European Child & Adolescent Psychiatry (2019) 28:1159–1167
https://doi.org/10.1007/s00787-018-1208-y

REVIEW

Early warning signs in misrecognized secondary pediatric psychotic disorders: a systematic review

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Received: 18 December 2017 / Accepted: 24 July 2018 / Published online: 27 July 2018

Abstract

Childhood psychotic symptoms are not uncommon, but lack an evidence-based diagnostic approach. Hallucinations, delusions and other psychotic symptoms, without endangered vital symptoms, can be the result of a primary psychiatric disorder or can be the presenting symptom of an underlying somatic disease. It is important to discriminate between these origins because their diagnostic and therapeutic approaches differ substantially. We searched the existing literature to present a first overview of warning symptoms of underlying somatic disease in children with psychotic symptoms. We obtained data through a study of major textbooks and guidelines, and through a systematic review in PubMed, Embase and PsycINFO databases. We included case reports, cohort studies, and reviews. Results show that symptoms related to an underlying somatic disease are quite diverse and resemble symptoms of a primary psychotic process to a large extent. So there exist no (new) early warning signs. These findings are, crucial as they are mainly in contrast to current common knowledge and make the differential diagnosis even more critical and complex. A further prospective cohort study is necessary in an attempt to create a diagnostic algorithm for psychotic symptoms in children.

Keywords Psychotic disorders · Hallucinations · Delusions · Childhood · Warning signs · Diagnostic algorithm

Introduction

Childhood psychotic symptoms are not uncommon and affect 17% of 9–12-year olds and 7.5% of 13–18-year olds [1]. Reported symptoms include hallucinations, delusions, disorganized thoughts and speech, and disorganized psychomotor skills [2]. They vary from benign and transient to malignant and enduring once they intervene in daily life or child development. Benign phenomena, like the presence of an imaginary friend, have little clinical relevance, while more severe psychotic symptoms in childhood confer risk for the development of psychiatric illnesses at later age [3].

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Like in adults, childhood psychotic symptoms can be caused by external factors (such as stressors or trauma) and somatic diseases. Therefore, the differential diagnosis is extensive [4]. Based on the absence or presence of an identifiable cause (such as drug abuse or thyroid disease), psychotic disorders are generally classified as primary or secondary. This distinction is challenging to make; however, since the complex interplay between genetics, environmental factors and physical features (i.e., diseases) causes a gray area in between. Moreover, a direct causal relationship between psychotic symptoms and underlying diseases cannot always be proven. For the clarity of the current review, we defined secondary psychosis as psychotic symptoms that are the result of a detectable and treatable cause.

It is well-known that hallucinations can be the result of thyroid disease or other more rare conditions. Potential aspects of the organic workup in children with hallucinations have been suggested [5]. However, there is no consensus on which investigatory tests should be performed as a standard, and which examinations carry unnecessary patient burden and healthcare costs [6, 7]. Whereas psychotic symptoms in the context of pediatric delirium and severe illness have been well-described, literature on the differential diagnosis

of psychotic symptoms as a possible consequence of less "eye-catching" somatic diseases is scarce [8, 9]. Especially in children that solely present with psychotic symptoms (without endangered vital signs or other [neurological] symptoms), the distinction between a primary and secondary psychiatric disorder is difficult [10]. Possible underlying diseases (which are 'silent' other than for the psychotic symptoms) are easily missed. On the one hand, it is crucial to detect such causes at an early stage to start treatment timely and to improve the prognosis and well-being of the child. On the other hand, not every child should be subjected to all possible examinations, since the excessive use of diagnostics tests causes the diagnostic process to become intrusive, traumatic and expensive. Lumbar puncture is an example of an invasive diagnostic tool that should only be performed when deemed essential for clinical decision-making. So how to find the right balance? To shed a first light on this dilemma, we performed a systematic review of the literature about secondary psychotic symptoms in children. Our key research question is: "what are discriminating warning signs of unrecognized somatic ('silent') illnesses in children with psychotic symptoms and without critical illness, in all types of settings (e.g., general practitioner, hospital or psychiatric hospital)?"

