Early-Onset Schizophrenia in a paediatric population of French psychiatric and medico-social care centres: A cross sectional study

Emmanuelle Dor-Nedonsel1,2*, Marie-Line Menard1,2, Arnaud Fernandez1,2, Charlotte Sakarovitch3, Eric Fontas3, Xavier Salle-Collemiche4, François Poinso4, Anne-Lise Tosello1, Fanny Maria1, Valeria Manera2, Florence Askenazy1,2, Susanne Thümmler1,2

1 University Department of Child and Adolescent Psychiatry, Children’s Hospitals of Nice CHU-Lenval, Nice, France, 2 CoBTek, University Côte d’Azur, Nice, France, 3 Direction de la Recherche Clinique, University Hospital, Nice, France, 4 University Department of Child and Adolescent Psychiatry, Public Assistance-Hospitals of Marseille, France

* dor.nedonsel@lenval.com

Abstract

Background

Early-Onset Schizophrenia (EOS) is rare but severe mental health disorder in children and adolescents. Diagnosis of schizophrenia before the age of 18 years remains complex and challenging, especially in young children. In France, there are no recent reliable epidemiological data about the prevalence of EOS. The present study evaluates the EOS rate in a target clinical population of children and adolescents in psychiatric and medico-social care centres in the South-East of France.

Methods

Psychiatric and medico-social centres for children and adolescent in the geographical area have been contacted, and after receiving their agreement to participate in the study, eligible patients corresponding to inclusion criteria were selected based on patients’ medical records. Main inclusion criteria were age 7 to 17 years and intelligence quotient > 35. EOS categorical diagnosis was assessed by Kiddie-SADS Present and Lifetime psychosis section.

Results

37 centres participated and 302 subjects have been included in the study. The main result was the categorical diagnosis of EOS in 27 subjects, corresponding to a rate of 8.9% in the study population. Half of the patients presented mild to moderate intellectual deficiency. Interestingly, only 2.3% had a diagnosis of schizophrenia spectrum disorder noted in their medical records before standardized assessment.
Conclusions

The results of the study highlight the importance of using a standardized diagnostic tool for the diagnosis of schizophrenia in the paediatric population. In fact, EOS might be underdiagnosed in children and adolescents with neurodevelopmental disorders and subnormal cognitive functioning.

Trial registration

NCT01512641. Registered 19 January 2012; https://clinicaltrials.gov/ct2/show/NCT01512641

Background

Diagnosing schizophrenia before 18 years remains very complex. Indeed, there are no specific criteria for Early-Onset Schizophrenia (EOS) in standard classifications such as ICD-10 [1], DSM IV-TR [2] or DSM-5 [3]. To date, the prevalence of EOS has not been clearly identified. There is only a very limited number of epidemiological studies. Incidence data with diagnoses based on standardised clinical assessments such as the Schedule for Affective Disorders and Schizophrenia for School Age Children (Kiddie-SADS-PL) [4], are still rare in the paediatric population [5, 6]. Epidemiological studies concerning EOS are rare and of heterogeneous results [7, 8]. Observations from the National Institute of Mental Health cohort indicate that Childhood-Onset Schizophrenia (COS), with onset before 13 years, is very rare with an incidence of less than 0.04% [7]. In another study, prevalence is described as less than one in 10,000 children between 2 and 12 years of age [8]. In addition, other studies revealed that EOS represents less than 4% of all the schizophrenia diagnoses [6]. Specific and general care for EOS remains difficult and very challenging, and its outcome is worse than for other psychotic disorders [9].

In France, children and adolescents with neurodevelopmental disorders also including EOS are likely to be treated in the medico-social sector (MSS) offering educational support and the child psychiatric health sector (PHS) focusing on psychiatric care. Various types of institutions funded by Social Security (government subsidies), have been developed in both areas accommodated to the specific needs of the populations.

The French Equality of Rights and Chances law ensures that disabled persons in each sub-region [10] are directed to adapted MSS structures, based on detailed criteria including clinical, psychosocial and intellectual ability assessment. The institutions are composed of multidisciplinary teams, with psychiatrists being present only a few hours per week.

Orientation towards MSS or PHS is based on the clinical judgment of the referring psychiatrist according to ICD-10 [1], without mandatory standard diagnostic assessment. In consequences, there is no real benchmark of EOS rate in France.

According to our clinical experience, we hypothesised that EOS is underdiagnosed in current practice in France among the population of children and adolescents integrated in the centres described above.

The aim of this study was to estimate the rate of EOS in the pediatric population integrated in medico-social centres or in psychiatric outpatient care in South-East France using a standardized instrument, the Kiddie-SADS-PL [4]. In addition, the study aimed at characterising the clinical and neurocognitive profile of patients diagnosed with EOS.
Methods
The study has been approved by the Ethic Committee "Sud Méditerranée V" (ref.2011-A00787-34) and the French National Agency for Medicines and Health Products Safety (ANSM, n° B111395-70). The study has been registered on ClinicalTrials.gov (NCT01512641).

Design of the study
The study aimed at exploring the rate of the categorical EOS diagnosis using the psychosis section of the Kiddie-SADS-PL [4] and was part of a broader study investigating dimensional EOS diagnosis and neurocognitive exploration of subjects fulfilling DSM-IV-TR diagnostic criteria for schizophrenia.

