episode of ATPD in vulnerable individuals. Data from three developing countries (Ibadan, Nigeria, and India) on acute brief psychoses reported similar psychosocial factors (departure from parental village in case of females and job distress in case of males) and biological factors (fever) to have strong association in the etiology of acute brief psychoses [42•, 43•]. Further, studies have revealed good pre-morbid functioning and better socio-occupational functioning in patients with ATPD than those with schizophrenia [44•, 45].

Studies on the symptomatology of ATPD have been consistent with its varied polymorphic presentation (fleeting hallucinations and delusions, mood instability, agitation, fluctuating anxiety symptoms, and few negative symptoms), which are completely different from the symptomatology and presentation of schizophrenia/schizoaffective disorder [21, 23••, 45–47]. Rapid recovery from the episode with a shorter duration of illness (< 1 month), and very short hospital stay with minimal or almost no negative symptoms has been consistently reported [45, 48].

Biological Studies in ATPD

Validation of a disorder needs studies to be conducted with regard to biological markers, genetic association, common symptom dimensions, and neuropsychological functioning. With regard to ATPD, studies in these areas, though limited, have been continued to be pursued by researchers over the last few years.

Familiality and Genetics

The few family studies which have been conducted since 1990s suggest that ATPD has a strong familial aggregation with its heritability three times more in first degree relatives of patients with ATPDs [40••] and that conversion to schizophrenia more often occurs in those who have a family history of schizophrenia [40••]. Another study by the same group of authors affirming the stress-vulnerability hypothesis in patients with ATPD reported that in patients with a positive family history of ATPD, there were fewer total life stressful events compared to those without a positive family history, suggesting that ATPD may manifest in those high genetic vulnerability despite lower or lesser stress level/factors and vice versa in these subjects [35•]. Higher psychiatric morbidity in family members of ATPD has been reported when compared with healthy controls, though higher rates of psychotic disorders have not been found [21]. A large-scale Danish psychiatric register-based population family study which compared family psychiatric morbidity in ATPD with schizophrenia and bipolar subjects found the relative risk of ATPDs to be 1.93 times higher if the patients with ATPDs had at least one first degree relative admitted with any mental disorder than those without any family psychiatric history and a further higher additional risk if the patients with ATPDs had either schizophrenia (2.06 relative risk) and/or bipolar disorder (1.55 relative risk) [49].

Further, a genome-wide association study (GWAS) of atypical psychosis (described as a close variant of ATPD) carried out in Japan found some putative genes (*CHN2/CPVL genes*, *COL21A1 gene*, and *PYGL/TRIM9 genes*) to overlap with schizophrenia but not with bipolar disorder [50•]. This study suggested that there may be some significant genetic enrichment between schizophrenia and atypical psychosis, though further studies are required to determine the casual variant [50•]. No other genetic studies have yet been carried out in the ATPD. The weight of evidence in genetic studies in ATPD so far, though meagre, points towards the possibility of its genetic distinctiveness, and genetic overlap with schizophrenia only in cases of ATPD with schizophrenic symptoms, and lack of genetic relationship with BPAD.

Neurophysiology

Neurophysiological studies using event-related potentials such as P300, P50, and mismatch negativity (MMN) reflective of sensory gating have been well-studied in schizophrenia and some of them such as P50 suppression, lower P300 amplitude, and increased latency have been regarded as viable endophenotypes for schizophrenia [51, 52].

With this background, a recent neurophysiological study from India explored P300 auditory event-related potentials in 25 subjects with ATPD during clinical remission and compared with 25 schizophrenia subjects in remission and 25 biologically unrelated healthy controls (age/gender matched) [53••].

