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An overview of medical risk factors for childhood psychosis: Implications for research and treatment

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ABSTRACT

Objective: Psychotic disorders in childhood and early adolescence often progress to chronic schizophrenia, but in many cases there are diagnosable medical and genetic causes or risk factors. We reviewed our clinical experience and the relevant literature to identify these factors and to define their clinical features, appropriate work-up and treatment.

Method: We reviewed the results of comprehensive medical evaluations of 160 psychotic children and adolescents in our center. We also searched the Medline database (January 1994 to December 2015) with the following keywords and combinations: early onset schizophrenia, childhood onset schizophrenia, early onset psychosis, first episode psychosis, inborn errors of metabolism (IEM), genetic syndrome, copy number variants, autoimmune disorders, endocrine diseases, nutritional deficiencies, central nervous system infections, movement disorders, and epilepsy.

Results: In our center, 12.5% of cases had medical disorders likely to be contributing to psychosis. Based on 66 relevant papers and our experience, we describe the clinical features of multiple genetic syndromes, IEM, and autoimmune, neurological, endocrinological and nutritional disorders that increase the risk of psychotic disorders in childhood and adolescence. We propose an algorithm for systematic laboratory evaluation, informed by clinical examination, emphasizing common and/or treatable factors.

Conclusions: In children and early adolescents with psychotic disorders, systematic medical work-up is warranted to identify medical and genetic factors. Not every rare cause can be worked up, thus careful clinical examinations are required to detect medical, neurological and genetic signs. Comprehensive medical evaluation can detect treatable diseases among cases of early-onset psychosis.

1. Introduction

Psychotic symptoms are observed in patients with many different medical, neurological and genetic diseases in children and adolescents, although the frequency and clinical characteristics of these associations are not well-studied (Trifiletti and Packard, 1999). Psychotic symptoms can present as part of a syndrome that includes physical symptoms (e.g., Prader-Willi syndrome), or they can predominate at the onset of progressive systemic conditions (e.g., systemic lupus erythematosus). The work-up of children presenting with psychotic disorders is challenging because of the large number of possible organic factors, many of them quite rare – Benjamin et al. (2013) reported 60 congenital and acquired illnesses that can present as an organic psychosis in youth – and because of the variability of the mode of onset and course of some of the underlying diseases.

Many children have delusional or hallucinatory experiences that remit without evolving into clinically significant disorders (Linscott and van Os, 2013; Poulton et al., 2000; Fusar-Poli, et al., 2016); little is known about the contribution of medical disorders to these phenomena, although clinical experience suggests that they are sometimes related to diverse neurodevelopmental problems. We focus here on children and early adolescents with psychotic symptoms as a major component of their presentation for clinical treatment, leading to diagnoses in the schizophrenia spectrum (schizophrenia, schizoaffective disorder,

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schizophreniform disorder, psychotic disorders not otherwise specified, major depression with psychotic features). The clinical dilemma is when and how to carry out an appropriate medical evaluation, given that it is not feasible to test for every possible very rare cause. Perhaps because of this dilemma, screening is currently often limited to EEG and brain neuroimaging (to search for epilepsy, brain tumors or major vascular alterations) and detection of abused substances (Adams et al., 1996; McKay et al., 2006; Williams et al., 2014).

There are several compelling reasons to prioritize medical evaluation for these patients. First, organic factors are relatively common – we identified such factors in 20% of children and adolescents with the syndrome of catatonia (Consoli et al., 2012) (usually including psychotic symptoms), and in at least 12.5% of all referrals to our tertiary care referral center (see Results). Second, specific and sometimes curative treatments are available for some disorders, e.g., immunomodulatory treatment of *anti*-NMDA encephalitis, or treatment of inherited errors of metabolism (IEM) which can rarely present with predominanly psychiatric rather than neurological signs (Bonnot et al., 2014). Third, even where treatment is not available, diagnosis may have important implications for aspects of the patient's care, e.g., the many medical and neurological comorbidities of 22q11.2 deletion syndrome and other genomic copy number variants (CNVs). Fourth, increased knowledge about the associations between psychotic and medical disorders is likely to focus attention on the need for research into biological mechanisms underlying those associations, e.g., the occurrence of intellectual disability, autism and epilepsy among individuals who carry a set of of CNVs that also confer a high risk of psychotic disorders (Rees et al., 2014).

Here we review genetic syndromes, IEM, and autoimmune, neurological, endocrinological and nutritional disorders that can present with psychotic symptoms. We also propose a practical algorithm for evaluating organic factors in children and early adolescents with psychotic disorders, focusing on the most treatable conditions.

2. Materials and methods

Several Medline searches were performed to review all of the relevant literature from January 1994 to December 2015 the following keywords were used: *early onset schizophrenia*, *childhood onset schizophrenia*, *early onset psychosis*, *first episode psychosis* (FEP), *inborn errors of metabolism* (IEM), *genetic syndrome*, *copy number variants* (CNVs), *autoimmune disorders*, *endocrine diseases*, *nutritional deficiencies*, *CNS infections*, *movement disorders*, and *epilepsy*. We selected studies or reviews published in English that included only human subjects who received a diagnosis of schizophrenia and other schizophrenia spectrum disorders according to the DSM [(DSM); APA, 2013] or the International Classification of Disease (WHO, 1993). From the 1160 papers retrieved from the database searches, only 46 papers were judged suitable for the review. In the present search, we excluded literature regarding brain tumors and substance abuse, because these medical conditions are actively screened in most emergency and hospital departments.