Selection of centres (Fig 1)
We included three out of the five French sub-regions constituting the South of France region Provence Alpes Côte d’Azur (PACA, Fig 1) which represent more than 4/5 of the PACA population (2,15 million in 2012 [11]). All centres referred on the official list of the Regional Agency of Health (ARS) of the PACA Region were contacted [12]. The total number of subjects attending these centres was approximately 6160 [12]. We contacted the 228 eligible centres by sending a letter explaining the study and asking for their agreement to participate in the study.

Sample selection and inclusion of the study population
The investigators were four trained neuropsychologists specialised in schizophrenic disorders in children. Upon agreement of the eligible structures, they visited the centres in order to propose the study to all children and adolescents fulfilling inclusion criteria based on their medical records. Inclusion criteria were: age between 7 and 17 years; French speaking; IQ > 35 (WISC III/IV [13, 14]) or diagnosis of mild (F70) or moderate (F71) intellectual disability according to CIM-10 [1].

After obtaining written informed consent from the children and their parents, inclusion visits were scheduled. All subjects were included between February 2012 and May 2013.

Data collection
We recorded socio-demographic and neonatal data, ICD diagnoses, intellectual abilities, IQ, therapeutic care, rehabilitation, socio-educational activities and pharmacological treatment, interviewed parents and reviewed the child’s medical record.

Psychiatric diagnosis of EOS
Assessment of categorical DSM-IV-TR diagnosis of schizophrenia was undertaken using the psychosis section of Kiddie-SADS-PL [4]. Kiddie-SADS-PL is a semi-structured diagnostic interview which assesses current and past episodes of psychopathology in children and adolescents according to DSM IV-TR criteria. It consists of a first part which detects psychiatric disorders (one section per disorder) and additional sections that confirm the diagnosis. This instrument is constituted by two interviews, firstly, the parent(s) or the care-giver, and secondly, the child or adolescent; followed by a synthetic evaluation including all sources of information. When no symptoms are found, the administration of the first part takes 20 minutes. The length of the appointment increases as the number of diagnosed disorders increases, and can last up to two hours with the child and then with the adult.
Statistical analysis

Qualitative variables are presented as percentages with 95% confidence intervals using binomial approximation of the normal distribution. Quantitative variables are presented as mean and standard deviation or median. The McNemar’s Chi-squared test with continuity correction was used to compare the proportion of EOS diagnosis between the ICD and the Kiddie-
SADS-PL methods. The analysis was performed using SAS software (Version 9.3 package, SAS Institute, Cary, North Carolina, USA).

Results

Participation of centres and inclusion of subjects

Of the 228 qualifying structures, 37 (16.2%) accepted to participate in the study. Of the total number of 1200 subjects followed up in the 37 participating centres, 896 met inclusion criteria. 302 accepted inclusion in the study (33.7%). The flow chart of the study is presented in Fig 2.

Analyses of the total sample

Socio demographic characteristics (Tables 1 and 2). Of the 302 children included, 228 (75.5%) were followed up in MSS, and 74 (24.5%) in PHS. The mean age was 11.90 years (SD = 2.8) with a sex ratio male/female of 2.8 (222 males, 80 females). Of the 302 children, 157

![Flow chart of study](https://doi.org/10.1371/journal.pone.0236241.g002)
(52%) lived in a nuclear family setting, 78 (25.8%) in a single parent family, 49 (16.2%) in a recomposed family, and 15 (5%) were foster kids.

**Pregnancy and birth.** Concerning pregnancy, among the 278 mothers who answered the question regarding medication or toxin intake during pregnancy, 97 (34.9%) declared having taken tobacco (69, 24.8%); alcohol (7, 2.5%), illicit drugs (5, 1.8%) or psychotropics (5, 1.8%).

Birth parameters were within the normal range. The average pregnancy term was 37.8 weeks (SD = 2.7), birth weight was 3.09 kg (SD = 6.1), birth size was 49 cm (SD = 3), and the average head circumference was 34 cm (SD = 2.2).

**Rate of EOS in the sample.** After inclusion, two children were excluded from the study because of severe language disorders not permitting assessment by Kiddie-SADS-PL.

300 participants constituted the final sample. 27 out of 300 had a diagnosis of EOS according to the Kiddie-SADS-PL psychosis section criteria, corresponding to 8.9% of the sample (CI 95%: [6.2%; 12.7%]).

**Intellectual ability.** For the majority of participants, 214/302 (70.9%), an encrypted Full Scale Intellectual Quotient (WISC III/IV [13, 14]) was recorded. For 69/302 children (22.8%), intellectual disability was recorded based on ICD-10 classification [1]. For the remaining 19/302 (6.3%) children, only some WISC subtests were available, but no Full Scale Intellectual Quotient (FSIQ). In total, 151/302 (50.0%) had intellectual disability (details in Table 1) and the average of the FSIQ was 66.3 (SD = 20.4) (Table 2). The average FSIQ among males was slightly higher than among females (p = 0.01).

