

Differential Diagnosis of Schizophrenia: Psychotic Symptoms in Neurodevelopmental Disorders and Psychotic Disorders due to other Medical Conditions



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SUMMARY

This review focuses on the differentiation of schizophrenia in the setting of adult psychiatry from neurodevelopmental disorders (NDD's) and psychosis due to other medical conditions (PDMC). Psychotic disorders in early adulthood are most frequently diagnosed with the schizophrenia spectrum or mood disorders. However, they may be the manifestation of neurologic, endocrine or immunologic disease. Individuals with NDD's such as the autism spectrum disorder (ASD) or intellectual developmental disorder (IDD) may also present initially in adulthood. Therefore it is not uncommon that the psychiatrist is the first physician to assess a psychotic patient with underlying medical illness or a NDD. Failure to identify the underlying cause will delay appropriate management. Overdiagnosis of primary psychiatric disorders may be misleading in planning the treatment, as evidence-based treatment algorithms relevant to psychosis are intended for primary psychotic disorders like schizophrenia, and symptomatic treatment may result in unnecessary exposure to antipsychotic drugs. Exclusion of other medical conditions and NDD's is essential before establishing a diagnosis of schizophrenia.

Keywords: psychosis, schizophrenia, differential diagnosis, comorbidity

Why is it important to diagnose psychosis due to another medical condition or a neurodevelopmental disorder?

Behavioral symptoms can be the manifestation of medical conditions other than primary psychiatric disorders. In fact, many conditions like multiple sclerosis, epilepsy, subdural hematoma etc. can manifest with psychosis, mood symptoms or other psychiatric symptoms. Likewise, relatively mild disorders on the autism spectrum and disorders of intellectual development (mild intellectual disability or borderline intellectual functioning) that were not diagnosed in childhood can manifest with a variety of psychiatric symptoms in adulthood, including mood or psychotic symptoms. However, there is a tendency in adult psychiatric practice to ascribe psychotic symptoms to primary psychiatric diagnoses like schizophrenia or bipolar disorder without ruling out other potential causes

(Keshevan and Kaneko 2013). Neurodevelopmental disorders (including the disorders of intellectual development and autism spectrum) (NDD's), typically diagnosed in childhood are also less likely to be recognized in adults (Atbaşoğlu and Sakarya 2011). In fact, the diagnosis of ASD at the initial assessment of an adult patient used to be unusual until recently (Hofvander et al. 2009, Fombonne 2012).

When another medical condition is demonstrated, or judged by the clinician, to be the cause of psychosis, the official DSM-5 diagnosis is Psychotic Disorder Due to Another Medical Condition (PDMC). For the psychotic symptoms that manifest during the course of a NDD, the diagnosis of schizophrenia is reserved for cases with prominent delusions or hallucinations in addition to the other symptoms of schizophrenia. Therefore a thorough medical assessment and

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developmental history are essential before establishing the diagnosis.

One implication of distinguishing PDMC's and NDD's from schizophrenia is on treatment, including duration, the choice of medication and psychosocial interventions. Evidence-based treatment algorithms relevant to psychosis are intended specifically for schizophrenia and mood disorders, while the treatment of PDMC should be directed to the underlying cause as appropriate and to the symptoms of the individual patient. Psychotic disorders due to other medical conditions may be brief or episodic. Management of those cases along the lines of treatment algorithms for chronic disorders like schizophrenia may result in unnecessarily extended exposure to antipsychotic drugs and several side effects that could potentially be avoided (Atbaşoğlu and Gülöksüz 2013, Fombonne 2012). Longer than necessary treatment with antipsychotics and use of high doses are known to be related with lower social and occupational functioning and the quality of life (Hagerman and Polussa 2015), therefore other medical or psychotherapeutic options should be considered whenever possible. Another therapeutic implication is the risk of delay in the management of the underlying condition. Some disorders that manifest with a clinical picture similar to schizophrenia require early, and sometimes urgent, intervention. Delay in managing those cases, e.g., epilepsy, brain tumors, etc, can cause substantial harm (Khandanpour et al. 2013). In addition to this, the medical condition causing psychosis could be a heritable disease that can be definitively identified, allowing genetic counselling with strict figures of risk in the patient's offspring as well as the diagnosis of affected presymptomatic relatives (Novak and Tabrizi 2011).

In the case of mild and short-lived psychotic symptoms that manifest during the course of NDD's, a thorough assessment with developmental history and psychiatric examination will reduce the risk of two potentially harmful outcomes: One is an overdiagnosis of schizophrenia, in which case the unwanted consequences will be similar to those described for PDMC. Another harmful outcome is missing the diagnosis of the NDD that previously went undiagnosed because of a mild presentation and / or limited awareness in the adult psychiatric setting. This will deprive patients and their families of potentially beneficial psychotherapeutic interventions and appropriate rehabilitation programs (Hagerman and Polussa 2015).