The current work will discuss the secondary psychotic symptoms in children, described in case studies, case series, and other article types, to give an overview of the reported symptoms. To compare this to the common knowledge, a summary of the major textbooks on psychiatry and pediatrics is presented in Table 1. In this manner, we will describe possible warning signs in 'silent' secondary psychotic disorders.

We hypothesized a priori, based on common knowledge from textbooks, that there exist several alarm signs for somato/neurological causes of psychotic disorders [4, 10–16]:

1. A typical age of onset of psychotic symptoms; younger age in children (prepubertal age).
2. Clinical features, such as visual hallucinations.
3. Cognitive deficits, higher cortical dysfunctions and (subtle) focal neurological abnormalities.

Methods

We conducted a comprehensive literature study focusing on possible discriminating factors in psychotic children with an underlying somatic disease, who were encountered in various clinical settings. We analyzed major textbooks [4, 10–16] and two main guidelines for psychotic disorders in children [6, 7]. A systematic review of the existing literature was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2015 statement [17]. We searched for relevant studies in PubMed, Embase, and PsycINFO. Keywords based on the

Table 1 Suggested components of work-up based on major textbooks

History	Recent (infectious) illness/surgery/treatment Behavioral changes like excessive laughing/hypersomnia—sleeplessness-lethargy Drug use (prescribed, unprescribed), vitamin, caffeine) Headache/photophobia/seizures/auras Decline in cognitive functions, loss of performance Weight loss—weight gain/poor growth Nausea, vomiting, food resistance, loss of appetite, hyperphagia
Physical examination	Dysmorphic features Cutaneous stigmata (like hyperpigmentation) Weight, height and head circumference deviations Fever High blood pressure/tachycardia/palpitations Neurological deficits: [like diplopia, visual impairment, nystagmus, speech problems (mutism, aphasia, dysarthria or incoherent speech, hypologia)] dystonia/tremor/chorea or rigidity Repetitive swallowing/lip smacking Kayser–Fleischer rings (eyes) Organomegaly, broad appearance
Familial history	Metabolic diseases Inherited diseases Psychotic symptoms Mental retardation
Diagnostic tools	Laboratory test (like infection parameters) Urine toxicology CT/MRI EEG Lumbar puncture

research question (all variants of the terms: "child", "psychotic disorder", and diseases that are known to be associated with psychotic symptoms) were used to search in titles and/or abstracts. We combined keywords to narrow down our findings and consequently focused on papers addressing psychotic symptoms in children with somatic causes. Cross-references were also included if deemed appropriate. Due to a large number of hits, a timeframe was set from January 2005 to November 2015, and the search was limited to the main database (PubMed). Furthermore, articles in any language other than English, German, French or Dutch were excluded. This strategy yielded 5904 articles. Titles and abstracts were screened for their eligibility to answer our research question based on the following inclusion criteria:

- age (children and adolescents up to 18 years);
- presentation of psychotic symptoms (such as hallucinations, delusions, confusion, or formal thought disorders);
- a somatic disease that is accountable for these psychotic symptoms.

We excluded studies that reported on either psychotic or somatic symptoms, but without the combination of the two. Furthermore, studies that focused on psychotic disorders as a long-term consequence of an earlier somatic disease (like schizophrenic disorders following perinatal infection) were excluded. Finally, we excluded papers on children presenting with critical illness, endangered somatic vital signs, loss of consciousness, catatonia, and delirium, because in these cases the clinical focus is already on underlying somatic illnesses. Eventually, 519 articles were included. To organize our findings as clearly as possible, we divided the articles into groups, based on the type of illness (i.e., neurological, infectious, metabolism, medication or intoxication, malignancy, auto-immune, endocrine, genetic disorders, post-operation or trauma, and dermatological). In the subgroup 'overall' we included guidelines or other types of articles that describe general recommendations for physical examination in children with psychotic symptoms. The remaining articles were independently studied by the three authors and included based on consensus. The flow chart is presented in Fig. 1.

Results

We finally included 244 articles. Most are case reports or case series on patients presenting with psychotic symptoms caused by a somatic disease (see Table 2). We analyzed the presenting psychiatric symptoms to elucidate their characteristics. We also searched for other (somatic) signs, like abnormalities on physical examination, to indicate other possible discriminating factors.