Table 1. Socio-demographic, cognitive, clinical and therapeutic description of the total sample.

| TYPE OF CENTRES                              | N = 302 | %   |
|----------------------------------------------|---------|-----|
| Psychiatric Health Sector (DH, CATTP)        | 74      | 24.5|
| DH                                           | 66      | 21.8|
| CATTP                                        | 8       | 2.6 |
| Medico-Social Sector (IME, ITEP, SESSAD)     | 228     | 75.5|
| IME                                          | 108     | 35.8|
| Inpatient                                    | 48      |     |
| Outpatient                                   | 60      |     |
| ITEP                                         | 66      | 21.8|
| SESSAD                                       | 54      | 17.9|
| SEX                                          |         |     |
| Female                                       | 80      | 26.5|
| Male                                         | 222     | 73.5|
| HOUSEHOLD COMPOSITION                        |         |     |
| Nuclear family                               | 157     | 52.0|
| Single-parent                                | 78      | 25.8|
| Recomposed family                            | 49      | 16.2|
| Placement–Host family                        | 10      | 3.3 |
| Placement–Foster Home                        | 5       | 1.7 |
| Other                                        | 3       | 1.0 |
| INTELLECTUAL ABILITY                         |         |     |
| No Mental Retardation (IQ ≥ 70)              | 132     | 43.7|
| Mild Mental Retardation (50 > IQ > 69)       | 75      | 24.8|
| Moderate Mental Retardation (35 > IQ > 49)   | 76      | 25.2|
| Global IQ lacking/heterogeneity              | 19      | 6.3 |

(Continued)
ICD-10 diagnosis (Table 1). Main reported ICD-10 psychiatric diagnoses notified in the medical records were: F84-Pervasive Developmental Disorders (n = 67, 22.2%); F71/F79-Mental Retardation (n = 69, 21.9%); F91-Conduct Disorder (n = 44, 14.6%), F81-Specific Developmental Disorders of scholastic skills (n = 44, 14.6%); F60-Specific Personality Disorders.
For 214 patients (70.9%), at least one mental disease has been referenced, for 69 (22.8%) at least two, and for 30 (9.9%) at least three. 88 individuals (29.1%) had no encrypted diagnosis other than intellectual deficiency noted in their medical record.

Indeed, a significant difference ($X^2 = 16.409$, df = 1, p-value < 10e-5) was found between EOS rate notified in the records (2.3%, ICD-10 diagnosis [1]) versus EOS rate diagnosed using standardized assessment (8.9%, Kiddie-SADS-PL [4]).

**Therapeutic care, rehabilitation, socio-educational activities and pharmacological treatment** (Tables 1 and 3). 182 of 302 participants (60%) had individual psychotherapy, 144 (47.7%) speech therapy, and 109 (31.5%) psychomotor, educational or physical therapy. At inclusion, 112 (37%) participants were treated with at least one medical drug, 42/112 (37.5%) took at least two, and 11/112 (9.8%) three or more drugs.

### Table 2. Mean age and mean FSIQ of the total sample and mean FSIQ by sex.

|                | N   | Mean | SD  | Median | Min  | Max  |
|----------------|-----|------|-----|--------|------|------|
| Mean Age (ys)  | Total sample | 302  | 11.90 | 2.85   | 12.00| 7.00 | 18.00|
| Mean FSIQ*     | Girls | 57   | 60.26 | 18.14  | 55.00| 38.00| 110.00|
|                | Boys  | 157  | 68.43 | 20.79  | 68.00| 36.00| 137.00|
|                | Total | 214  | 66.25 | 20.40  | 64.00| 36.00| 137.00|

*FSIQ: Full Scale Intellectual Quotient.

(n = 29, 9.6%); schizophrenia, schizotypal and delusional disorders (n = 9, 4.3%) and F20-Schizophrenia (n = 7, 2.3%).

For 214 patients (70.9%), at least one mental disease has been referenced, for 69 (22.8%) at least two, and for 30 (9.9%) at least three. 88 individuals (29.1%) had no encrypted diagnosis other than intellectual deficiency noted in their medical record.

Indeed, a significant difference ($X^2 = 16.409$, df = 1, p-value < 10e-5) was found between EOS rate notified in the records (2.3%, ICD-10 diagnosis [1]) versus EOS rate diagnosed using standardized assessment (8.9%, Kiddie-SADS-PL [4]).

### Table 3. Pharmacological treatment of the total sample.

| Medicinal drugs | N = 112 patients | %  |
|-----------------|------------------|----|
| Allergology     | 5                | 3.8|
| Anti-inflammatory| 5                | 3.8|
| Antibiotic      | 1                | 0.8|
| Cardiology      | 1                | 0.8|
| Endocrinology   | 4                | 3.1|
| Gastroenterology| 2                | 1.5|
| Neurology       | 12               | 9.2|
| Pneumology      | 6                | 4.6|
| Psychiatry      | 90               | 69.2|
| Homeopathy      | 1                | 0.8|
| Metabolism-Nutrition | 3   | 2.3|
| Psychotropic drugs |              |    |
| Antipsychotics  | 68               | 53.1|
| Psychostimulants| 15               | 11.7|
| Antiepileptics  | 10               | 7.8|
| Anxiolytics     | 12               | 9.4|
| Mood regulators | 9                | 7.0|
| Antidepressants | 6                | 4.7|
| Hypnotics       | 6                | 4.7|
| Antiparkinsonians| 2               | 1.6|

https://doi.org/10.1371/journal.pone.0236241.t003
Analyses of EOS sub-sample

Socio-demographic characteristics (Tables 2 and 4) and psychiatric family history. The mean age of the EOS subgroup was 12.4 years (SD = 3.25) with 14 children being younger than 13 years. The majority of children with EOS were boys (16/27, 59.3%).