The study findings demonstrated that there were significant differences in all the P300 parameters between schizophrenia and ATPD subjects during remission phases of both disorders. While the mean P300 amplitude in microvolts (highest trough in the waveform at both parietal and central sites) was significantly lower ($p < 0.001$) in the schizophrenia subjects than those of ATPD subjects, the mean P300 latency in milliseconds (distance between point stimulus to attainment of peak voltages at both sites) was longer in the schizophrenia subjects (difference being significant at $p < 0.001$) than the ATPD subjects. These findings suggest that P300-evoked potentials can easily distinguish between ATPD and schizophrenia during

remission phase of both disorders and additionally re-establish the reduced P300 amplitude and high P300 latency to be characteristic trait-like disease markers in schizophrenia.

But the more interesting and unique finding of the study was that even during the clinical remission phase in ATPD subjects (i.e., after 3 months after the acute symptomatic period), the subjects with ATPD had lower mean P300 latency at parietal site and overall low mean reaction time when compared with healthy controls which were statistically significant suggesting that even during symptomatic remission, the subjects with ATPD are possibly in a cerebral hyper-arousable state [53••]. There is a lack of similar studies and no comparable data is available to validate this, but these findings strongly suggest that ATPDs differ from schizophrenias and from normal healthy subjects neuro-physiologically to a large extent.

Another study on EEG recordings which was conducted to test if there occurs any increased epileptiform activity in patients with ATPD did not find any significant differences between ATPD and schizophrenia/schizoaffective disorder [54]. Further studies in this regard on different neurophysiological parameters are needed to see if any of these can be regarded as viable endophenotypes for ATPD, similar to their value in schizophrenia.

Neuroimaging

A recent, yet-unpublished study from India by our group looked at regional cerebral glucose metabolism (rCGM) using positron emission tomography (PET) in patients with first-episode acute psychosis within 2 weeks of onset, and compared those who were eventually diagnosed as ATPD at 3-month follow-up (i.e.,, remitted completely within 3 months, $n = 17$) with those diagnosed as schizophrenia ($n = 12$) using ICD-10 criteria for ATPD and schizophrenia, respectively. The study found global hypermetabolism in ATPD, which was specifically pronounced in several regions including frontal and temporal lobes bilaterally (Fig. 1) [55••]. In contrast, patients with schizophrenia were found to have frontal hypometabolism, a finding that has been frequently replicated in PET studies of schizophrenia previously [56]. A highlight of our study of ATPD was that these differences were detectable during the acute phases of the illness itself, at which point typically these disorders are difficult to differentiate clinically, and only after a longitudinal follow-up a clinical distinction can be made. This further enunciates that there are possibly different underlying neurobiological mechanisms between the two disorders, possibly over-arousal in ATPD and under-arousal of the areas studied in schizophrenia. However, there are no other similar neuroimaging studies in ATPD published so far to compare or validate our findings.

From these findings, we can infer that frontal hypometabolism (reduced glucose uptake) in FDG-PET studies in schizophrenia (in different phases of illness) has been replicated suggesting it to be more of a neurodegeneration process after the onset of illness and has been found to be strongly associated with cognitive deficits in schizophrenia [57–59]. However, the findings of above-mentioned study [55••], i.e., hypermetabolism in frontal and temporal regions biltaerally (more uptake of glucose) in ATPDs during and after the acute psychotic episode, suggest that dominant functional brain abnormality in ATPDs is completely different from that in schizophrenia; possibly, one could think of a neuroinflammatory or metabolic derangement.

Extensive recent structural and functional neuroimaging studies in schizophrenia have lent support to its burgeoning 'neurodevelopmental' hypothesis, which posits that genetic vulnerability and environmental risk factors such as perinatal insults interact to cause aberrations in cortical plasticity, which manifests in early adulthood as psychosis [60–63]. There is also evidence that certain other manifestations of these aberrant neurodevelopmental processes, such as neurological soft signs or neurocognitive deficits, along with neurophysiological and neuroimaging endophenotypic markers are detectable prior the onset of overt psychotic symptoms [64–68]. It can thus be hypothesized that the frontal hypometabolism seen in the schizophrenia group may have pre-dated the onset of acute psychotic episode. Although hypermetabolism in the ATPD group clearly suggests different underlying pathophysiological mechanisms, much more research is needed to further our understanding in this area. As patients in the acute phase of the illness usually present with florid psychotic symptoms, high levels of agitation, and suicidality, it is difficult to carry out neuroimaging studies, particularly with MRI. Thus, of particular interest would be to look for neuroimaging markers in remitted patients with a stable diagnosis of ATPD in comparison to schizophrenia to see where the two disorders may overlap or differ from each other. Findings of these two studies, i.e., reporting hypermetabolism in FDG PET [55••] and hyperarousal on P300 [53••] in ATPD vs hypometabolism and hypoarousal in schizophrenia, respectively, seem to converge and give an important lead for future research into underlying biological mechanisms in these two conditions.