The primary reasons for excluding certain publications were as follows: editorials, annotations, commentaries and other papers that did not report on clinical findings ($N = 91$); focus on bipolarity, adolescence, other clinical areas, or animal models ($N = 349$); focus on adult patients information was missing regarding age range or number of patients ($N = 673$). Additional studies were reviewed using cross-referencing within retained papers. In the case of duplicate publications the data from the sample were included only once. The analysis included both retrospective and prospective studies. Consequently, the current review is based on 66 reports. The primary focus of the selected studies was as follows: IEM ($N = 9$), genetic syndromes and most significant CNVs ($N = 17$), auto-immune disorders ($N = 15$), endocrine diseases ($N = 4$), nutritional deficiencies ($N = 2$), CNS infections ($N = 6$), and other neurological diseases ($N = 13$). The information on each syndrome in Tables 1–3 is drawn from clinical experience, the referenced papers, Online Inheritance in Man (http://www.omim.org/), and additional sources (Fernandes et al., 2006; Whitford et al., 2012; Yolken and Torrey, 2008).

We also report below on the genetic syndromes and organic diseases that were diagnosed in 160 children and adolescents evaluated by our group at Pitié-Salpetrière Hospital (Paris, France) between 2009–2016 who initially received psychiatric diagnoses in the schizophrenia spectrum.

3. Results

3.1. Clinical experience in our center

Between 2009–2016, our center clinically evaluated 160 children and adolescents with psychotic symptoms who received schizophrenia spectrum diagnoses based on their psychiatric features. A comprehensive medical workup was completed whenever possible, depending on presenting features. We detected nine CNVs with well-documented associations with schizophrenia (7 with 22q11.2 deletions, 1 with 16p11.2 duplication and 1 with 16p11.2 deletion); four other genetic syndromes (Steinert myotonia; Ondine syndrome; Rubinstein-Taybi syndrome [22q13 deletion], and GLUT1 deficiency syndrome); three autoimmune disorders (one CNS lupus; and two cases with catatonic features and EEG findings consistent with encephalopathy, presumed to be autoimmune disorders because they remitted with plasmaphoresis); two brain malformations (cavernomas; rhomboencephalosynapsis); and two IEMs (Niemann-Pick type C; Hunter syndrome). Thus 20 patients (12.5% of the cohort) were shown to have organic factors that were likely to be causing or contributing to their psychotic disorder. We would note that the observed rate of 22q11.2 deletions is likely to be an overestimate of the true prevalence in psychotic children, because our center includes a tertiary care clinic for rare diseases where cases with suspected features of 22q DS are likely to be referred. Most of the other cases were not known to have organic diagnoses prior to evaluation in our department.

Some of the disorders that we detected are extremely rare. If several cohorts of similar size were comprehensively screened, it is likely that they would include different subsets of the rarer disorders that can present with psychosis. Therefore, we review here the wide range of disorders that should be considered in the evaluation of psychotic children and adolescents.

3.2. Inborn errors of metabolism (IEMs)

An IEM is a physiological defect or malfunction with pathological consequences for a biochemical pathway, due to full or partial loss of gene function due to mutation. IEMs are usually autosomal recessively inherited enzyme defects; thus the patient will have inherited a mutated gene from each parent, so that heterozygous “carrier” status can be common while homozygous disease status remains rare. In some cases, the disease may be dominant (requiring only one copy of the mutated gene and partial loss of function) or sex-linked (the mutated gene is carried on a sex chromosome and thus is observed primarily in males, who have only one copy of that gene). Multiple diverse pathways are affected by IEMs, with very different pathophysiologies and clinical features.

IEMs that have an impact on the central nervous system can present with psychosis, depression, anxiety or mania (Bonnot et al., 2014; Fernandes et al., 2006; Nia, 2014; Staretz-Chacham et al., 2010; Walterfang et al., 2013). For each IEM, early clinical manifestations can be variable. Psychiatric symptoms may be present early in the course of illness during childhood, before neurological symptoms occur (Sedel et al., 2007). Clues to the possible presence of an IEM include a history of severe hypotonia and/or delayed growth, dysmorphic features, nausea, diarrhea and other gastro-intestinal signs, catatonia and

cognitive decline. Some IEMs are reversible or treatable with dietary modification, enzyme replacement and other biochemical strategies, making them particularly gratifying to detect; on the other hand, in our clinical experience, these patients seem to be particularly sensitive to the adverse effects of antipsychotic drugs.

Table 1 summarizes the IEMs that are reported to be associated with psychotic symptoms in children. Sedel et al. (2007) proposed that it is clinically useful to group IEMs in relation to onset and course: 1) clinical emergencies, characterized by an acute episode followed by recurring episodes of confusion (e.g., urea cycle disorders and porphyria); 2) chronic treatable diseases (e.g., Wilson disease and some lysosomal storage disorders); 3) chronic less treatable diseases (e.g., homocystinurias and late onset metachromatic leukodystrophy). It has been suggested that IEMs should be considered in patients with atypical psychiatric features (Anglin et al., 2012; Dejean de la Batie et al., 2014; Nia, 2014; Sedel et al., 2007; Szakszon et al., 2014; Hendriksz et al., 2017). However, childhood psychotic disorders in general may have more "atypical" psychotic features compared with adult schizophrenia (Cutting, 1987), including visual hallucinations (David et al., 2011), disorganized signs, catatonia (Consoli et al., 2012) and treatment resistance (David et al., 2013). Metabolic work-up might be particularly useful in patients with psychosis in combination with autism spectrum disorders (ASD), developmental delay and intellectual disability (ID) (Cleary and Green, 2005; Gadow, 2013; van Karnebeek and Stockler, 2012). The presentation of Niemann-Pick Type C is particularly variable, and is more likely to present with psychosis in adolescents and young adults, so it is often missed without screening (Hendriksz et al., 2017).

Table 1
Inborn errors of metabolism (IEM) associated with psychosis in children.