Summary of textbooks and current guidelines on psychotic disorders in children

Table 3 provides an overview of the characteristics of primary versus secondary symptoms, based on the major textbooks in (adult) psychiatry, pediatrics, and the guidelines. These psychotic symptoms may point in the direction of the presence of a somatic illness. It is emphasized that it is important to perform a basic physical examination and further investigations to detect or exclude comorbidity. Most often mentioned are laboratory investigations, electroencephalography (EEG) to diagnose epilepsy, magnetic resonance imaging (MRI) to exclude tumors, and urine drug screen to prove illicit drug use [14]. In addition, these examinations provide a baseline measurement to monitor potential pharmacotherapy. Although all these recommendations are sound, they are nowhere justified, especially in the context of benefits versus costs and risks.

In Table 4, we summarize abnormalities in physical and mental examination in children with psychotic symptoms due to a somatic disease. These signs were described in retrospect.

Psychotic symptoms caused by a somatic disease

We found multiple cases of children with slowly developing psychotic symptoms that were a consequence of somatic diseases like brain tumors [18, 19]. Due to the absence of neurological or other abnormalities at first presentation, they were interpreted as a primary psychotic disorder. Important warning signs of underlying undetected somatic diseases, like headache or refractoriness to treatment, appeared later [20]. Hallucinations not only presented as only visual or tactile, but also appeared in multiple sensory modalities. Furthermore, the secondary psychotic symptoms presented in a "typical bizarre schizophrenic" manner: paranoid delusions, chaotic behavior, developing slowly over time with a prodromal-like phase, with bizarre delusions or complex hallucinations [21–23].

Other warning signs in secondary psychotic symptoms

In hindsight, most cases with secondary psychotic symptoms did show peculiarities either before presentation with these symptoms at the beginning of the illness, or later along the course (Table 4). These were abnormalities that were discovered on physical examination (like fever or minor neurological abnormalities [21]), abnormalities in family history [24], (refractory) anorexia [25], and physical illness in the recent history [26]. More specifically, neurological deficits that may point to an underlying somatic disease are a developmental and or cognitive decline, loss of acquired skills,