Stigmatization of schizophrenia is one of the major factors complicating the differential diagnosis of psychosis. This is because inherent in the stigmatizing attitude towards an illness is, alongside a judgemental attitude and societal discrimination, a presumption of uniformity among individual cases and of the specificity of its symptoms, although schizophrenia is essentially a heterogeneous disorder and psychosis is far from being specific to the disorder. Symptoms like psychosis,

disorganized behavior and formal thought disorder are attributed by many health professionals to a primary psychiatric disorder, often to schizophrenia. Furthermore, those are among the symptoms that are the easiest to identify, which also increases the likelihood of a hasty diagnosis (Wilson and Sponheim 2014).

Before the publication of the DSM-IV (APA 1994) psychosis due to nonpsychiatric causes was classified under a separate category: The Organic Psychotic Disorders in the DSM-III (APA 1980) was based on the organic – functional distinction (Guinjoan 2013). It must be emphasized, however, that the reliability of this distinction depends on the physician's experience as well as the sophistication of the available laboratory assessments. Both those factors largely vary across settings and conditions of service provision. It has been common practice to ascribe separate diagnostic categories to all symptom groups. This tends to increase the number of comorbid diagnoses and to hamper a global approach (Cichocki et al. 2012). Clinicians tend to profession also may change the diagnosis of same patient (Lolas 2009).

Effects of Physical and Neurological Symptoms on the Differential Diagnosis of Schizophrenia

Patients with chronic psychotic disorders have various physical complaints, however any medical condition causing the physical complaints have been diagnosed in a few patients (Stone et al. 2005). Furthermore, many physical complaints such as weakness, lack of energy, and pain in schizophrenia patients appear due to cognitive and perception distortions of the patient (Truyers et al. 2011). However, those physical complaints have been approved as a comorbidity in many patients (Stone et al. 2005). For example, a patient presenting with excitation and ketoacidosis together may probably be diagnosed with type 2 diabetes mellitus comorbidity, especially in the patients whom were followed-up with the schizophrenia diagnosis (Enuh et al. 2014). Considering another possible cause, such as autoimmune disorder due to anti-GAD antibodies, is a low probability although the diagnostic criteria of schizophrenia remark the exclusion of all medical conditions (Malter et al. 2010).

A factor challenging the differential diagnosis is the tendency to diagnose comorbidities of doctors which increase the number of wrong diagnosis (Cichocki et al. 2012). Physical symptoms observed in the comorbidity of schizophrenia and anxiety disorder are chronic pain, weakness, and dyspeptic symptoms, while dizziness and tremor are neurologic symptoms frequently found in this comorbidity (De Groot et al. 2011, Braga et al. 2013). Also adverse effects of antipsychotics may mimic negative symptoms of schizophrenia that may challenge differential diagnosis (Kranzler and Cohen 2013).

In this article we review the major diagnostic categories of PDMC and NDD's with an emphasis on differential diagnosis.

Neurodevelopmental Disorders

In neurodevelopmental disorders, Numerous physical complaints can be found in the patients of neurodevelopmental disorders and, schizophrenia. (Jonas et al. 2014). Both schizophrenia and neurodevelopmental disorders begin in younger ages and affect functionality significantly. Social adaptation difficulty, disorganized behaviours, and cognitive impairment are mutual symptoms of neurodevelopmental disorders and schizophrenia (Paula-Pérez 2012). However social adaptation difficulty and lack of behaviour flexibility are typical symptoms of neurodevelopmental disorders, sometimes it is difficult to separate them from desorganisation symptoms of schizophrenia. Stereotypic speech and language defects are usually seen in ASD patients. Even if the speech content is sufficient atypical verbal expression and, association can be noticed. Desorganised speech in schizophrenia and atypical verbal speech can be distinguished by experience. The neurodevelopmental disorders which have a high risk of schizophrenia misdiagnosis are autism spectrum disorders (ASD) and intellectual developmental disorders (IDD) (Sullivan et al. 2013, Barneveld et al. 2011).

Intellectual Developmental Disorders

Moderate or severe cases of IDD (intellectual disability, mental retardation) are easily recognized and typically diagnosed in childhood. Milder cases of IDD or individuals with borderline intellectual functioning pose a difficulty in diagnosis, as the presentation tends to be more susceptible to the influence of cultural norms and expectations (Benjamin et al. 2013). Poor academic achievement may not be readily apparent until the difference from peers becomes significant with age (Wieland et al. 2014). Increased load of psychosocial demands during adolescence might trigger psychiatric symptoms such as irritability, anhedonia and problems in social adaptation. Brief episodes of psychosis can manifest in the face of higher psychosocial challenge so that psychosis is not uncommonly the initial clinical presentation of a mild case with an IDD (Wieland et al. 2014). In a population-based study on intellectual disability (ID) and co-occurring psychiatric illness Morgan et al. (2008) found that the rates for life-time rate of psychosis and schizophrenia among all cases of ID were 8.4 and 3.6 %, respectively. Individuals with accompanying psychiatric illness were significantly more likely to have IQ levels in the borderline and mild ranges (64.3% of those with a dual diagnosis compared with 53.6% of those with ID alone) and less likely to be severely or profoundly affected (9.2% compared with 18.3%).

Delusions that occur during the course of an IDD tend to include less detail, paralleling the poor thought content, and systematization is rare (Benjamin et al. 2013). Auditory hallucinations are not common in IDD per se, and their presence during co-occurring psychosis suggests the comorbid diagnosis of schizophrenia (Horovitz et al. 2014).