IEM (OMIM)	Gene (*mode of inheritance*)	Major features (other than psychosis)	Treatment
α- and β-mannosidosis (248500, 248510), oligosaccharidosis	MAN2B1 (*AR* MANBA (*AR*))	Immune deficiency, skeletal dysplasia, hepatosplenomegaly, cognitive difficulties, ataxia	Hematopietic stem cell transplantation
Acute porphyrias (176000, 176200, 121300, 612740), disorders of heme biosynthesis	HMBS, PPOX, CPOX (*AD*) PBGS (*AR*)	Acute attacks with neurovisceral symptoms (abdominal pain, neuropathy); anemia; hypertension, tachycardia, fine tremors; nausea, vomiting, constipation or diarrhea	Mild attacks: high carbohydrate diet, haem arginate; severe attacks: emergency admission
CerebroTendinous Xanthomatosis (213700), disorders of bile acid synthesis	CYP27A1 (*AR*)	Chronic diarrhea, ataxia, spastic paraparesis, peripheral neuropathy, parkinsonism, bilateral catarats, achilles (or other) tendon xanthomas	Chenodeoxycholic acid remplacement therapy
Hyperhomocysteinemia (277400, 277410, 236270, 277380, 250940), disorders of cobalamin and folate transport and metabolism	MMACHC, MMADHC, MTRR, LMBRD1, MTR (*AR*)	Seizures, ataxia, pyramidal signs, strokes, peripheral neuropathy, cerebral atrophy, megaloblastic anemia, thromboembolic events (lens dislocation and Marfan-like appearance in Cystathionine β-synthase deficiency)	Hydroxycobalamin (or cyanocobalamin, or methylcobalamin), oral betaine
Krabbe (245200), disorders of sphingolipid metabolism	GALC (*AR*)	Change in gait (cerebellar ataxia), paraplegia, hemiparesis, dysarthria, optic neuropathy, peripheral neuropathy, pes cavus	Hematopietic stem cell transplantation
Metachromatic leukodystrophy – late onset (250100), disorders of sphingolipid metabolism	ARSA (*AR*)	Seizures, abnormal movements, cognitive impairment or dementia	Hematopietic stem cell transplantation
Propionic acidemia – late onset (606054), branched-chain organic aciduria	PCCA, PCCB (*AR*)	Chronic vomiting, protein intolerance, hypotonia, abnormal movements, cardiomiopathy, cognitive regression	Dietary protein restriction; L-carnitine and biotin supplementation
Ornithine transcarbamylase deficiency – late onset (311250), urea cycle	OTC (*recessive X-linked*)	Vomiting, dyspnea, lethargy, ataxia, change in speech, seizures, poor coordination, stroke-like episodes, irritability, learning difficulties, ADHD-like signs	Dietary protein restriction; ammonul
Maple syrup urine disease (248600), branched-chain organic aciduria (acute intermittent late onset form)	BCKDHA, BCKDHB (*AR*)	Lethargy, ataxia, focal neurological signs as hemiplegia, hemianopsia, signs of cerebral edema	Dietary restriction of branched amino-acids; judicious supplementation with isoleucine and valine
Mucopolysaccharidoses type IIIa-d (252900,252920, 252930, 252940), lysosomal	SGSH, NAGLU, HGSNAT, GNS (*AR*)	Developmental delay (especially affecting speech), hyperactivity, severe sleep disturbances, slow cognitive deterioration after 10 years old, seizures, retinitis pigmentosa	Hematopietic stem cell transplantation
Neurroferritinopathy (606159), brain iron accumulation	FTL (*AD*)	Chorea or dystonia (often asymmetry), action-specific dystonia with dysarthrophonia; cognitive impairment	Symptomatic
Niemann-Pick type C (257220), disorders of sphingolipid metabolism	NPC1, NPC2 (*AR*)	Abnormal movements, ataxia, seizures, vertical supranuclear ophtalmoplegia, hepatosplenomegaly	Miglustat
Wilson (277900), disorder in the transport of copper	ATP7B (*AR*)	Abnormal movements, dysarthria, tremor, rigidity, drooling and swallowing problems, jaundice, hepatitis, cirrhosis, Kayser-Fleischer rings	Chelating agents
X-Adrenoleukodystrophy (300100)	ABCD1 (*recessive X-linked*)	Adrenal insufficiency, weakness of legs, sphincterial impairment, impotence, hyperactive signs, academic failure, impaired auditory and visual discriminatory	Hematopietic stem cell transplantation Dietary restriction of saturated VLCFA

Abbreviations: ABCD1, ATP-binding cassette, sub-family D, member 1; AD: autosomal dominant.; AR: autosomal recessive; ARSA, arylsulfatase A; ATP7B, ATPase copper transporting beta; BCKDHA, branched chain keto acid dehydrogenase E1, alpha polypeptide; BCKDHB, branched chain keto acid dehydrogenase E1, beta polypeptide; C2, Niemann-Pick disease, type C2; CLN, ceroid-lipofuscinosis; CPOX, coproporphyrinogen oxidase; CYP27A1, cytochrome P450 family 27 subfamily A member 1; DBT, dihydrolipoamide branched-chain transacylase; FTL, ferritin, light peptide; GALC, galactosylceramidase; GNS, glucosamine (*N*-acetyl)-6-sulfatase; HGSNAT, heparan-alpha-glucosaminide N acetyltransferase; HMBS, hidroxymethylbilane synthase; LMBRD1, LMBR1 domain-containing protein 1; MAN2B1, mannosidase, alpha, class 2B, member 1; MANBA, mannosidase, beta A, lysosomal; MMACHC, methylmalonic aciduria (cobalamin deficiency) CblC type, with homocystinuria; MMADHC, methylmalonic aciduria (cobalamin deficiency) CblD type, with homocystinuria; MTR, 5-methyltetrahydrofolate-homocysteine *S*-methyltransferase; MTRR, 5-methyltetrahydrofolate-homocysteine methyltransferase reductase; NAGLU, *N*-acetyl-alpha-glucosaminidase; NPC1, Niemann-Pick disease, type C1; OTC, ornithine carbamoyltransferase; PBGS, porphobilinogen synthase; PCCA, propionyl CoA carboxylase, alpha polypeptide; PCCB, propionyl CoA carboxylase beta subunit; PPOX, protoporphyrinogen oxidase; SGSH, N-sulfoglucosamine sulfohydrolase; VLCFA, very long-chain fatty acids.