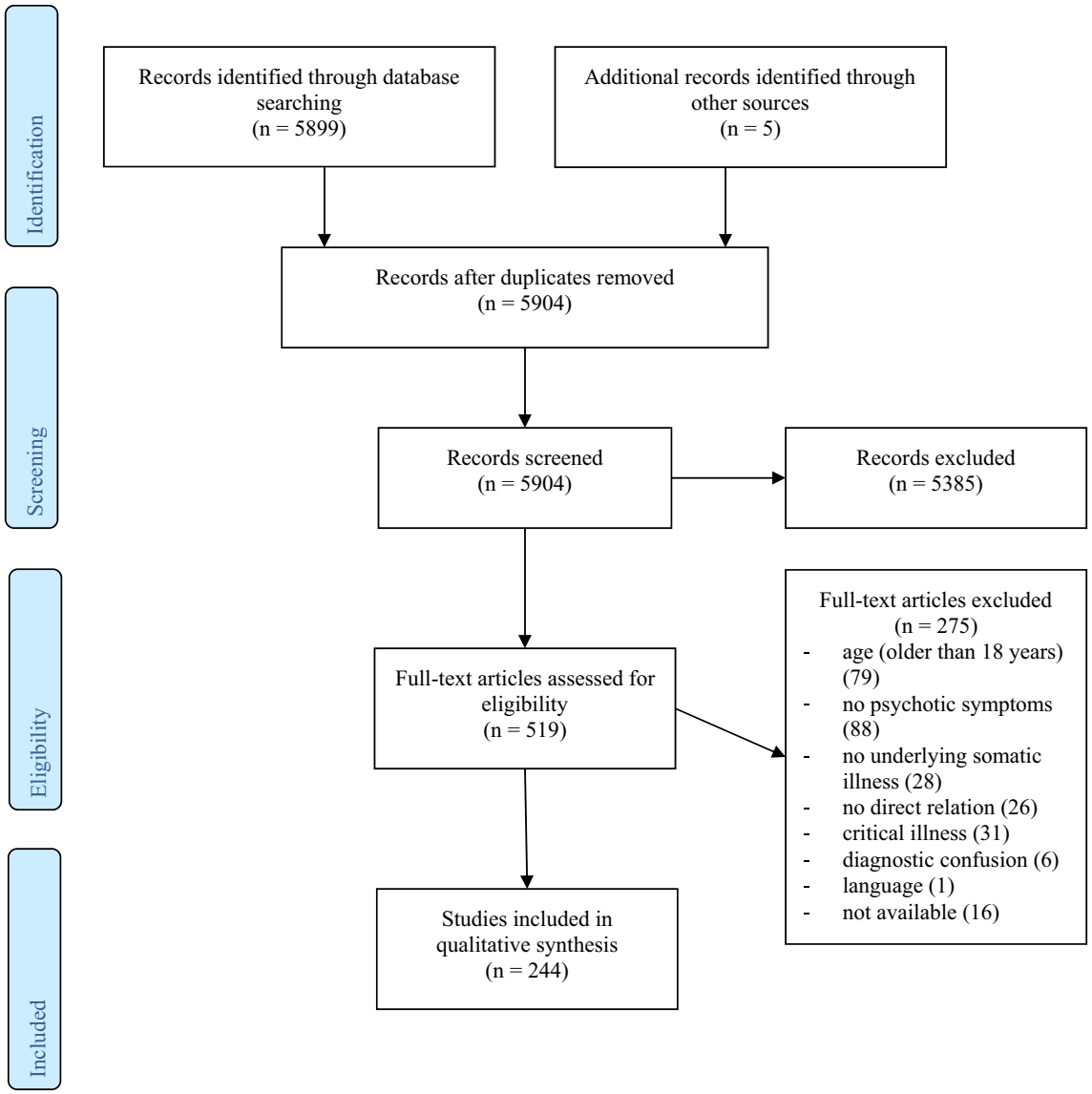

Fig. 1 Flow chart of the search strategy

speech problems, mutism, subtle higher cortical dysfunctions, Parkinson-like symptoms, and movement disorders (subtle chorea).

Signs of underlying somatic disease in children, in whom a somatic diagnosis was "missed" at first evaluation, were mostly refractoriness or worsening of the psychotic symptoms despite treatment. Also, the development of somatic symptoms in the course of psychosis can be a sign of an underlying disease, as not all somatic symptoms were present at first presentation [23, 27, 28]. The final diagnosis was made in hospitals, by either pediatricians or pediatric neurologists.

It is well-known that neurological disorders (such as encephalitis, migraine, and epilepsy disorders) can be complicated with hallucinations and delusions. Prominent neurological deficits can be absent at first presentation. Consequently, psychotic symptoms may be the main and only presentation. Anti-*N*-methyl-D-aspartate receptor (anti-NMDA receptor) encephalitis is particularly notorious for such a presentation [29].

A confusional migraine might be hard to distinguish from a primary psychiatric cause, when there is no complaint of a headache [30]. Key signs for a migraine as origin for hallucinations may be a positive family history, the complete resolution of symptoms within a couple of days, and recurrence in a typical pattern in time.

Multiple metabolic disorders, like Wilson disease, thiamin metabolism disorders and acute Wernicke disease [31], can present with psychotic symptoms. In the cases found, some physical symptoms (such as diplopia, nausea or

Table 2 Number of articles found per underlying somatic disease

Group of disorders	Articles found (*N*)	Articles included (case reports/cohort study/retrospective study/review)
Auto-immune	100	52 (35/6/5/6)
Dermatology	4	1 (0/0/0/1)
Endocrine disorders	6	2 (2/0/0/0)
Genetic disorders	48	10 (6/1/0/3)
Inborn error of metabolism/metabolic disorders	48	32 (25/1/3/3)
Infectious diseases	53	11 (8/0/3/0)
Malignancy	18	9 (9/0/0/0)
Medication/intoxication	93	62 (50/3/5/4)
Neurology	123	61 (47/2/7/5)
Post-operative/trauma	7	1 (1/0//0/0)
Overall	19	3 (1/0/0/2)

anorexia [25]) were—in hindsight—present, but not recognized, at first presentation.