Immunological/Biochemical Markers

Biochemical studies have revealed metabolic alterations in amino acid pathways [69] and elevated bilirubin levels in ATPD as compared to schizophrenia subjects [70]. Another study which compared blood levels of the dopamine metabolite homovanillic acid, brain-derived neurotrophic factor, and amino acids related to glutamate neurotransmission in patients with cycloid psychosis (which has good concordance with ICD-10 diagnosis of ATPD) [71] and those with schizophrenia reported elevated levels of glycine and low levels of tryptophan in patients with cycloid psychosis as compared to

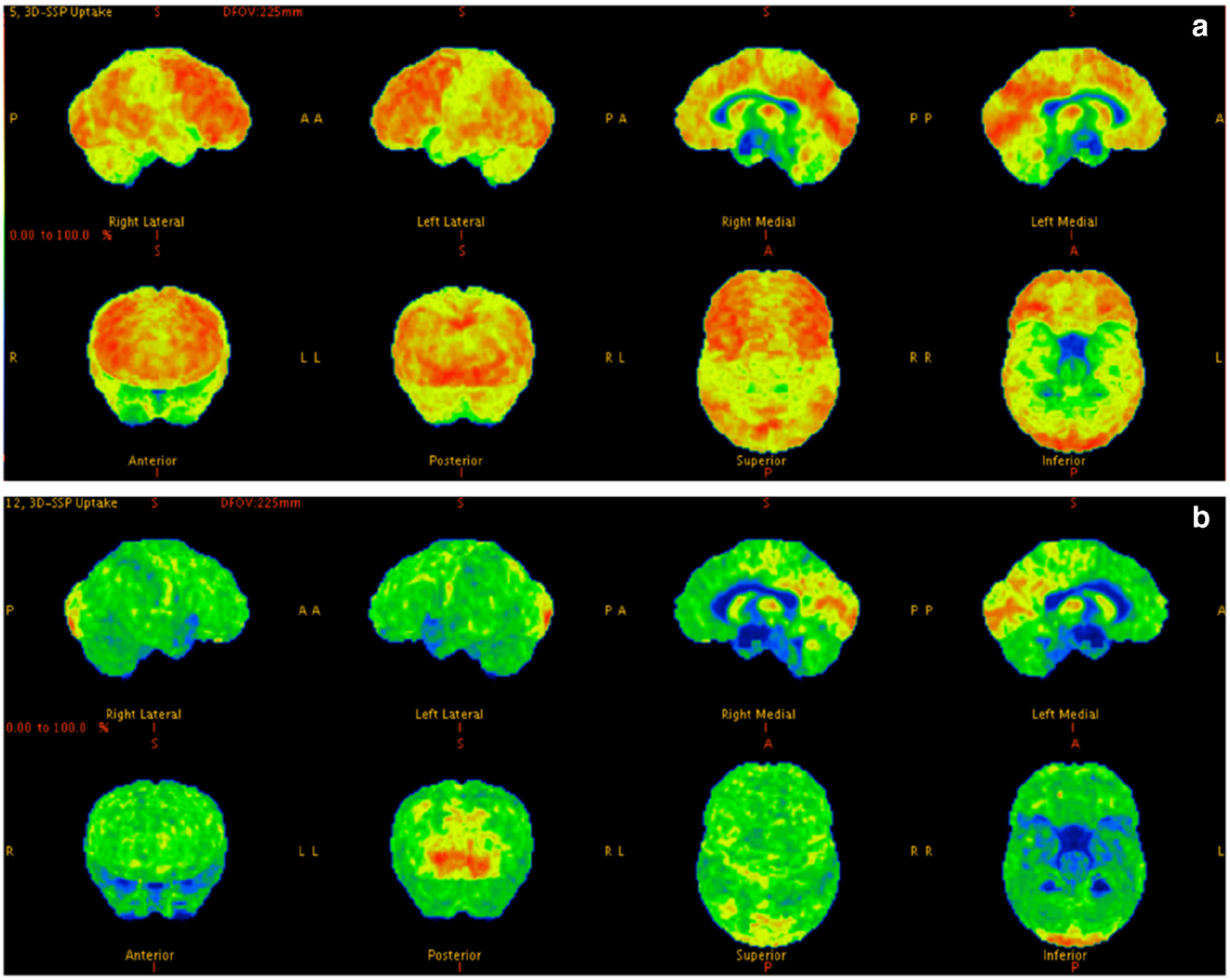

Fig. 1 Reconstructed ^{18}FDG-PET images showing distinct regional cerebral glucose metabolism (rCGM) findings in single representative subjects from the **a** ATPD and **b** schizophrenia groups during the acute phase of the illnesses [55] *Copyright obtained from all authors of the study. Two authors of the study are the authors of this article.* **a** ATPD subjects and **b** schizophrenia subjects

schizophrenia, while glutamate levels were increased in both groups suggesting better neuroplasticity in cycloid psychosis and necessitating demarcation of cycloid psychosis within psychosis spectrum disorders [72]. More recently, an exploratory study of immune markers in patients with ATPD (n = 41) found elevated levels of IL-6, TNF-alpha, TGF-beta at the baseline, and significant increase in levels of TNF-alpha at follow-up suggesting a prolonged pro-inflammatory response in patients with ATPD as compared to healthy controls [73•]. All these findings do suggest that there exists certain different biochemical/metabolic abnormalities in ATPD than schizophrenia further hinting upon a new arena of research to explore if the immune hypothesis of psychosis is similar or different in both the disorders.

