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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