It is important to bear the possibility of a mild IDD that went unrecognized, especially when there is a history of long-standing disability. This will help with a better understanding of the patient's needs and more appropriate care (Wieland et al. 2014). Unnecessary use of antipsychotic drugs and their adverse effects can also be avoided (Horovitz et al. 2014).

Autism Spectrum Disorder

An initial diagnosis of autism spectrum disorder (ASD) is rare in adults. This is surprising, given that ASD is not rare and clinical features include neither a shorter life-span nor full recovery. One possible explanation is that awareness among physicians about the milder forms of ASD is low compared to other NDD's and schizophrenia. Neurodevelopmental symptoms of some verbal individuals with Asperger Disorder or Pervasive Developmental Disorder-Not Otherwise Specified (APA 1994) may not be as apparent as in classical autism. The latter, which corresponds most closely to the DSM-IV Autistic Disorder (APA 1994), is at the severe end of the spectrum, and it is usually diagnosed in childhood. This typological approach has prevailed for a long time among physicians, limiting awareness about the milder forms. The DSM-IV description of PDD's included onset before age 3 as a diagnostic criterion, restricting the diagnosis in adult individuals (Sullivan et al. 2013). Review of the medical history regarding the first three years of life is easier and more reliable with young patients. In addition, young patients are more likely to be accompanied by a reliable informant. Furthermore, the terms of initial presentation, onset, and initial diagnosis are sometimes used interchangeably. It is known that milder cases of neurodevelopmental disorders tend to manifest relatively later, and identification of a behavior or a cognitive feature as symptomatic is not independent from cultural norms, i.e., the same manifestation of an ASD may be regarded as symptomatic and present to medical care at a later stage of life in some cultures, while it is recognized as abnormal at an earlier age in others. The new definition of ASD in the DSM-5 (APA 2000) does not limit the initial manifestations to the first 3 years of life and this provides the liberty to take into account the fact that presentation may vary with the severity of the disorder and cultural attitudes towards the typical symptoms.

The age criterion in the DSM-IV TR stipulating that the symptoms be present before the age of 3 (APA 1994) limited the diagnosis of these disorders to the setting of child and adolescent psychiatry, and to some extent, to pediatric neurology and general pediatrics, especially for syndromic cases.

Adult patients with ASD may present with psychosis. In the young individuals with ASD and psychotic symptoms the differential diagnosis between ASD and schizophrenia is the main task. Some of those individuals will fulfill both diagnostic criteria and receive a comorbid diagnosis.

Barneveld et al. (2011) investigated the frequency of psychotic symptoms accompanying autistic symptoms and positive symptoms accompanying autistic symptoms is found to be 14%, symptoms of desorganization is found to be 13-19% in frequency. Behaviour characteristics, presence of social anxiety, presence of delusions during remission and cognitive functions are the features that must be evaluated to differentiate the two disorders.

The symptoms shared by schizophrenia and ASD include difficulties in social adaptation difficulty, disorganization and excitation, they are seen in both disorders frequently (Bevan Jones et al. 2012). Disorganised behaviours can be triggered by social stress and they form a repetitive and ritualistic pattern (Sullivan et al. 2013). Disorganised behaviours in schizophrenia show a more constant course including almost all behaviours. Disorganised behaviours usually don't show a ritualistic pattern in schizophrenia unlike ASD. Excitation isn't a determining factor on the differential diagnosis (Bevan Jones et al. 2012).

Common symptoms of two syndromes are social interaction and communication deficits (Sullivan et al. 2013) while

focusing on details in certain issues is a atypical faeture of ASD (Waris et al. 2013). Having special interest on some issues and knowing almost everything about interested issue point out ASD rather than psychotic disorders. Apathy, anhedonia are core symptoms of schizophrenia while avolition become apparent in the following period of schizophrenia (Pagsberg 2013). Konstantareas and Hewitt (2001) stated that core symptom of ASD is social communication difficulty with lower anxiety while paranoid delusions and social anxiety indicate psychotic disorders. However social withdrawal due to frustrations in society can be common in both disorders. Thus social skills and social communication difficulties should be evaluated in details.

ASD, in which multiple nonspecific physical symptoms can be found is a substantial differential diagnosis of schizophrenia during childhood and adolescence (Nylander and Gillberg 2001). In recent years, some patients getting treatment for schizophrenia have been diagnosed ASD through increased research about ASD (Benjamin et al. 2013, Vortsman and Ophoff 2013). Even though there is a big variation among researchs, 5-30% of patients with ASD have epilepsy and %30-50 of them have been diagnosed with psychiatric disorders (Sullivan et al. 2013). IDD, psychosis and mania are most common psychiatric disorders observed in ASD patients (Paula-Perez 2012). A study researching on the patients with ASD reveal that many patients had been diagnosed and treated as schizophrenia before a detailed assessment for ASD

Table 1. Differential Diagnosis of Schizophrenia: Neurodevelopmental Disorders and Psychotic Disorders Due to Other Medical Conditions