More recently, there are studies and case reports where NMDA receptor antibodies [74, 75] and limbic encephalitis associated with antibodies against neuronal cell membrane antigens, e.g., NMDA receptor (NMDAR) and voltage-gated potassium channel (VGKC) [76] are described in patients of acute first onset psychosis. In a most recent review article, it is reported that in most of the first onset acute psychosis cases, autoimmune encephalitis should be considered as a differential diagnosis and investigated for antineuronal antibodies particularly NMDAR antibodies [77].

Most common cause of psychosis due to autoimmune etiology is NMDAR encephalitis where psychosis presents with characteristic picture of acute onset, florid psychotic symptoms, catatonia, autonomic instability, altered sensorium, and possible seizures. This clinical picture significantly mimics the descriptions of broadly inclusive ATPDs. These patients of NMDAR encephalitis respond to steroids and immune therapy. It is hypothesized that NMDAR antibodies may inhibit the presynaptic gaba-ergic interneurons leading to reduction in GABA release and disinhibition of postsynaptic glutamatergic

neurotransmission and glutamate-dopamine dysregulation. This might contribute to production of psychotic symptoms and dyskinesias [78]. It is possible that with more research in this area, our outlook for ATPDs may completely change and these may in fact turn out to be neuroinflammatory conditions.