For causes that involve medication/intoxication, most secondary psychotic symptoms were due to intoxication with (illegal) drugs. Ingestion in small children is mostly accidental. There is a substantial body of evidence that describes the effects of cannabis, amphetamine and its derivates in children of all ages. The literature on the consequences of withdrawal is scarce. The clinical distinction between intoxication and withdrawal is hard, perhaps impossible to make. To detect possible drug use as a cause, proper anamnesis and urine test are essential [5]. Especially in adolescents, history taking is preferably obtained in the absence of the parents, because of guilt, fear of punishment, and legal consequences.

Discussion

In this systematic review, we investigated the current literature on secondary psychotic symptoms in children. As a variety of somatic diseases may first present with hallucinations and delusions, these manifestations are easily misjudged to be an expression of a primary psychiatric disorder. Particularly in children who do not have any other (physical) abnormalities at presentation, the distinction between a primary and secondary psychosis is hard to make. This is underlined by the number of case reports we found on this matter. Recently, Giannitelli et al. [32] studied 160 children and adolescents with schizophrenia-like symptoms and found underlying organic factors in 12.5% of cases. However, as this was a cohort from a tertiary hospital, children with secondary psychotic symptoms are likely to be overrepresented.

We hypothesized that we would find (1) atypical age of onset; (2) atypical clinical features of the psychotic symptoms, and (3) cognitive deficits and focal neurological abnormalities as possible warning signs. Nonetheless, results show that psychotic symptoms in secondary psychosis can resemble, or even are the same as, primary psychotic symptoms. We also found that important warning signs are not primarily found within the psychiatric symptoms, but also in the (mild) physical abnormalities, refractoriness or progression of the symptoms despite treatment, or in the development of other neurological deficits at a later stage. Moreover, essential clues are in the history and family history. These can, however, also be misleading (for example, a psychiatric family history can point towards a vulnerability of psychosis, but can also be the result of an underlying genetic disease, such as in 22q11 deletion syndrome). It is crucial to evaluate if there is indeed either a causal relationship between the

Table 3 Characteristics of 'primary' versus 'secondary' psychotic symptoms

	Primary psychosis	Secondary psychosis
Age of onset	Usually early adolescence	All ages
Course of symptoms	Insidious onset Ultra-high risk: regression or kink in development, social isolation Psychotic symptoms responsive to treatment	Sudden onset Refractory or aggravation to antipsychotic treatment Asymmetric side effects
Hallucinations	Acoustic, imperative with loss of insight	Visual most common Tactile: drug abuse Loss of insight may be present
Delusions	May be more complex, paranoid, bizarre	Usually not complex
Formal thought disorder	May be	Thought disorders/iteration
Cognitive functioning	Speech delay in early onset schizophrenia Lower IQ	Normal premorbid Higher cortical dysfunctions
Historical information	Family history positive of psychiatric disorders	Illness in previous history Positive family history of physical illness

Table 4 Summary of abnormalities in physical and mental examination in secondary psychosis found in case studies/series

