Childhood Onset Schizophrenia: Evaluation and Treatment

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Question 1

- Prodromal symptoms of early-onset schizophrenia may include all of the following except?

A) Deficits in attention

B) Impaired language and verbal memory

C) Excellent coordination and motor skills

D) Dysphoria, anxiety and physical complaints

E) Social withdrawal and isolation

Question 2

- All of the following clinical characteristics have been reported to be reliably diagnosed in children except:

A) Hallucinations

B) Delusions

C) Illogical thinking

D) Loosening of Associations

E) Poverty of speech

Question 3

- Neurobiological findings that have been associated with schizophrenia may include all of the following except:

A) Deficits in smooth eye pursuit movements

B) Impairments in autonomic responsivity

C) A progressive decrease in ventricular size

D) Smaller total cerebral volume

E) Frontal lobe dysfunction

Question 4

- The two atypical antipsychotics approved by the FDA for treatment of schizophrenia in adolescents include:

A) Risperidone and Olanzapine
B) Quetiapine and Olanzapine
C) Ziprasidone and Quetiapine
D) Aripiprazole and Risperidone
E) Olanzapine and Aripiprazole

Question 5

- Factors associated with a better prognosis in childhood onset schizophrenia include all except:

A) Earlier age of onset
B) Higher premorbid intelligence
C) More positive symptoms
D) Less negative symptoms
E) Family support and cooperation in treatment

Teaching Points

- Very Early Onset Schizophrenia, Early Onset Schizophrenia and Schizophrenia of more traditional time of onset share multiple neurobiological similarities
- The early diagnosis of VEOS and the implementation of early intervention are crucial to a better prognosis
- Psychosocial interventions are essential to maximize the treatment
- Risperidone and Aripiprazole have been approved for treatment of schizophrenia in adolescents
- Prognosis is guarded

Outline

- History
- Diagnosis
- Clinical characteristics
- Course
- Outcome
- Differential diagnosis
- Treatment:
  - Psychosocial interventions
  - Pharmacological agents
- Conclusions

History

- Rare cases of Childhood onset schizophrenia in the literature
- Cases were noted in the past and date back to the observations of Kraepelin

Diagnosis

- Diagnostic criteria are the same for all ages with minimal modifications for Early Onset Schizophrenia (EOS; onset before age 18 years) and Very Early Onset Schizophrenia (VEOS; onset before age 13 years)
- Children should have at least two of the following characteristic symptoms for at least one month: delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, negative symptoms

Diagnosis

- Hallucinations and delusions are less complex than in adults
- Failure to achieve expected levels of interpersonal, academic, or occupational achievement
- Some symptoms must be present for 6 months
- Other psychotic conditions must be ruled out

Epidemiology

- VEOS occurs predominantly in males
- Ratio M/F: 2/1
- Prevalence rates have not been established
- In a longitudinal patient study: of 312 patients over 13 years, only 4 were VEOS and 28 EOS (Thomsen, 1996)
- Youngest cases:
  - 3 years of age (Russel et al., 1989)
  - 5.7 years of age (Green and Padron-Gayol, 1986)
- No sufficient evidence to justify categorizing EOS, VEOS as a separate subcategory

Clinical Characteristics

- Prodromal period is often prolonged in EOS:
  - Insidious onset is more common in children
  - Acute onset is more often in adolescents
- Prodromal symptoms often include:
  - Deficit in attention
  - Impaired language and verbal memory
  - Poor coordination and gross motor skills
  - Impaired academic performance
  - Limited Social skills
  - Social withdrawal and isolation
  - Some degree of functional impairment and aggression
  - Dysphoria, anxiety, physical complaints, sleep changes
  - Idiosyncratic or bizarre behaviors/preoccupations

Clinical Characteristics

- In most series, majority of children have received a psychiatric diagnosis prior to the onset of psychotic symptoms
- Most common previous diagnoses:
  - Pervasive Developmental Disorders
  - ADHD
  - Depressive disorders
- Other diagnoses: ODD, CD, Early onset personality disorders

Clinical Characteristics

- Once symptoms appear, phenomenology is similar to that seen in adults
- Most common characteristics:
  -- Hallucinations: 80%, AH > VH
  --Delusions: 60%
  -- Blunting of affect
  --Disorganized speech: less common
- Progressive increase in complexity as the child is getting older
- Illogical thinking and Loosening of Associations can be reliably diagnosed but not poverty of speech and incoherence; Catatonia is rare