Neuropsychology

Research on neuropsychological functions have provided valuable insights and improved our understanding of several psychiatric disorders, particularly schizophrenia and bipolar disorder. Deficits in various neuropsychological aspects such as working memory, processing speed etc. have been established as putative endophenotypes in these disorders. Neuropsychological studies in ATPD, however, are very limited and suggest cognitive impairment in the acute phase but rapid improvement, particularly in the domain of processing speed within 6 months after the acute phase [79]. This study by Ayesa-Arriola et al. explored whether there are distinguishable neurocognitive profiles in diagnostic subgroups of first-episode non-affective psychosis (FEP) patients. Four hundred and eighty-seven individuals with diagnoses of non-affective psychosis disorders were evaluated 6 months after first contact with psychiatric services. Individuals with schizophrenia (n = 257), schizophreniform (n = 141), brief psychotic disorder (n = 54), and psychosis not otherwise specified (n = 35) were compared on baseline neuropsychological variables using analyses of variance and covariance with potential clinical, premorbid, and sociodemographic confounders. The brief psychotic disorder subgroup was the least impaired on global cognitive function, in particular when compared to the schizophrenia subgroup, and specifically on executive function, processing speed, and motor dexterity domains. However, with the exception of the processing speed domain, profile differences could be explained by sex, age, positive psychotic and negative symptoms, years of education, and premorbid IQ. These results suggest processing speed as a diagnostic marker for brief psychotic disorder in FEP patients. Further, there are quantitative and qualitative differences across the schizophrenia spectrum disorder subgroups, indicating different profiles with varying degrees of deficit. Another study which had compared cognitive functions in patients with brief psychotic disorder, schizophreniform disorder, schizophrenia (diagnosed as per DSM-IV), and healthy controls revealed that patients in all the three groups performed significantly worse than healthy controls on all cognitive domains with cognitive deficits being most pronounced in verbal and working memory, attention, motor speed, and executive functions; however, no significant differences were found between the three patient groups [80].

There is ample amount of literature to suggest that there exists both neurocognitive deficits in almost all the domains of neurocognitions (verbal memory, visual memory, attention, processing speed, problem solving, reasoning, and executive functions) and social cognitive deficits in patients with schizophrenia during stable/remission phase [81–83]. Further, studies have suggested that these neurocognitive deficits are stable after acute psychotic breakdown and have been significantly associated with poor clinical and functional outcome in patients with schizophrenia, suggesting them to be regarded as endophenotypes of schizophrenia [84, 85]. However, in view of lacunae of research of neurocognitions and social cognitions in patients with ATPD, it is difficult to ascertain if any deficits exist in these domains of neuropsychology after the acute psychotic episode and future research in this area is essential to answer these queries.

Diagnostic Stability, Course, and Outcome of ATPD

There are more than 25 papers which have explored the course and outcome in patients with ATPD. The follow-up studies have been as long as 20 years and have demonstrated that a significant proportion of subjects with ATPD retain their diagnosis, i.e., diagnosis remained unchanged in 30–73% of the cases [17, 28, 42•, 80, 86, 87, 88••, 89–94]. Meta-analysis of studies of first episode psychosis (n = 42 studies) which included patients with ATPD and had an average follow-up of 4.5 years estimated a prospective diagnostic stability to be around 0.56 (95% Cl 0.62–0.60) and the risk of relapse ranged between 30 and 38% in the initial 2 years and up to about 54% in subsequent years [95••]. Another meta-analysis of the studies on prognosis of brief psychotic episodes (n = 82 studies) which included studies on patients with first episode psychosis, acute and transient psychotic disorder, brief psychotic disorder (BPD), brief intermittent psychotic symptoms (BIPS), and brief limited intermittent psychotic symptoms (BLIPS) revealed no prognostic differences in risk of psychotic recurrence between ATPD, BPD, BLIPS, and BIPS constructs of brief psychotic episodes, but overall, there was a consistent meta-analytical evidence for better long-term prognosis of brief psychotic episodes compared with remitted first-episode schizophrenia [96].