3.3. Genetic syndromes

Table 2 summarizes genetic disorders and syndromes that are most commonly associated with psychotic disorders. These include four classical chromosomal anomalies that produce childhood genetic disorders (Cassidy and Driscoll, 2009; Eckstrand et al., 2008; Letort and Gonzalez-Alegre, 2013; Ribai et al., 2007; Soni et al., 2008): Juvenile-Onset Huntington's Disease (defined as onset below age 20, seen in 5% or more of cases), Prader-Willi syndrome, Turner Syndrome and (less commonly) Klinefelter Syndrome. The remaining syndromes in the table are due to structural genomic changes known as copy number variants (CNVs) – deletions or duplications of DNA segments. The association of each of these CNVs with increased risk of schizophrenia has been demonstrated in large genome-wide association study (GWAS) analyses using single nucleotide polymorphism (SNP) microarrays (Bassett et al., 2010; International Schizophrenia Consortium, 2008; Kirov et al., 2009; Levinson et al., 2011; McCarthy et al., 2009; Rees et al., 2014; Stefansson et al., 2008). These studies used large cohorts of mostly adult patients, because the rarity of psychosis in childhood has made it difficult to collect large samples.

Studies to date suggest that 1–2% of schizophrenia cases carry CNVs that have been clearly associated with elevated schizophrenia risk, and that an additional proportion of cases carry large CNVs that are too rare to permit statistical association testing, some of which are likely to contribute to risk. The NIMH childhood-onset schizophrenia cohort has a higher frequency of these large and very rare CNVs than is observed in adult cohorts (Walsh et al., 2008), and also of CNVs with known association with SCZ risk, such as those at 22q11.2, 2p25.3, 15q13.3, and 16p11.2 (Ahn et al., 2014). Shown are the CNVs with the strongest statistical support for association with schizophrenia risk. The highest odds ratios (30-fold or greater increased risk in carriers) have been observed for deletions in chromosomes 22q11.2 and 3q29, while approximately ten-fold increases in risk have been reported for deletions of 1q21, 2p16.3 (neurexin-1) and 15q13.3 and duplications of 16p11.2 (Bassett et al., 2010; Levinson et al., 2011). Deletions in 15q11.2, while more common, produce the smallest increase in risk (two- to three-fold). Most of these CNVs are also associated with autism, epilepsy and intellectual disability, suggesting an overlap in the mechanisms that contribute to the risks of these disorders (Rees et al., 2014).

The most frequent genetic syndrome implicated in schizophrenia is 22q11.2 deletion syndrome (DS). Population estimates of its incidence are in the range of 4300–7000 live births, based on clinical detection during infancy (Botto et al., 2003; Goodship et al., 1998; Oskarsdottir et al., 2004), although these must be underestimates given that some cases without early symptomatic cardiac symptoms or developmental delay may be diagnosed later or not at all (reviewed in McDonald-McGinn et al., 2015). The best estimate of the rate of 22q11.2 deletions in large SCZ cohorts is approximately 0.3% in European-ancestry cases (Rees et al., 2014). Approximately 20% to 25% of individuals with 22q11.2 microdeletion develop schizophrenia (Green et al., 2009). Psychiatric phenotypes are also seen in children with 22q11.2 deletions, including schizophrenia spectrum disorders (10% of adolescents in a

Table 2
Genetic syndromes implicated in childhood psychotic disorders.

Syndrome (OMIM), mode of inheritance, frequency	Major features (other than psychosis)
Juvenile Huntington Disease (143100) Elongated CAG repeat (>36) in huntingtin gene (4p16.3). 1–9 CE/1,000,000 (pop), 6% of HD cases	Initial: academic difficulties, subtle changes in handwriting, clumsiness, choreic movements, aggression/disinhibition, apathy, suicide. Subsequent: speech difficulties, seizures, rigidity, tremor, myoclonus, cognitive decline, severe generalized motor disturbance, physical dependence.
Klinefelter 47, XXY aneuploidy Not inherited. 6–9/10000 (pop)	Childhood: long legs. After puberty: small firm testes; symptoms of androgen deficiency; average height; painless bilateral gynaecomastia (50%); insulin resistance or diabetes; deep vein thrombosis; seizures; tremor; hypotonia. Psychiatric: psychomotor delay (language > motor), academic difficulties, ADHD.
Prader Willi (176270) Heterogenous mutations in critical region 15q11-q13. Not inherited. 1–9/10,000	Neonatal/infancy: hypothalamic-pituitary abnormalities; hypotonia; failure to thrive; epilepsy. Childhood: morbid obesity; eye problems; scoliosis; hypogonadism; small hands/feet; developmental delay. Psychiatric: ASD; hyperphagia; hoarding; mild-moderate ID; learning and behavioral problems.
Turner Complete/partial absence of an X chromosome, Not inherited. 1–5/10,000 (pop)	Medical: short stature; scoliosis; osteoporosis; premature ovarian failure; hypothyroidism; skeletal malformations; heart defects (coarctation of the aorta, bicuspid aortic valve); horseshoe malformation of kidney; lymphoedema. Dysmorphia: webbed neck; low posterior hairline; lymphedema of hands and feet. Psychiatric: developmental delays;nonverbal learning disabilities; behavioral problems; psychosis.
1q21.1 deletion (612474) 0.17[a] 1q21.1 duplication (612475) 0.13[a]	Variable. Psychomotor delay; ID; ASD; microcephaly (del); macrocephaly (dup); seizures; ADHD.
NRXN1 deletion (614332). Deletion of exons of neurexin-1 gene. 0.18[a]	Variable. Psychomotor delay, seizures, ID, ASD, ADHD, learning disorder, multiple congenital anomalies (heart and skeletal)
3q29 deletion (609425) 0.082[a]	Variable. ID, seizures, gait ataxia, ASD, learning disorder, schizophrenia
Williams-Beuren region (7q11.23) duplication (609757) 0.066[a]	Variable. Hypotonia; seizures; developmental delay; ID; speech and language delay; visuospatial difficulties; ASD; ADHD.
Prader-Willi/Angelman (PWS/AS) duplication (608636) (15q11-q13). 0.083[a]	Variable. Hypotonia; seizures; global developmental delay; ID; ASD; anomalies at brain MRI; behavioral problems; ADHD; frank psychosis
15q11.2 deletion (615656) Deletion in PWS/AS region. 0.59[a]	Variable. Hypotonia, ataxia; seizures; speech or motor delay; ID; ADHD; coordination disorder; learning disorders; ASD; behavioral problems.
15q13.3 deletion (612001) 0.14[a]	Variable. Developmental delay; ASD; ID; variable dysmorphia; seizures; ADHD; learning disability; coordination disorders.
16p11.2 duplication (614671). 0.35[a]	Variable. Developmental delay; ID; ASD; ADHD; behavioral and learning problems.
16p13.11 duplication (613458). 0.31[a]	Variable. Developmental delay, ID, ASD.
22q11.2 deletion syndrome 0.29[a]	Variable. Medical: Conotruncal anomalies; palatal anomalies; feeding/swallowing difficulties; hypoparathyroidism (±hypocalcemia); mild facial dysmorphia. Psychiatric: Developmental delay (motor and language); learning problems (verbal; mathematic skills); ASD; rarely ID; ADHD; anxiety; schizophrenia in 20–30%.