Cognitive Delays

- 10-20% have an IQ in the borderline to mentally retarded range
- Actual numbers may be higher because some studies have excluded patients with mental retardation
- Language and communication deficits are common
- Neuropsychological testing:
  - Difficulties with complex information processing
  - Consistent with the adult literature

(Arasnow et al., 1994)

Neurobiological Deficits

- Deficits in smooth eye pursuit movements
- Impairments in autonomic responsivity
- Neuroimaging findings:
  - A progressive increase in ventricular size
  - Smaller total cerebral volume
  - Decrease in cortical grey matter
  - Frontal lobe dysfunction
- No diagnostic value for laboratory evaluations and neuroimaging techniques
- Essential to rule out other medical disorders

Psychological and Social Factors

- There is no evidence that psychological or social factors cause schizophrenia
- Environmental factors may potentially interact with biological risk factors to mediate the timing, the course, and severity of the disorder
- Psychosocial stressors influence the onset and/or exacerbation of acute episodes and relapse rates
- The relationship between schizophrenia and SES is unclear: predominance of sample inpatient

Familial Pattern

- Increased family history of schizophrenia and schizophrenia spectrum disorders
- Increased family history of affective disorders, primarily depression
- Communications deficits are often found in families of children with VEOS

Course

- Acute phase: Predominance of positive symptoms; generally lasts 1 to 6 months; shift from positive to negative over time
- Recuperation/Recovery phase: significant impairment with negative symptoms
- Residual phase: Some youth with EOS may have prolonged periods between acute phases with limited symptoms. Most continue to be impaired with negative symptoms
- Chronically ill patients: Some patients will remain chronically ill → most severely impaired children will require the most comprehensive treatment resources

Outcome

- Mostly retrospective studies: limitations
- Premorbid characteristics, treatment response and adequacy of therapeutic resources
- VEOS longitudinal study (Eggers, 1978, 1989):
  - 10 year follow-up study:
    - 57 patients, onset between 7 and 13 years of age
    - 28% had schizoaffective disorder
    - 50% significant impairment
    - 30% good social adaptation
    - 20% remission
    - Onset before age 10 (n = 11) $\rightarrow$ poor outcome
  - 42 year follow-up study:
    - 25% complete remission
    - 25% partial remission
    - 50% chronic impairment

Outcome

- In general, the earlier the onset of COS, the poorer the prognosis.
- Predictors of better prognosis include higher premorbid intelligence, more positive than negative symptoms, and cooperation of family in treatment (Remschmidt 2002)
- Long-term follow-up over 6-40 years indicates that significant impairment persists into adulthood; only 7% of the sample were able to maintain a stable relationship; 59% were unmarried and living alone; 73% had some form of employment, 27% were unable to work (Eggers, 2002).

Outcome in COS

Authors	F/U period (y)	Age at onset (y)	N	Female (%)	Male (%)	Criteria	Value (%)
Lay[35]	10	11 through 18	96	41 (43)	55 (57)	Social disability	No dysfunction: 8 (12) Minimum: 5 (8) Obvious: 9 (14)
Remschmidt[27]	42	5 through 14	38	15 (39)	23 (61)	Global assessment scale	Good: 6 (16) Moderate: 9 (24) Poor: 23 (60)
Eggers[7]	42	6 through 14	44	25 (57)	19 (43)	Course of illness	Complete remission: 11 (25) Partial remission: 11 (25) Poor: 22 (50)
Asarnow[28]	1 to 7	6 through 11	21	6 (29)	15 (71)	Course of illness	Remission: 6 (33) Chronic schizophrenia: 12 (67)
Werry[36]	4.3 ± 3.2	7 through 17	30	15 (50)	15 (50)	*DSM-III-R*	Serious social disability: 22 (55) Remission: 7 (23) Subchronic: 4 (13) Chronic: 19 (64)
Inoue[30]	3	10 through 17	19	9 (47)	10 (53)	Occupational situation	Fully employed: 3 (16) Same level: 4 (21) Below level: 3 (16) Limited ability: 5 (26) Hospitalized: 4 (21)
Kimura[37]	> 3	12 through 17	23	9 (39)	14 (61)	Course of illness	Remittent: 7 (30.5) Fading: 7 (30.5) Scanty: 6 (26) Persistent: 3 (13)

COS, childhood-onset schizophrenia; F/U, follow-up.