Further, studies have reported that up to about 60% of the patients with ATPD maintained remission without medications [20, 21, 86]. Favorable outcome with no deficits has been well demonstrated across the studies [21, 45, 97]. Among the various sub-types of ATPD, those with acute polymorphic type of ATPD without symptoms of schizophrenia had the highest diagnostic stability than those with symptoms of schizophrenia and predominately delusional subtype of ATPD [28, 87, 98, 99]. Diagnostic stability of ATPD also varies across the cultures, with high rates of temporal stability and low recurrence rates in patients from developing countries [91, 94, 100–104]. Having a positive family history of

schizophrenia, male gender and younger age of onset, having Schneiderian first rank symptoms and thought disorder in patients with ATPD are some of the clinical features which predicts the conversion of ATPD to schizophrenia [92, 98, 105, 106]. Studies have used either typical antipsychotics (haloperidol) [107] or atypical antipsychotics such as risperidone [108]/olanzapine [109] for treatment and have shown dramatic symptom resolution and minimal side effects within a period of 4 weeks.

Conclusions

Despite the lacunae in research on ATPD in the fields of epidemiology, neurobiology, and genetics, available evidence suggests that ATPD is a distinct clinical entity, quite different from the schizophrenias [11••]. Literature also suggests that ATPD is more commonly seen in the developing countries; more often affects women; with onset usually in early to middle adulthood; with pre-morbid good functioning and well-adjusted personality; often precipitated by socio-cultural and physiological stressors (including infection and fever, child birth); have a varied polymorphic presentation (intermixed psychotic and affective symptoms), and improves upon treatment with in a period of 4 weeks with almost no residual symptoms, i.e., complete functional recovery [11••, 110••, 111, 112••].

Most research so far points to the fact that ATPDs are distinct clinical psychotic conditions which are also distinct from schizophrenias in terms of underlying neurobiological mechanisms. Further research in ATPD also has the potential to elucidate the mystery about the nature of psychosis and psychotic conditions known so far.

If we look back into history, there is this concept of 'unitary psychosis' by the German Psychiatrist Zeller [113] which connotes that there is an absence of psychopathologically ascertainable nosological entities, i.e., there is only one form of psychosis and that its diverse clinical presentations can be explained in terms of endogenous and exogenous factors [113]. However, recent studies have changed this viewpoint of researchers and the idea of unitary psychosis has been regarded as illogical [114], as it is against the concept of the existence of natural nosological entities or multiple and distinguishable psychoses which show individual symptomatology, etiology [115]. Another viewpoint hypothesizes schizophrenia and ATPD to lie on a two-dimensional continuum of genetic vulnerability and environmental brain insult intersecting at different stages of life, where high genetic loading and/or early brain insults progress onto schizophrenia and low genetic loading and later life brain insults progress onto ATPD [110••].

Research interest in ATPD has grown to a great extent among researchers so as to find out the factors favoring good diagnostic stability and favorable outcome seen in many subjects (60%) vis-a-vis poor prognosis or development of persistent psychotic disorders in rest of the cases [116••]. Studies which have taken into account subjects with Clinical High Risk State for Psychosis (CHR-P) which includes the Brief and Limited Intermittent Psychotic Symptoms (BLIPS) subgroup have found substantial diagnostic (around 70% of BLIPS cases also meet ATPD criteria) [117] and prognostic overlap [96] with ATPD. There is emerging research to reconceptualize ATPD with in the CHR-P framework so as to develop early detection and preventive strategies [118]; yet, the clinical presentation of ATPD is distinct from high-risk cases of brief psychotic episodes/BLIPS. There is a dearth of neurobiological research in these entities, and therefore, it cannot be said that ATPD fits into the same framework of CHR-P. Due to all these issues, ATPDs continue to remain as a watershed area of research in psychiatry.

Till now, although the major nosological systems have accepted ATPD as a separate diagnostic entity, there are no treatment guidelines developed for it, and therefore, there is an utmost need to enhance the research in the field of ATPD to investigate various neurobiological and social aspects and identify the bio-psycho-social underpinnings of this clinical entity. We need to watch for emerging evidence in favor of autoimmune encepahlitis hypothesis and its treatment with steroids and immune therapy in at least a subgroup of ATPDs.

Compliance with Ethics Guidelines

Conflict of Interest Savita Malhotra, Swapnajeet Sahoo, and Srinivas Balachander each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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