Listed are major genetic syndromes in alphabetical order and genomic copy number variants (CNVs) in chromosomal order, associated with increased risk of psychotic disorders.
ASD, autism spectrum disorder; ID, intellectual disability; ADHD, attention deficit with hyperactivity disorder.
Population frequencies are shown for syndromes.

[a] For CNVs, frequency shown is that reported in cases by Rees et al. (2014) in a meta-analysis of genetic samples of 12,029–21,269 individuals with schizophrenia vs. controls ($N = 24{,}851$–$81{,}821$).

Table 3
Autoimmune and infectious encephalitides associated with childhood psychosis.

Disease	Major presenting signs	Diagnostic tests	Treatment(s)
Anti-NMDA receptor encephalitis	Prodrome: fever, headache, nausea, vomiting, diarrhea, upper respiratory signs. Onset: anxiety, agitation, frank psychosis. Progression: seizures, abnormal movements, aphasia/other language disorders, catatonia, behavioral changes, sleep problems, cognitive dysfunction, confusion. Other: autonomic instability.	LP: elevated lymphocytes; oligoclonal bands; Ab to NR1 subunit of NMDA receptor.	First-line: corticosteroids + i.v. ImmunoGlobulin (IVIG), plasma exchange (less safe in children). Second-line: immunosuppressive agents (rituximab, cyclophosphamide)
Neuro-psychiatric systemic lupus erythematosus (NPSLE)	Malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis (pleuritis), hematologic manifestations (leukopenia, lymphopenia, hemolytic anemia, thrombocytopenia), renal involvement with proteinuria, seizures, frank psychosis.	ANA; ANA subtypes (*anti*-Sm; *anti*-SSA; *anti*-SSB; anti-RNP); *anti*-dsDNA Ab; antiphospholipid Ab; low complement (C3, C4, CH50); anticardiolipin Ab.	Hydroxychloroquine, corticosteroids, immunosuppressive agents (azathioprine, mycophenolate, methotrexate, cyclophosphamide, rituximab).
Encephalopathy associated with autoimmune thyroid diseases (EAATD)	Seizures, stroke-like episodes, optic neuritis, atypical headaches, ataxia, lack of coordination, dysarthria, tremors, restlessness, weight gain, mixedema, changes in hair and skin. Behavioral changes, academic difficulties, cognitive impairment, psychosis, hypersexuality. 22% of cases present in childhood.	EEG (encephalopathy); LP (elevated protein and lymphocytes); serum Ab (*anti*-TPO, *anti*-TSH receptor, *anti*-TG, *anti*-alpha-enolase, antinuclear, antigliadin, antineuronal).	Methylprednisolone, L-thyroxine. Thyroidectomy in some cases.
Lyme disease	Stage 1: fever, headache, muscle/joint pain, stiff neck. Stage 2: meningitis, encephalitis, cranial neuritis, radiculo-neuropathies, muscle paralysis/weakness, palpitations, chest pain, cognitive impairment, sleep problems, depression, psychosis. Stage 3: abnormal movements, dementia, speech problems.	Serum IgM (*anti-Borrelia burgdorferi*). ECG, brain MRI, LP.	Antibiotic therapy (i.v., if neurological involvement).
Toxoplasmosis	Early congenital: intracranial calcifications, mental retardation, seizures, retinal damage. Later: lower IQ, psychosis, catatonia, confusion, seizures.	Ab (IgM and IgG); cranial CT scan (calcifications); brain MRI; LP.	Antibiotic therapy.
Viral encephalitis[a]	Fever, seizures, behavioral and cognitive changes, hallucinations, dysesthesia, paresthesia, disorientation, confusion, speech or hearing dysfunctions, double vision, muscle weakness, partial paralysis (arms, legs, sudden dementia, seizures, memory loss.)	Neurological examination; brain CT scan and MRI; serologic analysis of blood or CSF, followed by PCR	Antiviral therapy appropriate for the specific virus; corticosteroids and antiepileptic treatment in some cases.

Abbreviations: Ab, antibodies; ANA, antinuclear antibodies; C3, complement component 3; C4, complement component 4; CH50, total complement activity 50. Electroencephalography; CSF, cerebral spinal fluid; CSF, cerebral spinal fluid; dsDNA, double-stranded DNA antibodies; ELISA, enzyme-linked immunosorbent assay; Ig, immunoglobulin; IQ, intelligent quotient; LP, lumbar puncture; NMDA, *N*-methyl-D-aspartate; NR1, nuclear receptor 1; PCR, polymerase chain reaction.; SLE, systemic lupus erythematosus; TG, thyroglobulin; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.