Subgroup	Diseases	Possible warning signs
Neurology	Epilepsy (i.e., Lafora body disease) Narcolepsy Migraine/Alice in Wonderland phenomenon Encephalitis (herpes, limbic, subacute sclerosing panencephalitis) Posterior reversible encephalopathy syndrome Dandy walker variant Fahr Sydenham's chorea	History of seizures, oculomotor symptoms: tonic deviation of the eyes, repetitive eyelid closures, eyelid fluttering, blinking, ipsilateral turning of the head, sometimes followed by tonic–clonic seizure Progressive myoclonus, cognitive decline, dysarthria, ataxia. Cataplexy. Myoclonus, ataxia, chorea. Hemiparesis couple before psychotic symptoms. Adenoma sebaceum and Shagreen patch (tuberous sclerosis). Dysarthria, bilateral sensioneural hearing loss (neurobrucellosis). Visual–spatial agnosia, praxis deficits. Visual aura/somatosensory aura/motor aura. Sometimes followed/preceded by or accomplished with headaches, photophobia, phonophobia sometimes, nausea, vomiting, family history of migraine Cognitive deterioration, behavioral changes, disturbed nights. Confusion, disorientation to person and time, hypertension, tiredness, lethargy Premorbid difficulty swallowing, bulbar palsy
Auto-immune	Auto-immune encephalitis (anti-NMDA-receptor, Hashimoto, rest) Systemic lupus erythematosus Multiple sclerosis Neuro-Behcet Kleine Levin Subacute thyroiditis Acute disseminated encephalomyelitis	Acute onset, fever Headache (holocephalic/in prodromal phase/associated with photophobia). Seizures Aggravation to amnesia, aggravation despite therapy Cognitive decline and strange behavior Cataleptic/catatonic features Hypersomnia, hyperphagia. Tachycardia Intermittent drooling. Dizziness Sore throat, preceded by upper respiratory infection
Inborn error of metabolism/metabolic disorders	Vitamin B12 or folate deficiency Niemann–Pick type C Wilson disease Propionic acidemia Cobalamin C deficiency Urea cycle disorders Acute intermittent porphyria Juvenile Huntington disease Remaining	Seizures/epilepsy. Aphasia, (cerebellar) ataxia, gelastic cataplexy, extrapyramidal signs, vertical supranuclear gaze palsy, chorea, dysarthria, hypotonia, myoclonus, spasticity, tremor. Peripheral neuropathy, progressive motor weakness, mild hypertension (= autonomic dysfunction). Paresthesia. Deafness. Dementia. Mutism (as a consequence of neurotransmitter disorder). Gradual loss of previously acquired skills Oromandibular involvement, Kayser–Fleischer rings (eyes) Pigmentation of knuckles/hands and feet and hypopigmented easily pluckable hair, oral ulcers, pallor, fatigue Anorexia (nervosa, hyperemesis gravidarum, Crohn's disease, starvation). Vomiting, lethargy, abdominal pain, hepatosplenomegaly. Metabolic acidosis, ketosis, ketonuria, hyperammonemia, hyperglycemia (metabolic decompensation). Elevated cell count. Episodes of (ketonemic) vomiting, episodes of somnolence/hyperactivity after protein rich meals. Protein intolerance Mental retardation, executive disorders, psychiatric symptoms, prolonged neonatal jaundice
Genetic disorders	22q11 deletion Divers genetic disorders (Prader Willi, Klinefelter, microdeletions/CNV)	Intrauterine growth retardation, failure to thrive. Hypotonia Dysmorphic features, bone/connective tissue abnormalities, cardiovascular, dermatologic, genitourinary, splenic or hepatic, renal, endocrine, hematologic visual system, hearing impairment, neuropsychiatric (cognitive impairment/dementia, intellectual disability, movement disorder, peripheral neuropathy, seizures, spasticity, speech problems) history or behavioral problems Long duration of illness, responding poorly to treatment

Table 4 (continued)

Subgroup	Diseases	Possible warning signs
Malignancy	Germ cell tumor Pineal gland tumor Astrocytoma Craniopharyngiomas Cerebellar extraventricular Neurocytoma Dysembryoplastic neuroepithelial tumor Insulinoma Paraneoplastic neurological disorders	Mild left dysmetria in association with puerile attitude and spasmodic laughter. Psychomotor slowing with minimal spontaneous speech. Seizures, lateralization in motor symptoms. Hypologia, speech problems (slurred speech/mutism). Dyskinesia Polydipsia. Diabetes mellitus, hypothyroidism, 3-month history of headache, waking headache, tachycardia (may be from agitation). Palpitations. Tremulousness Diaphoresis, confusion and drowsiness related to hunger or exercise, relieved by juice and food intake Refractory to treatment
Endocrine disorders	Cushing disease Catamenial disorders	Years of history of weight gain, poor growth, known disorder of Cushing disease. Pattern coincided with menstrual cycle
Infectious diseases	Influenza, cytomegalovirus, human herpes virus Brucellosis, Lyme (neuro) borreliosis, streptococcus Neurocysteriosis	Acute onset (to several days), onset immediately after infection, disorientation. Repetitive swallowing and lip smacking. Spells in night, seizures Low-grade fever and headache 3 days prior to onset symptoms Chorea Immunosuppressed patients
Medication/intoxication	Intoxication Withdrawal	Abrupt onset, in time related with therapy, combination of medication, accidental wrong dosage/ingestion Accompanying symptoms; headache, raised blood pressure. Dry mouth. Delirious symptoms
Trauma/post OK	Head injury	Anamnestic in history (may be longer than direct consequence)
Dermatology	Psychocutaneous	Diagnosis usually made based on history