Diagnosis	Etiology	Clinical Symptoms	Psychiatric Comorbidity
Velokardiofacial Syndrome	Deletion on 22q11 chromosome	Heart defects, cleft palate, atypical facial dysmorphism, impulsive behaviours, social adaptation difficulties	Attention deficit hiperactivity disorder, autism spectrum disorder, mood disorders, learning disability
Fragile-X Syndrome	Increase of CGG trinucleotide repeat on Xq27.3 locus	Elongated face, large ears, palate anomalies, macroorchidism, kardiovascular anomalies, aggression, impulsive behaviours	Autism spectrum disorder, intellectual development disorder
Multiple Sclerosis	Damaged myelin sheath of brain and spinal cord by autoimmune antibodies	Sensorial and motor symptoms, presenting with attacks	Mood disorders, psychotic disorders
Temporal Lobe Epilepsy	Abnormality in brain activity	Tonic clonic seizures, oral and manual automatisms, mood and dissociative symptoms up to 3 minutes	Mood disorders, psychotic disorders
Autoimmune encephalopathies	Otoimmune antibodies	Mesiotemporal seizures, short time memory impairment, irritability, generalised anxiety, delusions and halucinations	Psychosis, mood disorders
Thyroid Function Disorders	Hyperthyroidism, hypothyroidism or rapid changes of thyroid hormones	Hyperthyroidism/ hypothyroidism symptoms	Mood disorders, depression, psychosis
Systemic Lupus Erytematozus	Otoimmune antibodies	Dermatologic lesions, arthritis, systemic symptoms	Depression, mania, psychosis
Wilson Disease	Copper acumulation in the liver and basal ganglions	Liver function disorders, Kayser-Fleischer ring, dysarthria, neurologic symptoms	Various psychiatric symptoms such as depression, euphoria, sexual preoccupations, hebefrenia, catatonia

(Jonas et al. 2014). Besides physical examination on ASD patients can provide to diagnose genetic syndromes like fragile-X and tuberous sclerosis (Guilmatre et al. 2009, Bora 2008).

Short time assessment in outpatient clinics and clinicians who don't know much about adult ASD result in schizophrenia misdiagnosis (Paula-Perez 2012, Jonas et al. 2014). While patients refer to psychiatry clinics in adult age, they usually have psychiatric disorders like depression, anxiety disorder or psychosis diagnosed with a simple assessment (Sullivan et al. 2013). If the patient is not questioned according to the specific symptoms, it is not possible to diagnose ASD (Benjamin et al. 2013, Sullivan et al. 2013). Besides severity of autistic symptoms and its features that impair adaptation decreases with age, therefore making its diagnosis in adult age needs experience and adequate knowledge (Shattuck et al. 2007).

Psychotic Disorders due to Other Medical Conditions

Although some medical conditions are known to be more commonly associated with psychosis, evidence on the incidence of psychosis in those disorders are not conclusive (Keshevan and Kaneko 2013). We focus on the conditions that we judged to be more important for psychiatrists. The choice of the conditions that are covered here is based on our clinical experience, their higher prevalence in the published case series, higher likelihood of a psychiatric presentation and the potential harm of misdiagnosis.

Genetic Disorders

Fragile-X Syndrome

Fragile X (FraX) syndrome, caused by the expansion of CGC nucleotide repeats in the 5'-untranslated region of the Fragile X mental retardation 1 (FMR1) gene on locus Xq27.3 (Tassone et al. 2014) is the most common inherited cause of mental retardation and also the most common single gene cause of autistic disorder (Bourgeois et al. 2009). Patients with 200 or more trinucleotide repeats, i.e. a full mutation exhibit the characteristic signs and symptoms of the syndrome (Tassone et al. 1999). Individuals with 55-200 repeats are carriers, also referred to as premutation cases (Fra-X PM), because the repeat number may increase during meiosis to cause a full mutation in the offspring. The typical dysmorphic symptoms are an elongated face, large ears, flat feet and macroorchidism, although they are not a precondition for the diagnosis (Tassone et al. 2014). Full mutations almost always cause intellectual disability. Individuals with a premutation usually have normal intelligence, although they might present with mild intellectual disability or an atypical neurodevelopment. Cases with FraX syndrome and an obvious IDD can be identified easily. Diagnosis is a challenge in patients with

milder IDD's, particularly in the FraX-PM (Hagerman and Polussa 2015).

There are two main challenges for the differential diagnosis between fragile-X and schizophrenia syndromes. First and main reason is the higher incidence of ASD symptoms in premutation cases with mild disability. Social disabilities, irritability, shyness and impulsive behaviours point out autism spectrum disorder due to fragile-X (Hall et al. 2008). It isn't repeated in this part as the difference is emphasized above. Psychosis may occur episodic in fragile-X and, it may be a challenge for differential diagnosis (Tassone et al. 1999).

Psychiatric disorders are common in premutation cases and the symptoms are milder than full mutation patients according to the reviews (Atbasoglu et al. 2013, Tassone et al. 2014). Anxiety disorder is the most common psychiatric disorder in fragile-X. Lifetime prevalence of social anxiety disorder is %18 and, panic disorder prevalence is %11,5 at the premutation carrier mothers of fragile-X children in a clinical study (Franke et al. 1998). Chronic psychosis is a rare case and, psychosis usually reveal after a stressful event or situation (Al-Semaan et al. 1999). Psychosis in fragile-X appear with hallucinations, delusions and, inappropriate affect (Khin et al. 1998). Dysmorphic face, family history and, clinical course are key points for the differentiation.