[a] Includes herpes simplex virus (HSV 1,2), flavivirus; varicella-zoster virus (VZV); cytomegalovirus (CMV); Epstein-Barr virus (EBV); human immunodeficiency virus (HIV); influenza H1N1 (hemagglutin type 1; neuraminidase type 1); rabies; enteroviruses.

sample of 802 children and adolescents with 22q11 DS), ASD, ADHD, anxiety disorders, and both bipolar and unipolar mood disorders (Schneider et al., 2014; Sporn et al., 2004). A longitudinal study showed that in children with 22q11 DS, early cognitive decline was a predictor of the subsequent transition to a psychotic disorder (Vorstman et al., 2015). In the NIMH childhood schizophrenia cohort (Ahn et al., 2014), children with 22q11.2 deletion did not have autistic features, confirming that psychosis and autism are at least partially independent and thus truly pleiotropic features of the 22q11 DS phenotype (Vorstman et al., 2015).

3.4. Autoimmune disorders

Some studies of first-episode psychosis have described cases with autoantibodies associated with limbic encephalitis (DeSena et al., 2014; Florance-Ryan and Dalmau, 2010), systemic lupus erythematosus (Hoffman et al., 2009; Lim et al., 2013; Malattia and Martini, 2013; Mantovani et al., 2012), or encephalopathy associated with autoimmune thyroid diseases (EAATDs) (Armangue et al., 2012; Van Mater, 2014), without any systemic signs. In Table 3, we show the major presenting symptoms, diagnostic tests and treatment of these disorders. Children and adolescents with catatonia are particularly likely to have organic conditions, including auto-immune diseases (Consoli et al., 2012; Parenti et al., 2016). Recent publications have emphasized the importance of *anti*-NMDA (*N*-methyl-D-aspartic acid) receptor encephalitis (Van Mater, 2014) as an immune-mediated illness that may mimic the clinical features and course of idiopathic schizophrenia in children and especially in adolescents. It has been proposed (Dalmau et al., 2011) that *anti*-NMDA encephalitis typically has a prodromal phase (characterized by headache, fever, nausea, vomiting, diarrhea or upper respiratory tract symptoms in 70% of the patients) followed by psychiatric symptoms (insomnia, delusional thoughts, withdrawal, and behavioral changes) and progression to catatonia. Armangue et al. (2013) reported that children more frequently showed a neurological presentation (e.g., movement disorders and seizures), whereas in adolescent patients, the authors found a high frequency of psychiatric features (45% of the sample). NMDAR antibodies are presumed to result in NMDAR hypo-function due to the internalization of receptors and, thus, reduced NMDAR synaptic content (Steiner et al., 2013), an effect which is consistent with the hypothesis of glutamatergic hypofunction in schizophrenia (Coyle, 2012).

3.5. Endocrine diseases

EAATD was discussed above because the relevant etiological mechanism is not related to hormone levels (Tamagno et al., 2010). Endocrine diseases such as thyrotoxicosis and hypothyroidism may present with psychiatric symptoms (emotional liability, mood changes and sleep problems) and, in rare cases, psychotic symptoms (Lee et al., 2013). The relationship between thyroid function and mood symptoms may be related to the fact that tri-iodothyronine (T3) receptors are highly prevalent in the limbic system and seem to play a role in the modulation of emotions, behavior and long-term memory (Bunevicius and Prange, 2006). Lee et al. (2013) suggested that psychotic symptoms in patients with thyrotoxicosis might be explained by increased adrenergic activity.

Psychosis secondary to endocrine disease in children appears to be rare, but can be severe. We found two papers (Lee et al., 2013; Smith and Beattie, 1998) on thyroid dysfunction with secondary psychosis in

children, and one case report (Hirsch et al., 2000) of pediatric Cushing disease in an adolescent with acute psychotic symptoms. Finally, hypothyroidism can present with isolated psychotic symptoms in children and adolescents (Smith and Beattie, 1998). Major presenting signs, diagnostic tests and therapeutic strategies are summarized in Table S1 (available online).

3.6. Nutritional deficiencies

Since the 19th century, pellagra (niacin deficiency) and Biermer's disease (vitamin B_{12} deficiency) have been known to present with neuropsychiatric manifestations along with gastrointestinal, dermatological and hematological symptoms in adults. We found two articles (Dogan et al., 2012; Lanska, 2010) on these disorders in children and adolescents, as summarized in Table S1. Note that inherited vitamin deficiencies have been classified as IEMs and appear in Table 1. It appears that clinical manifestations reported in youth are similar to those in adults. In children, psychosis is often co-morbid with ID and/or ASD which can be associated with abnormal eating behaviors (pica, food selectivity) which can lead to vitamin B deficiencies. There has been little systematic research on nutritional deficiencies in childhood psychosis, and their frequency might be particularly underestimated in economically impovershed populations.

3.7. CNS infections

Kraepelin proposed in 1896 that '*autointoxication*' by microbial agents could cause *dementia praecox*. There have been numerous studies of prenatal, perinatal and childhood infectious factors in psychosis (Koponen et al., 2004; Pedersen et al., 2012; Torrey et al., 2007). Mortensen et al. (2007) suggested that childhood infections could increase the risk of developing schizophrenia via immune reactions or subsequent reactivation of a neurotropic infection.

Many infections are known to present with psychotic symptoms in some cases, including *Borrelia burgdoferi* (Lyme disease), *Treponema pallidum* (syphilis), HSV-1, HSV-2, EBV, CMV, other non-HIV agents, and *Toxoplasma gondii*. Table S1 summarizes the clinical features, diagnostic analyses and treatments for infectious agents relevant to the pediatric population (Binalsheikh et al., 2012; Bransfield, 2012; Schneider et al., 2002; Yolken and Torrey, 2008) (i.e., excluding syphilis). There is a case report of a 7-year-old boy with Lyme disease who presented initially with auditory hallucinations and metamorphopsia (self and external objects becoming smaller - "Alice in Wonderland syndrome") (Binalsheikh et al., 2012).