psychotic illnesses on the one hand and the somatic symptoms on the other, as their presence can just be an incidental non-related finding like in a Dandy–Walker variant [33]. Therefore, we can reject hypothesis 2, and to certain extent, hypothesis 3. However, cognitive deficits, higher cortical dysfunctions, and (subtle) focal neurological abnormalities are indeed warning signs. We cannot conclude that younger age, as assumed in hypothesis 1, is a warning sign. Because we only studied the psychotic symptoms in children with physical illness (true positives), we cannot compare them with those of children without somatic disease (true negatives). This is, as we will discuss later, an important factor for future research.

Our findings have significant implications. First, the 'typical bizarre schizophrenic' manner of presentation can be misleading. The described psychotic symptoms in the literature did not only exist of simple visual hallucinations, but also of more complex hallucinations, paranoid delusions, and chaotic behavior. Therefore, a possible underlying disease should always be in mind. This means that we have to seek warning signs in other symptoms. These signs can be in the (mild) physical abnormalities, and in the (natural) course of the symptoms. Giannitelli et al. [32] also suggest an increased index of suspicion of organic factors, including (1) atypical aspects of the clinical history and course, (2) atypical symptomatic features and (3) presence of co-occurring physical symptoms. Further research is necessary to indicate these signals and complete this overview.

Second, our findings emphasize the need for a standard and thorough physical examination of psychotic children. This examination should not only be performed at first presentation, but also in the case of refractoriness or worsening of symptoms despite adequate treatment. Even minor abnormalities can point to a hidden physical illness. Guided by findings on physical examination, further diagnostic investigations should be performed.

Third, the collateral family history regarding (1) psychiatric, (2) somatic disorders and (3) unexplained deaths may give important clues. Furthermore, the course of the illness should be properly evaluated; is the treatment effective; are there new physical symptoms that point to underlying diseases or are there unexpected side effects of the treatment? The answers to these questions should be adequately documented, so that they can be compared later on. Finally, we should take into consideration that the distinction between primary and secondary psychosis, although very logical in itself, is artificial. In this light, psychotic symptoms must be

considered as a (serious) neuropsychiatric consequence of a variety of diseases.

Limitations and strengths

Limitations As discussed above, we searched for the literature regarding children with psychotic symptoms and somatic illness, so we cannot directly compare our findings with children with these symptoms, but without a related somatic disorder. This is due to the large number of articles (> 5000 articles).

We cannot ignore publication bias, in two ways. First, published cases are more often exceptional, so the other, more common ones are missed. Second, authors may feel ashamed or fear liability processes when presenting cases in which a 'common' diagnosis is missed. However, in the light of making an evidence-based approach of psychotic disorders in children, it is important to gather this information. Second, we are dependent on the more or less specific information on the presenting symptoms given in the case reports.

Strengths We gathered all the existing literature on childhood psychotic symptoms as a consequence of somatic illness in the period 2005–2015. It indicates the gap in the literature and warrants further research on the subject. So this systematic review also brings "clarity on unclarity".

Final conclusions

The bottom line is that every case of childhood psychotic symptoms should be routinely examined on critical somatic aspects, but to what extent is unclear. The possibility of a primary physical illness does not mean that, as a conditioned reflex, every child with psychotic symptoms should be subjected to all possible diagnostic investigations. The right balance in this crucial subject remains unclear.

Further directions

It is essential to create an evidence-based diagnostic algorithm in the diagnostic approach of general psychotic symptoms in children. Such an algorithm gives the clinician a more evidence-based approach in decision-making and should provide a balance between subjecting the child to all kinds of investigations and between missing valuable information and extra costs.

It furthermore shortens doctor's delay, reduces healthcare costs, and most importantly, minimizes disease burden for the children and their families.

A prospective cohort study in a multicentered and multidisciplinary approach makes it possible to obtain more clinical and decision-making information and this may next lead to a diagnostic algorithm of psychotic symptoms in children without delirium, catatonia or critical illness.

Compliance with ethical standards

Conflict of interest The authors declare that this manuscript does not contain clinical studies or patient data. The authors claim that they have no conflict of interest.

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