Considering fragile-X in the younger patients with atypical psychotic symptoms may reduce overdiagnosis of schizophrenia (Tassone et al. 1999). Absence of fragile-X patients at the family history can't exclude potential diagnosis though many premutation cases aren't diagnosed (Hall et al. 2008).

Velocardiofacial Syndrome

Velocardiofacial syndrome (VCFS) (22q11.2 deletion syndrome, DiGeorge syndrome) is rare with a prevalence of 1/5000 in the general population, but it is as common as 1-3% among individuals who present with the clinical picture of schizophrenia (Kobrynski and Sullivan 2007). Physical symptoms include congenital cardiac and vascular abnormalities, cleft palate or velopharyngeal insufficiency and dysmorphic faces (Murphy 2005). In addition to schizophrenia-like psychosis, VCFS can manifest with mood disorders and neurodevelopmental disorders including global intellectual delay, specific learning disabilities, attention deficit hyperactivity disorder and ASD (Murphy et al. 1999). Patients with a diagnosis of schizophrenia or individuals who present with a schizophrenia-like clinical picture should be assessed for VCFS when psychiatric symptoms are accompanied by the physical symptoms and the dysmorphic features of the syndrome (Shashi et al. 2010).

Twenty-five to thirty percent of the cases diagnosed with chromosomal analysis have delusions similar to those seen in paranoid schizophrenia. Impulsive behavior, problems in

social communication and blunted affect may also present in patients with VCFS (Murphy et al. 1999) as manifestations of the neurodevelopmental abnormalities that are part of the syndrome, and they may pose a diagnostic challenge with their similarity to the disorganized and negative symptoms of schizophrenia. Palatal abnormalities may not be readily apparent when the cleft is covered by palatal mucosa so that the manifestations are limited to dysphagia and cough spells resulting from a tendency to aspiration during feeding.

About 90 % of the cases are due to de novo mutations, therefore family history is not particularly relevant to the diagnosis of VCFS. Many of the neuropsychiatric symptoms are developmental and apparent from childhood onwards, although the likelihood of clinical detection largely depends on the severity of the cognitive and behavioral difficulties.

Despite the relatively high frequency of VCFS among adults who present with psychosis, many patients with a Psychotic Disorder Due to VCFS receive an official diagnosis of Schizophrenia (Shashi et al. 2010, Abbeduto et al. 2014). One reason for this could be lack of awareness and a tendency to favor comorbid diagnoses rather than seeking for global explanations for all clinical features. Another one, which is coincidental and independent from the nature of VCFS or schizophrenia is that psychosis in VCFS happened to be reported for the first time by geneticists (Lindsay et al. 1995), who were, naturally, not interested in the diagnostic principles of DSM (Murphy et al. 1999, Shashi et al. 2010). The name was not changed in consequent publications, so that today the official knowledge is that “6-30% of the cases with VCFS have schizophrenia” (Kobrynski and Sullivan 2007). This is a source of confusion as well as potential error in management, as we have no evidence indicating that the course and prognosis of the psychosis in VCFS is identical to the schizophrenia “proper”.

Patients meeting schizophrenia criteria with facial and palate anomalies should be considered for VCFS diagnosis (Shashi et al. 2010) in order to tailor management to the needs of the individual patients and to avoid the overdiagnosis of schizophrenia (Lindsay et al. 1995, Abbeduto et al. 2014).

Neurologic Disorders

Many neurologic disorders have behavioral manifestations. Epilepsy and multiple sclerosis (MS) are more likely than many others to initially present with psychiatric symptoms (Chwastiak and Ehde 2007) and to manifest at younger ages (Keshevan and Kaneko 2013).

MS is a demyelinating disease that might start at a young age, present with behavioral symptoms and cause significant disability (Ozdemir et al. 2014, Abbeduto et al. 2014, Kosmidis et al. 2010). In cases already diagnosed with MS psychiatric consultations are frequently needed (Sennou et al. 2014). In

addition to this, the psychiatrist is not uncommonly the first physician to assess a patient with MS, as behavioural symptoms at the initial presentation of MS are particularly common. In a study that reassessed a large epidemiologic cohort for MS with strict criteria, 16 % of the cases with definite MS were found to have initially presented with and treated for psychiatric symptoms. About half of the psychiatric symptom group had also reported complaints attributable to MS, and among them only one fifth had been identified as neurological (Skegg et al. 1988). Overlooking MS in the cases presenting with sensory or mood symptoms is more frequent than the cases initiating with motor features (Chwastiak and Ehde 2007, Lo Fermo et al. 2010).