3.8. Other neurological disorders

In several neurological conditions, multisensory hallucinations, behavioral changes, sleep problems and emotional liability may be present at initial onset in children and adolescents. (Note that we do not review here neurological disorders such as tumors, trauma and stroke which commonly present with non-psychiatric signs and symptoms and which are detected by neuroimaging studies that are already frequently used for medical screening.) Relevant features of epilepsy, narcolepsy and Leigh syndrome are summarized in Table S1. There is a long history of investigation of the relationship between schizophrenia and epilepsy, starting with the work of Gibbs (Gibbs and Gibbs, 1948; Gibbs, 1951). Several recent extensive reviews are available (Kanner and Rivas-Grajales, 2016; Besag et al., 2016; Nickels et al., 2016) A degree of shared genetic vulnerability has been hypothesized (Cascella et al., 2009; Clarke et al., 2012), and has been directly demonstrated in the case of rare CNVs that increase risk of both types of disorders (Levinson et al., 2011). Psychiatric co-morbidities are common in epileptic patients (Caplan et al., 1997; Lax Pericall and Taylor, 2010; Terra et al., 2014). Schizophrenia-like psychosis in epilepsy (SLPE) has been well-studied in adults (Elliott, 2009; Slater et al., 1963) but not in children. Matsuura and Trimble (2000) reported a prevalence rate of 0.7% for SCZ in a sample of Japanese children with epilepsy. SLPE can occur in four contexts (Kanner, 2000), with psychotic phenomenology related to 1) the ictal state itself (ictal psychosis); 2) the post-ictal state (seizure cessation); 3) brief or chronic inter-ictal psychosis (where psychosis is independent of the timing of seizures); and 4) iatrogenic psychosis due to anti-epileptic drugs or temporal lobectomy. We found two case reports of ictal psychosis in children and adolescents (La Vega-Talbot et al., 2006; Luat et al., 2008) and a study of hemispheric specialization of ictal auditory and non-auditory (visual and somesthetic) hallucinations (Guimond et al., 2009). We found four case reports of post-ictal psychosis in children (Joshi et al., 2006; Kaur et al., 2012; Nissenkorn et al., 1999; Walterfang et al., 2010). Post-ictal psychosis may follow complex partial seizures (often temporal epilepsy) as well as primary generalized epilepsy. The interval to remission varies from a few hours to several months. The psychotic episode may follow repeated or prolonged complex partial seizures with or without secondary generalization as well asstatus epilepticus. The phenomenology is often polymorphic but with a benign course. Chronic post-ictal psychosis is rare in adults and children. We did not find any reports of inter-ictal or iatrogenic psychosis in children and adolescents.

4. Discussion

Causative or contributory medical factors can be detected in a significant minority of youth with schizophrenia spectrum disorders. We propose that a comprehensive medical evaluation is appropriate in all such cases. Based on literature review and our own clinical experience, we discuss here the clinical features that appear to be most strongly suggestive of organic factors, and we propose an algorithm for laboratory evaluation.

Several clinical and historical features appear to warrant an ***increased index of suspicion of organic factors***:

(1) Atypical aspects of the clinical history and course, including:

(a) acute and/or very early onset;
(b) onset apparently triggered by surgery, viral infection, or medications;
(c) cognitive or developmental regression.

(2) Atypical symptomatic features:

(a) confusion;
(b) catatonia (Consoli et al., 2012);
(c) rare and serious neurological adverse reactions to treatment.

(3) Presence of co-occurring physical symptoms, for example:

(a) suspicion of seizures;
(b) malar rash;
(c) gastro-intestinal signs;
(d) dysmorphic features.

Table 4 provides a summary of the main clinical features of organic disorders that may be considered most likely to be detected in these patients. For the IEMs, these unusual features are well established for adult onset psychosis (Bonnot et al., 2014; Walterfang et al., 2013).

When psychotic symptoms occur at onset without physical signs or symptoms (e.g., Niemann-Pick type C, or the adolescent form of *anti*-NMDAR encephalitis), the features that are suggestive of organic causality include: intellectual disability, catatonic signs, neurological regression, confusion, and adverse events to treatment. For epilepsy as a cause of new psychosis, Kanner (2000) proposed increased suspicion in the presence of the absence of negative symptoms, good premorbid

Table 4
Psychiatric and physical features of selected medical causes of psychosis in childhood.

Disease	Acute psych onset	Isolated psych onset	Intellectual disability	Regression	Catatonia	Confusion	Hypotonia	Seizure	Gastro-intestinal	Hepatomegaly	EPS	Ataxia	Neuropathy	Stroke	Eye	Skin	Kidney	Heart
22q11 DS			±				+								±			+
Acute porphyrias	+				+	+			+	+			+			+		
AntiNMDA receptor encephalitis		+		+	+	+			+									
CTX		+	+	±	+				+			+	+		+	+		
EAATD				+		+		+	+		±	+			+			
Hallervorden-Spatz		+		+							+							
Huntington's disease		+		+				+			+							
Hyperhomocysteinemia		+	+	+	+	+			+		+			+	+		+	+
JCNL	+		+	+	+			+							+			
Krabbe disease		+	+	+				+		+		+			+			
Leigh syndrome		+		+			+	±	+		+		+					
Lyme disease	+			+		+			+		±		+		±	+		+
α-Mannosidosis	+		+	+			+	+			+	+						
β-Mannosidosis	+		+				+	+					+			+		
Maple syrup urine			+	+			+			+	+	+						
Metachromatic leukodystrophy – late onset		+		+				+		+		+	+		+			
MPS III (a–d)	±	+	+	+	+					+								
Neuroferritinopathy	+	+	+	+							+							
Niacin deficiency				+	+				+				+			+		
Niemann-Pick type C		+		+	+			+		+		+			+			
NPSLE	±	±		+		+									±	+		
OTC deficiency		+	+		+	+	+		+							+		
Propionic acidemia – late onset			+	+			+		+	+	+			+	±	+		+
Tay-Sachs	+		+	+				+		+	+	+			+			
Vitamin B_{12} deficiency				+	+			+	+			+	+			+		
Wilson disease	+	+	±		+					+	+				+			
X-ALD		+	+	+									+		+		±	

Abbreviations: ALD, adrenoleukodystrophy; CTX, cerebrotendinous xanthomatosis; DS, deletion syndrome; EAATD, encephalopathy associated with autoimmune thyroid disease.; EPS, extrapyramidal syndrome; JNCL, juvenile neuronal ceroid lipofuscinosis; MPS, mucopolysaccharidosis; NMDA, *N*-methyl-D-aspartate; NPSLE, neuropsychiatric systemic lupus erythematosus; OTC, ornithinetranscarbamylase; Psych, psychiatric (isolated – psychiatric symptoms can predominate at onset).

adjustment, and absence of deterioration compared to typical schizophrenia. However, systematic studies of child and adolescent patients are lacking.