Table 4. Socio-demographic, cognitive, clinical and therapeutic description of the EOS sub-sample.

| TYPE OF CENTRES | N = 27 | %   |
|-----------------|--------|-----|
| Psychiatric Health Sector (DH, CATTP) | 14 | 51.8 |
| DH | 13 | 48.1 |
| CATTP | 1 | 3.7 |
| Medico-Social Sector (IME, ITEP, SESSAD) | 13 | 48.1 |
| IME | 6 | 22.2 |
| Inpatient | | |
| Outpatient | | |
| ITEP | 5 | 18.5 |
| SESSAD | 2 | 7.4 |
| SEX | | |
| Female | 11 | 40.7 |
| Male | 16 | 59.3 |
| HOUSEHOLD COMPOSITION | | |
| Nuclear family | 14 | 51.8 |
| Single-parent | 6 | 22.2 |
| Recomposed family | 2 | 7.4 |
| Placement–Host family | 2 | 7.4 |
| Placement–Foster Home | 2 | 7.4 |
| Other | 1 | 3.7 |
| INTELLECTUAL ABILITY | | |
| No Mental Retardation (IQ ≥ 70) | 17 | 63.0 |
| Mild Mental Retardation (50 > IQ > 69) | 4 | 14.8 |
| Moderate Mental Retardation (35 > IQ > 49) | 4 | 14.8 |
| Global IQ lacking/heterogeneity | 2 | 7.4 |
| ICD-10 DIAGNOSIS in the children's file | ICD-10 Code | N = 27 | % |
| Disorders of psychological development | (F80-F89) | 16 | 59.2 |
| Pervasive Development Disorder | F84 | 13 | 48.1 |
| Specific Developmental Disorder of Scholastic Skills | F81 | 1 | 3.7 |
| Mental retardation | (F70-F79) | 1 | 3.7 |
| Unspecified Mental Retardation | F79 | 1 | 3.1 |
| Moderate Mental Retardation | F71 | 0 | 0 |
| Behavioural and emotional disorders with onset usually occurring | (F90-F98) | | |
| in childhood and adolescence | | 5 | 18.5 |
| Conduct Disorder | F91 | 4 | 14.8 |
| Disorders of adult personality and behaviour | (F60-F69) | 4 | 14.8 |
| Specific Personality Disorders | F60 | 3 | 11.1 |
| Schizophrenia, schizotypal and delusional disorders | (F20-F29) | 9 | 33.3 |
| Schizophrenia | F20 | 6 | 22.2 |
| Neurotic, stress related and somatoform disorders | (F40-F48) | 3 | 11.1 |
| Mood [affective] disorders | (F30-F39) | 3 | 11.1 |

(Continued)
Fourteen out of 27 (51.8%) participants lived in a nuclear family, 6/27 (22.2%) in single-parent family, 3/27 (11.1%) in recomposed family, 2/27 (7.4%) in host family and 2/27 (7.4%) in foster care.

Concerning psychiatric family history of the 27 EOS patients, 13 (48.1%) had at least one first or second degree family member with a psychiatric history (schizophrenia, bipolar disorder, depression, autism spectrum disorder or suicide).

**Neonatal data.** Concerning the pregnancy history, 12 of 27 mothers (44.4%) admitted medication or illicit drugs during pregnancy. Three mothers (10.3%) also mentioned traumatic events that occurred during pregnancy. Concerning birth parameters, the average pregnancy term was 38 (SD = 2.4) weeks. The average birth weight was 3.29 kg (SD = 5.9), birth size 49.7 cm (SD = 3.7), and head circumference 34.1 cm (SD = 2.2).

**Intellectual ability and ICD-10 diagnosis of EOS sample upon inclusion.** The majority of the 27 children with EOS had no intellectual disability (n = 19, 70.4%), and 4 (14.8%) presented mild to moderate intellectual disability. The mean of the Full Scale Intellectual Quotient (FSIQ) was 72.5 (SD = 21.4). Four patients (14.8%) did not have any additional psychiatric diagnosis in their medical record. ICD-10 psychiatric diagnoses at inclusion are presented in Table 4.

**Therapeutic care, rehabilitation, socio-educational activities (Table 4) and pharmacological treatment.** Twenty of the 27 EOS patients (74%) followed an individual psychotherapy, 5 (18.5%) received speech therapy, 3 (11.1%) had psychomotor re-education and 8 (29.6%) participated in socio-educational activities.
Concerning the use of psychiatric medication, 14 children had received psychiatric treatment before inclusion, with one child having received several types of drugs. Before inclusion, antipsychotic drugs represented 51.5%, antiepileptics 15.1%, psychostimulant drugs 12.1%, and benzodiazepines 6% of psychotropic prescriptions. Antiepileptics were used to treat epilepsy (n = 2) or as a mood regulator (n = 6); and benzodiazepines as anxiolytic drugs. Upon inclusion, 21 of the 27 EOS patients (77.8%) took at least one psychotropic drugs with 20 patients (74%) treated with at least one antipsychotic and one patient with psychostimulant. Seven patients were treated with at least two psychotropics, and 6 had no medication at all.

Discussion

The originality of this study is the use of standardized diagnostic assessment based on DSM IV-TR [2] in order to diagnose EOS in a large clinical sample of children and adolescents followed up in specific care structures (either in PHS or in MSS in France), half of them presenting mild to moderate intellectual disability.