Mood disorders are frequent and depression is the most common psychiatric disorder in MS. Mood symptoms may accompany the psychotic episodes due to MS. Delusions are the most frequent symptoms, while negative and other positive symptoms tend to be rare (Carta et al. 2014). Steroids administered during the exacerbations and interferon during the maintenance treatment of MS can trigger depression and less commonly psychosis (Sennou et al. 2014). Fewer exacerbations of the disorder predict less psychiatric morbidity, however evidence to any therapeutic action of maintenance treatment on psychosis is absent. In addition, psychosis is not necessarily more common during exacerbations in comparison to periods of remission. Antipsychotic treatment successfully control most cases of psychosis in MS, and treatment-resistant psychosis is rare. Drugs with less extrapyramidal side effects should be preferred (Lo Fermo et al. 2010). Antipsychotic treatment is known not to interfere with the course of the disorder (Carta et al. 2014).

Although the impact of delayed diagnosis on the course of MS is not specifically known, follow-up with the correct diagnosis of MS is crucial for the appropriate management of both neurologic and psychiatric symptoms (Sennou et al. 2014, Lo Fermo et al. 2010). Mood symptoms are of particular importance in the diagnosis of MS during the assessment of potential cases. Therefore MS should be considered in the assessment of young individuals who present with psychotic mood symptoms even when they do not completely fulfill the criteria for a manic episode (Feinstein 2007).

Distinguishing between epileptic and primary psychotic disorders is an important task in the practice of psychiatry. Both epilepsy and primary psychotic disorders are common and the psychotic symptoms in the two disorders may be very similar (Clancy et al. 2014). The symptoms of partial seizures may be the most difficult to distinguish from the schizophrenia spectrum. Mild and short-lived seizures that do not generalize are the most likely to be misidentified as manifestations of psychiatric illness (Hesdorffer et al. 2012), delaying appropriate treatment (Kanner 2009). The seizures that are most frequently misidentified as symptoms of schizophrenia are the

complex partial seizures of temporal lobe origin. Seizures that manifest as mood and dissociative symptoms and last for up to three minutes are not rare in temporal lobe epilepsy (TLE) (Hesdorffer et al. 2012). Prevalance of paranoid delusions encountered in TLE is about 20%. Electroencephalography EEG should be taken at the cases having agitation and dissociative symptoms which last for a short time (LaFrance et al. 2008).

Psychosis appeared in TLE is ictal psychosis which occur during the seizure. Phenytoin, carbamazepine, valproic acid can be used for complex partial seizures while phenobarbital and primidon shouldn't be chosen for their side effects on cognition and behaviour (Kanner 2009). Antiepileptic medicines usually improve psychotic symptoms while in some cases seizures can be stopped but psychosis persist (LaFrance et al. 2008). Even postictal seizures can be triggered by antiepileptic treatment. EEG pattern smooth down while mood symptoms and cognitive and, behavioral impariments occur in postictal seizures. Postictal seizures are also called forced normalisation (Trimble et al. 2010).

Antipsychotics are used in the cases in which psychosis resist to antiepileptics. Diminishing seizure threshold antipsychotics especially clorpromazine and clozapin shouldn't be used in TLE while quetiapine, risperidone, olanzapine, and haloperidol can be chosen (Hesdorffer et al. 2012, Trimble et al. 2010). Long time remission can be succeeded in a half of patients in TLE and prognosis is poor if seconder generalised seizures are included in clinical features (Hesdorffer et al. 2012). Surgery such as amigdalohypocampectomy, anterior temporal lobectomy, or removing intracranial mass can be used in TLE resistant to medical treatment (Trimble et al. 2010).

Endocrine Disorders

Thyroid disorders are relevant to the assessment of individuals with psychosis (Dayan and Panicker 2013). One reason for this is the reciprocal relationship between disorders of the thyroid gland and psychiatric disorders (Bunevicius ang Prange 2006). Another reason is the possible relationship between psychosis and both hypothyroidism and hyperthyroidism (Rizvi 2007). Thyroid dysfunction during the course of primary psychiatric disorders is not uncommon. Although thyroid disorders are associated with anxiety and depression more commonly than with psychosis per se, rapid fluctuations in thyroid function are also known to be a cause of psychosis. The initial manifestation of thyrotoxicosis can be a psychotic disorder, if not commonly (Rizvi 2007). Systemic manifestations of thyrotoxicosis are not helpful in suggesting the disorder as the cause of psychosis. Psychiatrists should therefore be familiar with all clinical features of thyroid dysfunction. Disorders of the thyroid gland are among the most frequent endocrine disorders. The hypothalamo-pituitary-thyroid (HPT) axis is of

central importance for mood regulation (Dayan and Panicker 2013). Auditory and visual halucinations and delusions may be found in psychosis due to hyperthyroidy (Bunevicius and Prange 2006) while mood fluctuation usually present with other symptoms (Radhakrishnan et al. 2013). Antipsychotic treatment is used until euthyroidy condition provided and maintenance antipsychotic treatment isn't needed almost all cases (Radhakrishnan et al. 2013, Brownlie et al. 2000). If needed first or second generation antipsychotics can be used (Radhakrishnan et al. 2013).

Thyroid disorders also influence on clinical course of psychosis. Putting the diagnosis is sometimes challenging due to mood fluctuations in thyroid disorders (Bunevicius and Prange 2006). Improving thyroid functions should be made in the hyperthyroidy patients with psychosis. Also it is necessary not to diagnose psychiatric disorders until the euthyroidy state (Brownlie et al. 2000) in which the symptoms need to be defined in details (Rizvi 2007, Brownlie et al. 2000).