Table 5 lists the laboratory evaluations that should be considered in evaluating onsets of psychotic disorders in children and young adolescents. Our own practice is to attempt to obtain the tests in the first section of the table in all patients (these are for diagnoses that are more common or poorly predicted by other clinical features), while those in the second section are ordered on the basis of clinical features that are useful for screening, as noted in the table. There are no widely-accepted, standardized recommendations or practice guidelines on the usefulness of neuroimaging, urine drug screen, EEG and endocrinogical workup for these patients (Williams et al., 2014). More aggressive medical workup has been proposed for patients with neurological symptoms or seizures (McClellan and Stock, 2013) or with "new onset psychosis or with an atypical clinical presentation" (APA, 2006). The availability of improved technologies for genetic testing of CNVs and other genetic disorders has increased the use of these tests, particularly in the presence of ID or features of ASD.

We recommend carrying out the comprehensive workup described in Table 5 at onset or as early in the course as possibleOne of these diagnoses will be detected in perhaps 10% of cases, and will either be potentially treatable or have clear implications for future psychiatric and medical management. Thus, while the cost-benefit ratio of each individual test is low, that of the comprehensive workup is reasonable, although further prioritization will be needed where clinical resources or cooperation of the patient or family are limited.

In conclusion, a large number of medical factors can cause or contribute to psychotic disorders in young people. We suggest that a more aggressive medical workup of these patients can improve diagnosis, clinical management (particularly when specific treatments are available), quality of life and outcome. Given the diversity of factors, a systematic and multidisciplinary approach is recommended.

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Contributors

MG, CLL and DC conceived of the review paper. MG carried out the literature review and wrote the first draft. CLL and DC supervised the work. DL supervised revision and formatting of the manuscript. AC and MR contributed expertise in psychiatric immunology and RJ in neurology. All authors read comment on and approved the manuscript.

Conflict of interest

During the last two years, David Cohen reported past consultation for or the receipt of honoraria from Otsuka, Shire, Lundbeck and IntegraGen. All other authors declare that they have no conflicts of interest.

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Table 5
Proposed laboratory work-up for childhood psychosis.

Type	Test	Comment (target diagnoses; clinical clues)
Recommended for all patients		
General medical	Metabolic panel, CBC	General medical screen
	C-reactive protein and ESR	Auto-immune and infectious diseases
	TSH, free T4	Thyroid disease
	Vitamin D	22q11 deletion syndrome (reduced)
	Blood/urine toxicology	Drugs of abuse
General medical	EKG	Baseline for medication treatment
Neurological screen	Brain MRI	T1 (tumor, injury, stroke, specific abnormalities); T2 (neuroferritinopahy, CTX)
	EEG	Epilepsy, encephalopathy
Serology	HIV1,2	With parents' permission
Plasma	Ammonemia	Ornithine Trans Carbamylase (OTC)
	Homocysteinemia	HHC
	Amino acid chromotography	IEMs; hyperprolinemia in 22q11 del
	Cholestanol	CerebroTendinous Xanthomatosis (CTX); fat accumulation; juvenile cataract; diarrhea; Achilles heel xanthomas
	Cholestane 3α,5α, 6β-triol and 7KC	Niemann Pick type C (treatable); vertical supranuclear gaze palsy (≥10)
	ANA, *anti*-dsDNA	SLE (lupus)
	Anti-TPO, *anti*-TSHr	Thyroid encephalopathies
	Anti Borrelia burgdoferi	Lyme disease
Urine	Amino acid chromotography	IEMs (e.g., homocysteinuria, inadequate diet)
	Organic acid chromotography	IEMs (e.g., fatty acid oxidation disorder, inadequate diet); mucopolysaccharidosis
Genetic	DNA microarray	With permission; CNVs
Recommended for selected patients (*see Comment*)		
General medical	Lactate – pyruvate (fasting + 3 h)	Mitochondrial disease (if ptosis present)
Lumbar puncture	*Anti*-NMDAR Ab; protein; WBC; ANA, dsDNA; *anti*-TPO, *anti*-TSHr	For abnormal EEG or any suspicion of auto-immune disease, encephalitis
Serology	HSV1,2; VZV; CMV; EBV	Acute onset - viral encephalitis
	Rabies; flavivirus[a]; enterovirus; H1N1	If possible exposure1
Plasma	Urinary porphyrobilinogen	Porphyria - acute episodes, GI pain
	Ceruleoplasmin, copper	Wilson's disease: if neurological signs are present, examine for Kayser-Fleischer rings
	Leukocyte arylsulfatase A (decreased); Urinary sulfatides (increased)	Metachromatic leucodystrophy; if suspected on MRI (metachromatic lipid deposits)
	Anti *Toxoplasma gondii*	Toxoplasmosis (suspected in presence of characteristic brain lesions – MRI or CT)
	Vitamin B12	Vegetarian diet; macrocytic anemia
Genetic	Genetic test for Huntington disease	Family history; chorea

[a] Flavivirus includes yellow fever, dengue, zika, west nile and other regional encaphalitides; test if exposure is plausible. Test enterovirus if clinical picture suggests explosure.

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