EOS diagnosis

The rate of 8.9% (CI 95%: [6.2%; 12.7%]) EOS diagnosis in this sample of children and adolescents aged 7–18 years is higher compared to 1–2% in children and 5% in adolescents of the psychiatric populations described by Remschmidt and Theisen [15]. It is much higher than the 0.2% found in a retrospective cohort study of a primary care sample using the South Carolina Medicaid Claims database [16].

The proportion of EOS diagnosis after assessment with Kiddie-SADS-PL [4] was significantly higher than in the children’s medical record (8.9% vs 2.3%). The fact that diagnoses were made by different evaluators, at different ages of the patient and in different context might explain part of this discrepancy. The difference of clinical classification systems should also be considered, even if there are few in ICD-10 [1] and DSM IV-TR [2] criteria for schizophrenia diagnosis. Nevertheless, the use of a standardized clinical assessment tool (Kiddie-SADS-PL [4]) by trained professionals specialized in childhood schizophrenia probably explains the under-diagnosis of COS in this specific paediatric population diagnosed with developmental disorders before this type of specific evaluation. Standard assessment has generally not been used in current clinical practice in medico-social or mental health structures at the time of the study. In fact, diagnosis of schizophrenia in children and adolescent is often very challenging, in particular because of its comorbidity with intellectual disability and / or ASD [7, 17, 18]. The difficulty in diagnosing EOS is also related to its overlap with developmental and other child psychiatric disorders. Other factors that need to be considered are the rarity of EOS, its similarity to mood disorders, and the presence of hallucinations in children with disorders other than schizophrenia [19]. In addition, resemblance between the course of thought disorders and infantile thoughts, as well as thought disorders due to developmental delay might also explain the risk of diagnosis error and underdiagnosis of COS.

ICD-10 diagnosis

ICD-10 diagnosis notified in the children’s medical records was present in the vast majority of cases, but for almost 30% we did not find any clear information concerning the absence of psychiatric disorder. This could be due to cases of intellectual disability without associated psychiatric disease or an omission in the record. The most frequent diagnosis was Pervasive Developmental Disorders (PDD). Our results are difficult to compare because there are no recent French epidemiologic studies and existing studies do not necessarily use ICD-10 diagnosis as reference. Indeed, two studies conducted in two French sub regions in 2009 and 2012
among MSS, using CFTMEA (French classification of psychiatric disease of child and adolescent) as reference found 10–16% of autism and other PDDs, 12–13% of infantile psychosis and 22–26% of other psychiatric diseases [20, 21]. Considering that autism and infantile psychosis of the CFTMEA cover the ICD-10 chapter of PDD (F.84), the rates are 22.7% and 28% respectively, and therefore similar to the PDD rate in our sample of 22.2%.

Concerning ICD-diagnosis recorded in the medical files of the 27 children with EOS, the most common diagnosis was PDD. The result is in line with clinical overlap between ASD and EOS [22–24] and several studies describing the comorbidities associated with EOS [7, 25].

**Age**

The mean age of our sample (11.90±2.8 years) was one year less than the mean age of the population in centres for disabled children and adolescents in France [11, 26]. In France, nearly half of institutionalised disabled children and adolescents are 15 to 19 years old, and 40% are 10 to 14 years old [26]. Admission to medico-social structures is rare for young children, representing less than 9% before age 10 [26]. In our sample, concerning the paediatric population between 7 and 17 years, children coming from the PHS were younger (10.6, years SD = 2.8) than those of the medico-social MSS (12.3 years, SD = 2.73).

The mean age of the children with EOS was under 13 years, and at least 50% of them presented COS.

**Sex ratio**

The sex ratio sample was in favour of boys (2.8:1), accordingly to what was found in the MSS and PHS populations [11]. Along these lines, Ravaud and Ville (2003) suggested that the population of institutions for disabled children is predominantly male [27]. Lai et al. (2012 [28]) compared the prevalence of intellectual disability in children by gender in Taiwan using data from 2004 to 2010. Each year, boy cases exceeded girl cases, and the male-to-female ratio generally decreased with age [28].

The sex ratio in the EOS sample was 1.4 males for 1 female. This result is in line with those mentioned by McGrath et al., 2008, who found the same sex ratio for lifetime incidence of schizophrenia [29]. On the other hand, Stentebjerg-Olensen and colleagues described in their systematic review a preponderance of males (ratio 1.6:1) which is slightly higher than in our sample [25].

**Pregnancy and birth**

Our sample reported more tobacco consumption and less alcohol use during pregnancy than the rates found in the national perinatal survey conducted in the general French population [26]. The value of the face-to-face declaration of alcohol consumption is questionable even though many prevention campaigns on the dangers of alcohol during pregnancy have been carried out in France. Birth parameters are within the standard of the French population.

**Household composition**

In regards to the household breakdown, nuclear families are dominant, followed by single parents then recomposed families, as in the French population at the same period [20]. In our sample, the rate of placed children is 20 times higher than in the general population in France [27, 30]. The household composition of EOS was not different from that of the global sample.
Cognitive assessment

The average IQ of the total sample lies in the mild intellectual disability range, which is not surprising as 35.8% of children in this sample are from IME, institutions for children with intellectual disability. The IQ of boys in our sample is higher than the IQ of girls, which can be partly explained by the fact that 23% of children are from ITEP, institutions integrating mainly boys with challenging behaviours and without intellectual disabilities.