Autoimmune Disorders

Autoimmune encephalopathy (AIE, called limbic encephalitis in the initial case reports) refers to a group of cognitive and behavioral symptoms caused by the interaction of systemic autoantibodies on the synaptic proteins (Benros et al. 2014). The typical clinical feature is that of delirium (encephalopathy), accompanied by seizures, mood symptoms and psychosis (Machado et al. 2012, Anderson and Barber 2008). The syndrome was described in 1960 as a rare paraneoplastic syndrome with a poor diagnosis in which antibodies found against over teratoma (Machado et al. 2012). It is later understood that AIE have been formed by many subtypes with several prognosis based on the antibodies that caused encephalitis (Kuppuswamy et al. 2014). The prognosis of AIE depend on many clinical factors and immunotherapy initiating at early phase is a main determinant on the treatment response (Machado et al. 2012). N-methyl D-aspartate (NMDA) receptors are approved as the most frequent antibodies causing AIE according to cases recognised up to now (Anderson and Barber 2008). Other antibodies causing AIE are glutamic acid decarboxylase (GAD) antibodies and antibodies against potassium channel antigens (Dalmau and Rosenfeld 2008).

The clinical features usually present in weeks or months rapidly (Dalmau and Rosenfeld 2008) and neurologic symptoms, especially confusion and mesiotemporal seizures have been found almost all cases of AIE (Kuppuswamy et al. 2014, Dalmau and Rosenfeld 2008). Family history of systemic and malignant diseases is more common in relatives of patients with AIE rather than schizophrenia (Meszaros et al. 2012). The core features of AIE are short time memory impairment, irritability, generalised anxiety while delusions and halucinations can be found in some cases (Anderson and Barber 2008). Due to the fact that AIE was commonly diagnosed

by neurologist, psychiatric symptoms have been defined with general terms such as behavioural change, psychosis or remarked as psychiatric features in case studies (Kuppuswamy et al. 2014). AIE should be considered in cases presenting with neurologic features with a rapid onset (Dalmau et al. 2007). Future researches should aim to describe psychiatric features of AIE cases in details.

SLE, in which one diagnostic criteria is about central nervous system regarding psychosis or epilepsy is a autoimmune disorder presenting with psychiatric symptoms (Meszaros et al. 2012). Psychosis usually occur before or during the diagnosis and it is rare after the initial years (Pego-Reigosa ve Isenberg 2008). Psychosis prevalence vary in a wide range (1-10%) and grandiose thoughts and delusions, auditory and visual hallucinations are frequent features in SLE patients with psychosis. The most common physical symptoms found in SLE patients during psychosis are dermatologic lesions arthritis (Pego-Reigosa and Isenberg 2008).

Steroid treatments which were commonly used in SLE patients usually cause improvement in the autoimmune disease and psychotic symptoms (Nayak et al. 2012). But still clinicians should be aware of worsening of psychotic symptoms as a side effect of steroid treatment. In cases with psychosis resistant to steroids antipsychotics can be used. Selection of the antipsychotic should be made considering side effects of each drug (Appenzeller et al. 2008). In young female patients having psychosis and systemic signs (especially dermatologic lesions) at the same time SLE should be considered (Meszaros et al. 2012).

Metabolic Disorders

Psychosis can be seen in mild forms of metachromatic locodystrophia, Niemann-Pick type-C, and Wilson disease among metabolic disorders (Black et al. 2003, Coffey et al. 2013). Severe forms of metachromatic locodystrophia and Niemann-Pick type-C die at early ages but very rarely seen mild forms

Table 2. Key Points on Differential Diagnosis of Schizophrenia: Neurodevelopmental Disorders and Psychotic Disorders Due to Other Medical Conditions