Cognitively, the EOS sample was on average at the limit of impairment (Mean FSIQ: 72.5, SD = 21.4). This result is in concordance with most studies which found a mean FSIQ in children with EOS being between 1–2 standard deviations below the general population norm [22, 31, 32].

Treatment

The majority of the children received reeducation and a large part followed individual psychotherapy. However, the type of psychotherapy was not identified. Almost 2/3 of children attended social and educational activities. Indeed, they are the main centres of MSS expertise. Also, there is some evidence supporting the effectiveness of psychological interventions in Early Onset Psychosis [33]. Very few children received cognitive remediation or workshops of social abilities. More than a third of children received medical drugs, specifically psychotropic drugs over half of which were antipsychotics. Nevertheless, about a quarter of children with EOS diagnoses were not treated with antipsychotics, the only available evidence-based treatment [34–36].

Limitations

We encountered a high rate of non-participation of centres (83.7%). Several reasons should be discussed. Firstly, some French psychiatrists might be opposed to standardized diagnosis criteria based on atheoretical classifications. Secondly, some physicians might have been worried by the families’ reaction to possible EOS diagnosis revealed by the study. Thirdly, some directors of MSS might have been concerned with regards to the staff’s reactions upon a diagnosis of schizophrenia.

We found a high rate of nonparticipation of families in the study (66.3%). In fact, many parents were themselves in precarious social situations and reluctant to devote time to this study which might explain part of this result. COS is a very challenging disease for diagnosis as well as follow-up with a high impact on patients but also on families. Compared to the literature, Lépine et al. (2000), also found a similar high nonparticipation rate (64%) in a study of the prevalence of psychiatric disorders and comorbidities study in the French general population, the ESEMED study [37]. Morton and colleagues (2005), found the reporting of participation varied significantly by type of epidemiologic studies and the participation information was not provided in any of the retrospective cohort studies [38]. Galea and Tracy (2007) observed that the participation rates for epidemiologic studies had steady declined over the past 30 years [39]. Thus, they showed that in ten years the participation rate reported in the epidemiological studies of prevalence of psychiatric disorders the National Comorbidity Survey (NCS) and NCS-replication decreased from 82.4% to 70.9%.

Because of the low participation rate of centres and families, the sample might not be sufficiently representative of the study population and the results can therefore not be extrapolated. However, study results underline the importance of improving the diagnosis of EOS in the pediatric population with early developmental disorders in France. Our study demonstrates that the assessment of EOS diagnosis by standardized diagnostic tools involving the child, parents as well as the support team, is feasible in the pediatric population with
neurodevelopmental disorders and intellectual deficiency. In order to adapt therapeutics and care of EOS children, follow-up assessments with standardized instruments covering clinical symptoms and functioning should be implemented in PHS and MSS centers. A correct and early diagnosis of COS using standardized assessment tools such as K-SADS-PL [4] seems also very important in order to allow early prescription of antipsychotic treatments, the only available evidence-based treatment in this indication [34–36]. Nevertheless, pharmacological treatment should not be a single treatment approach for these very complex patients and families.

Conclusion

The results of this study highlight the importance of using a standardized diagnostic tool for the diagnosis of schizophrenia in the paediatric population. In fact, EOS might be underdiagnosed in children and adolescents with neurodevelopmental disorders and subnormal cognitive abilities. Indeed, diagnostic assessment of schizophrenia in children is very challenging and should involve children, parents as well as support teams. Nevertheless, the fact that this disorder is often unrecognized seems to lead to suboptimal interventions which are likely to have repercussions on long term outcomes. We should therefore ensure that diagnosis of COS and its comorbidities are based on robust standardized assessment in order to enable the early use of validated treatments such as antipsychotics and to adjust therapies, thus improving short, medium and long term prognosis and outcome for children with COS.

Acknowledgments

We thank all patients and their families for their participation in this study. We are very grateful to the collaboration with Gaelle LAURE, all implicated professionals of medico-social and child psychiatric care centres and Monaa (Monaco Against Autism).

Author Contributions

Conceptualization: Emmanuelle Dor-Nedonsel, Marie-Line Menard, Eric Fontas, Valeria Manera, Florence Askenazy, Susanne Thümmler.

Data curation: Emmanuelle Dor-Nedonsel, Xavier Salle-Collemiche, Anne-Lise Tosello, Fanny Maria, Susanne Thümmler.

Formal analysis: Emmanuelle Dor-Nedonsel, Charlotte Sakarovitch, Eric Fontas, Fanny Maria, Susanne Thümmler.

Funding acquisition: Emmanuelle Dor-Nedonsel.

Investigation: Emmanuelle Dor-Nedonsel, Arnaud Fernandez, Xavier Salle-Collemiche, François Poinso, Anne-Lise Tosello, Fanny Maria, Florence Askenazy, Susanne Thümmler.

Methodology: Emmanuelle Dor-Nedonsel, Arnaud Fernandez, Charlotte Sakarovitch, Eric Fontas, Anne-Lise Tosello, Fanny Maria, Valeria Manera, Florence Askenazy, Susanne Thümmler.

Project administration: Emmanuelle Dor-Nedonsel, Florence Askenazy, Susanne Thümmler.

Resources: Emmanuelle Dor-Nedonsel, Florence Askenazy, Susanne Thümmler.

Software: Emmanuelle Dor-Nedonsel, Susanne Thümmler.

Supervision: Emmanuelle Dor-Nedonsel, Marie-Line Menard, Florence Askenazy, Susanne Thümmler.
Validation: Emmanuelle Dor-Nedonsel, Marie-Line Menard, Florence Askenazy, Susanne Thümler.

Visualization: Emmanuelle Dor-Nedonsel, Marie-Line Menard, Florence Askenazy, Susanne Thümler.

Writing – original draft: Emmanuelle Dor-Nedonsel, Marie-Line Menard, Arnaud Fernandez, Anne-Lise Tosello, Florence Askenazy, Susanne Thümler.

Writing – review & editing: Emmanuelle Dor-Nedonsel, Marie-Line Menard, Arnaud Fernandez, Charlotte Sakarovitch, Eric Fontas, Xavier Salle-Collemiche, François Poinso, Anne-Lise Tosello, Fanny Maria, Valeria Manera, Florence Askenazy, Susanne Thümler.

References

1. World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Organization. 1992. http://www.who.int/iris/handle/10665/37958. Accessed 20 Jan 2019.

2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM IV-R), (4th ed. Revised). Washington, D.C: American Psychiatric Association; 2000.

3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM 5). Washington, D.C: American Psychiatric Association; 2013.

4. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (Kiddie-SADS-PL): initial reliability and validity data. J Am. Acad Child Adolesc Psychiatry. 1997; 36:980–8. https://doi.org/10.1097/00004583-199707000-00021 PMID: 9204677

5. Tandon R, Gaebel W, Barch DM, Bustillo J, G run RE, Heckers S, et al. Definition and description of schizophrenia in the DSM-5. Schizophr Res. 2013; 150:3–10. https://doi.org/10.1016/j.schres.2013.05.028 PMID: 23800613

6. Hälfler H, Nowotny B. Epidemiology of early-onset schizophrenia. Eur Arch Psychiatry Clin Neurosci. 1995; 245:80–92. https://doi.org/10.1007/BF02190734 PMID: 7654792

7. Driver DI, Gogtay N, Rapoport JL. Childhood Onset Schizophrenia and Early Onset Schizophrenia spectrum disorders. Child Adolesc Psychiatr Clin N Am. 2013; 22:539–55. https://doi.org/10.1016/j.chc.2013.04.001 PMID: 24012072

8. Burd L, Kerbeshian J. A North Dakota Prevalence Study of Schizophrenia Presenting in Childhood. J Am Acad Child Adolesc Psychiatry. 1987; 26:347–50. http://doi.org/10.1097/00004583-198705000-00012 PMID: 3496327

9. Clemmensen L., Vernal D., Steinhausen H.C. A systematic review of the long-term outcome of early onset schizophrenia. BMC Psychiatry. 2012. 12:150. http://doi.org/10.1186/1471-244X-12-150 PMID: 22992395

10. LOI n° 2005–102 du 11 février 2005 pour l’égalité des droits et des chances, la participation et la citoyenneté des personnes handicapées. JORF. 2005. https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT00000809647&categorieLien=id. Accessed 20 Jan 2019.

11. Artaud D., Laffond D. Bilan démographique—La croissance démographique portée par les naissances. Insee. 2015.

12. ARS PACA. 8 100 places dans les établissements et services pour enfants et adolescents handicapés de la région Provence-Alpes-Côte d’Azur en 2006. InfoStat. 2009;(8):1–8. http://dress.solidarites-sante.gouv.fr/IMG/pdf/Infostat8. Accessed 31 Jan 2011.

13. Prifitera A, Saklofske DH. WISC-III Clinical Use and Interpretation: Scientist-Practitioner Perspectives. 1st ed. Academic Press; 1998.

14. Flanagan DP, Kaufman AS. Essentials of WISC-IV Assessment. John Wiley & Sons; 2004.

15. Remschmidt H, Theisen F. Early-onset schizophrenia. Neuropsychobiology. 2012; 66:63–9. https://doi.org/10.1159/000338548 PMID: 22797279

16. Jerrell JM, McIntyre RS. Factors Differentiating Childhood-Onset and Adolescent-Onset Schizophrenia: A Claims Database Study. Prim Care Companion CNS Disord. 2016; 18(2).

17. Ross RG, Heinlein S, Tregellas H. High rates of comorbidity are found in childhood-onset schizophrenia. Schizophr Res. 2006; 88:90–5. https://doi.org/10.1016/j.schres.2006.07.006 PMID: 16916600
Early-Onset Schizophrenia in a French paediatric population

18. McClellan J, Stock S. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Schizophrenia. J Am Acad Child Adolesc Psychiatry. 2013; 52:976–90. https://doi.org/10.1016/j.jaac.2013.02.008 PMID: 23972700

19. Askenazy FL, Lestideau K, Meynadier A, Dor E, Myquel M, Lecrubier Y. Auditory hallucinations in prepubertal children. A one-year follow-up, preliminary findings. Eur Child Adolesc Psychiatry. 2007; 16:411–5. https://doi.org/10.1007/s00787-006-0577-9 PMID: 17468968

20. Peintre C, Bouquet-Y sos C. Les enfants et adolescents pris en charge dans les établissements et services en faveur des personnes handicapées en Ile-de-France (ES2006). 2009. https://drees.solidarites-sante.gouv.fr/etudes-et-statistiques/ Accessed 01 July 2015.