Velokardiofacial Syndrome (VCFS)	Congenital cardiac and vascular abnormalities, cleft palate or velopharyngeal insufficiency and dysmorphic faces are common features. Twenty-five to thirty percent of the cases diagnosed with chromosomal analysis have delusions similar to those seen in paranoid schizophrenia. Patients meeting schizophrenia criteria with facial and palate anomalies should be considered for VCFS diagnosis.
Fragile-X Syndrome	Individuals with a premutation usually have normal intelligence, although they might present with mild intellectual disability or an atypical neurodevelopment. Social disabilities, irritability, shameness and impulsive behaviours point out autism spectrum disorder due to fragile-X. Chronic psychosis is rare and, psychosis usually reveal after a stressful event or situation. Dysmorphic face, family history and, clinical course are key points for the differentiation.
Multiple Sclerosis (MS)	In cases already diagnosed with MS psychiatric consultations are frequently needed. Delusions are the most frequent symptoms, while negative and other positive symptoms tend to be rare. Mood symptoms are of particular importance in the diagnosis of MS during the assessment of potential cases. Therefore MS should be considered in the assessment of young individuals who present with psychotic mood symptoms even when they do not completely fulfill the criteria for a manic episode.
Temporal Lobe Epilepsy (TLE)	The symptoms of partial seizures may be the most difficult to distinguish from the schizophrenia spectrum. Mild and short-lived seizures that do not generalize are the most likely to be misidentified as manifestations of psychiatric illness. Prevalance of paranoid delusions encountered in TLE is about 20%. Seizures up to 3 minutes long including mood and dissociative symptoms point out TLE. Electroencephalography should be taken at the cases having agitation and dissociative symptoms which last for a short time.
Autoimmune encephalopathies (AIE)	The typical clinical feature is that of delirium (encephalopathy), accompanied by seizures, mood symptoms and psychosis. Confusion and mesiotemporal seizures have been found almost all cases of AIE. Neurologic symptoms, especially confusion and mesiotemporal seizures have been found almost all cases of AIE. The core features of AIE are short time memory impairment, irritability, generalised anxiety while delusions and hallucinations can be found in some cases. AIE should be considered in cases presenting with neurologic features with a rapid onset.
Thyroid Function Disorders	Although thyroid disorders are associated with anxiety and depression more commonly than with psychosis per se, rapid fluctuations in thyroid function are also known to be a cause of psychosis. The initial manifestation of thyrotoxicosis can be a psychotic disorder, if not commonly. Systemic manifestations of thyrotoxicosis are not helpful in suggesting the disorder as the cause of psychosis. Auditory and visual hallucinations and delusions may be found in psychosis due to hyperthyroid while mood fluctuation usually present with other symptoms. Improving thyroid functions should be made in the hyperthyroid patients with psychosis. Also it is necessary not to diagnose psychiatric disorders until the euthyroid state.
Systemic Lupus Erytematozus (SLE)	Psychosis prevalence varies in a wide range (1-10%) and, grandiose thoughts and delusions, auditory and visual hallucinations are frequent features in SLE patients with psychosis. The most common physical symptoms found in SLE patients during psychosis are dermatologic lesions and arthritis.
Wilson Disease (WD)	Wilson disease is a more frequent metabolic disease in our clinical practice. Delusions and formal thought disorder are most frequent psychotic symptoms of WD. Mood disorders accompany psychosis in many cases. Besides euphoria, sexual preoccupations, catatonia and, desorganisation are other psychiatric symptoms found in WD. WD should be considered in cases presenting mood features, psychiatric symptoms, and neurologic features (especially movement disorder) together.

may present with social disabilities, aggression and amnesia (Black et al. 2003). Also paranoid psychosis and hallucinations can be found in some cases. Epileptic seizures and dyskinesia are typical neurologic findings observed nearly all of cases (Gieselmann and Krägeloh-Mann 2010, Black et al 2003). If psychosis and neurological symptoms coexist in a patient, clinicians should be kept in mind that metabolic disorders could be the cause of the situation. And if clinical signs are well match a Magnetic Resonans Imaging (MRI) should be performed (Gieselmann and Krägeloh-Mann 2010)

Wilson disease (WD) is a more frequent metabolic disease in our clinical practice. Even it isn't a frequent cause of psychosis, it should be kept in mind at psychotic cases presenting with systemic symptoms (Demily and Sedel 2014). WD which copper accumulates in liver and basal ganglions usually begins with neurological symptoms (Coffey et al. 2013). But there are still patients having psychotic symptoms at the beginning of the disease and various psychiatric features can be found in these patients (Demily and Sedel 2014).

Tremor, dystonia, gait disturbance, and seizures are neurologic features seen in WD (Zimbrea and Schilsky 2014). Misdiagnosis is fewer in cases initiating with neurological features than psychiatric symptoms. According to this in cases presenting with psychiatric symptoms neurological signs could be unclear (Sunderland et al. 2008) and the diagnosis may delay (Coffey et al. 2013). Prevalance of psychosis in WD is about 2-10% (Zimbrea and Schilsky 2014). Delusions and formal thought disorder are most frequent psychotic symptoms (Zimbrea and Schilsky 2014). Mood disorders accompany psychosis in many cases (Demily and Sedel 2014). Euphoria, sexual preoccupations, catatonia and, disorganisation are other psychiatric symptoms (Zimbrea and Schilsky 2014). WD should be considered in cases presenting together with mood features, psychiatric symptoms, and neurologic features (especially movement disorder) (Svetel et al. 2009).

CONCLUSIONS

Although schizophrenia is a descriptive syndrome neurodevelopmental and medical disorders causing psychosis aren't routinely considered in the differential diagnosis of a patient presenting with symptoms of psychosis or disorganized thought or behavior (von Gontard et al. 2013). Thus this approval cause overdiagnosis of schizophrenia and incorrect treatment of the patient (Atbaşoğlu and Gülöksüz 2013). As there are many medical and neurodevelopmental disorders mimicing schizophrenia it wasn't possible to include all of them. So in this review it was aimed to discuss autism spectrum disorder and intellectual developmental disorder among neurodevelopmental disorders and, as well as neuropsychiatric syndromes based on our clinical experience, their higher prevalence in the published case series, higher likelihood of a

psychiatric presentation and the potential harm of misdiagnosis. To make differential diagnosis is essential due to stigmatization of schizophrenia and, to appropriate treatments needed in earlier ages. Finally, schizophrenia is a heterogenous syndrome which should be diagnosed by excluding all possible reasons.

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