21. Marabet B. Les IME: Qui sont-ils? Où vont-ils? CREAHI AQUITAINE. 2012. http://www.crea-aquitaine.org/wp-content/uploads/2014/12/2013_05_01Etude IME_.pdf

22. Kumra S, Wiggs E, Bedwell J, Smith AK, Arling E, Albus K, et al. Neuropsychological deficits in pediatric patients with childhood-onset schizophrenia and psychotic disorder not otherwise specified. Schizophr Res. 2000; 42:135–44. https://doi.org/10.1016/s0920-9964(99)00118-8 PMID: 10742651

23. Hommer RE, Swedo SE. Schizophrenia and Autism—Related Disorders. Schizophr Bull. 2015; 41:313–4. https://doi.org/10.1093/schbul/sbu188 PMID: 25634913

24. Spek AA, Wouters SGM. Autism and schizophrenia in high functioning adults: Behavioral differences and overlap. Res Autism Spectr Disord. 2010; 4:709–17.

25. Stenteberg-Olesen M, Pagsberg AK, Fink-Jensen A, Correll CU, Jeppesen P. Clinical Characteristics and Predictors of Outcome of Schizophrenia-Spectrum Psychosis in Children and Adolescents: A Systematic Review. J Child Adolesc Psychopharmacol. 2016; 26:410–27. https://doi.org/10.1089/cap.2015.0097 PMID: 27136403

26. Blondel B, Kermarrec M. Les naissances en 2010 et leur évolution depuis 2003. Enquête nationale Perinatale 2010, 2011. http://social-sante.gouv.fr/IMG/pdf/Les_naissances_en_2010_et_leur_evolution_depuis_2003.pdf. Accessed 20 Jan 2019.27.

27. Ravaud J.F., Ville I. Les disparités de genre dans le repérage et la prise en charge des situations de handicap. Rev Fr Aff Soc. 2003; 1–2:225–53. http://www.cairn.info/resume.php?id_ARTICLE=RFAS_03110225.

28. Lai D-C, Tseng Y-C, Hou Y-M, Guo H-R. Gender and geographic differences in the prevalence of intellectual disability in children: analysis of data from the national disability registry of Taiwan. Res Dev Disabil. 2012; 33:2301–7. https://doi.org/10.1016/j.ridd.2012.07.001 PMID: 22877930

29. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev. 2008; 30:67–76. https://doi.org/10.1093/epirev/mxn001 PMID: 18480098

30. Pla A, Beaumel C. Bilan démographique 2011 La fécondité reste élevée. INSEE. 2012: 1385. http://www.insee.fr/fr/ccp/ipweb/ip1385/ip1385.pdf.

31. Fagerlund B, Pagsberg AK, Hemmingsen RP. Cognitive deficits and levels of IQ in adolescent onset schizophrenia and other psychotic disorders. Schizophr Res. 2006; 85:30–9. https://doi.org/10.1016/j.schres.2006.03.004 PMID: 16626945

32. White T, Ho B-C, Ward J, O'Leary D, Andreasen NC. Neuropsychological Performance in First-Episode Adolescents with Schizophrenia: A Comparison with First-Episode Adults and Adolescent Control Subj ects. Biol Psychiatry. 2006; 60:463–71. https://doi.org/10.1016/j.biopsych.2006.01.002 PMID: 16566898

33. Anagnostopoulou N, Kyriakopoulos M, Alba A. Psychological interventions in psychosis in children and adolescents: a systematic review. European Child & Adolescents Psychiatry. 2019. https://doi.org/10.1007/s00787-018-1159-3.

34. Kendall T, Hollis C., Stafford M., Taylor C., On behalf of the Guideline, Development Group. Recognition and management of psychosis and schizophrenia in children and young people: summary of NICE guidance. BMJ. 2013; (346:j1150). https://doi.org/10.1136/bmj.j1150 PMID: 23344308

35. McClellan J, Stock S. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Schizophrenia. J Am Acad Child Adolesc Psychiatry. 2013 Sep 1; 52(9):976–90. https://doi.org/10.1016/j.jaac.2013.02.008 PMID: 23972700

36. National Collaborating Centre for Mental Health(UK). Psychosis And Schizophrenia In Children And Young People. Leicester (UK): British Psychological Society (NICE Clinical Guidelines, No. 155.); 2013

37. Lépine J-P, Gasquet I, Koves V, Arbabzadeh-Bourcier S, Nègre-Pagès L, Nachbaur G, et al. Prevalence and comorbidity of psychiatric disorders in the French general population. Encephale. 2005; 31:182–94. https://doi.org/10.1016/s0013-7006(05)82385-1 PMID: 15959445

38. Morton LM, Cahill J, Hartge P. Reporting Participation in Epidemiologic Studies: A Survey of Practice. Am J Epidemiol. 2006; 163:197–203. https://doi.org/10.1093/aje/kwj036 PMID: 16339049

39. Galea S, Tracy M. Participation rates in epidemiologic studies. Ann Epidemiol. 2007; 17:643–53. https://doi.org/10.1016/j.annepidem.2007.03.013 PMID: 17553702