Khurana, et al. Feb 2007

Differential Diagnosis

- Thorough review of presenting symptoms, course, and premorbid functioning
- Adherence to DSM-IV criteria
- Clinician must have familiarity with normal development, general psychopathology, and how psychotic symptoms present in children:
- Determination of family psychiatric history

Mood Disorders

- Both schizophrenia and psychotic mood disorders present with a variety of affective and psychotic symptoms
- In VEOS negative symptoms may be mistaken for depression
- Mania often presents with florid psychosis
- Psychotic depression may present with mood-congruent or incongruent psychotic features
- One half of children with VEOS or EOS with bipolar disorder may be originally misdiagnosed with schizophrenia
- Longitudinal reassessment is crucial

General Medical Conditions

- Thorough pediatric and neurologic evaluation
- Delirium, seizure disorders, CNS lesions (brain tumors, congenital malformation), neuro-degenerative disorders (Huntington's chorea, lipid storage diseases) , metabolic diseases (endocrinopathies, Wilson's disease), DD (VCF), toxic encephalopathies (PCP, THC), and infectious (HIV).
- Laboratory tests:
  - CBC, Thyroid Function Tests, Serum chemistry, UA, toxicology
  - Chromosomal analysis, HIV
  - Neuroimaging studies, EEG

Nonpsychotic Behavioral and/or Emotional Disorders

- PTSD: dissociative episodes with depersonalization and/or derealization, anxiety phenomena
- Lower rates of negative symptoms, bizarre behavior, and thought disorder
- N=209 children with schizophrenia → 21% personality disorders at 10 year follow-up (Thomsen, 1996)

Schizoaffective Disorder

- Early onset schizoaffective disorder has not been well defined
- Follow-up studies have found low rates persisting
- 28% of EOS had schizoaffective psychoses at follow-up (Eggers, 1989)
- Better outcome than VEOS

Pervasive Developmental Disorders

- Absence or transitory nature of psychotic symptoms
- Predominance of the characteristic deviant language pattern
- Aberrant social relatedness
- Early age of onset < 3 years of age for autism versus > 5 years for VEOS

Other disorders

- OCD: Intrusive thoughts and repetitive ritualistic behaviors may be difficult to differentiate from psychosis in children
- Developmental Language Disorders: speech abnormalities mistakenly diagnosed as being thought disorder
- Schizotypal and schizoid personality disorders
- Multidimensionally Impaired: deficits in attention, impulse control, affect regulation, and transient or subclinical psychotic symptoms → Risk for schizophrenia versus a distinct disorder?

Treatment

- Must involve both the child and the family
- Combination of psychosocial and pharmacological treatment approaches
- Developing a support system: siblings, friends, peers, and teachers
- Most recommended treatments are based on trials in adults with schizophrenia
- Risperidone and Aripiprazole recently approved for treatment of schizophrenia in adolescents

Psychosocial Therapies

- Social skills training
- Intensive in home therapy:
  - Mobile therapy
  - Family Based Service Unit
- Individualized educational program
- Targeting high emotional expression and identifying and addressing environmental stressors
- Psychoeducational programs
- Day treatment, partial hospitalization programs, after school, and summer programs
- Inpatient treatment for stabilization

Pharmacological Approaches

Special considerations

- Children metabolize medications faster than adults: may need to consider multiple daily doses; plasma half-life versus brain half-life
- Higher density of D2 receptors in children compared to adults
- Likely more sensitive to side effects than adults
- Low body fat
- Long-term side effects unclear

Conventional Antipsychotics

- Double-blind, controlled trials have shown that haloperidol and loxitane are effective for treating children with schizophrenia
  - Haloperidol found to be effective in reducing symptoms of thought disorder, hallucinations and persecutory ideation
  - Loxitane and haloperidol superior to placebo
- Single-blind trials support the effectiveness of thiothixene and thioridazine with improvement in psychotic symptoms in about 50% in youth with chronic schizophrenia
- Same side effect profile as in adults: EPS (↓ in children, ↑ in adolescents), sedation, TD and NMS

Clozapine

- Sporn et al, 2007: 54 children & adolescents participated in a double-blind (N=22) or open-label (N=32) clozapine trial.
- Clinical improvement as per Brief Psychiatric Rating Scale strongly correlated with N-desmethylclozapine/clozapine ratio at 6-weeks.
- Rate of side effects higher than typically seen in adults

Clozapine

- NIMH study: N=21 with VEOS (Kumra et al., 1996):
  - Clozapine (176 ± 149 mg/day) superior to haloperidol (16 ± 8 mg/day)
  - Both positive and negative symptoms improved
  - In the clozapine group: 5 developed neutropenia and two had seizures, but no agranulocytosis
  - Tremor, akathisia, and EPS in 15%
- Case studies:
  - Types of side effects similar to what is seen in adults
  - One case of acute pancreatitis
  - Clozapine-induced obsessive compulsive symptoms
  - Dose: 50mg/day up to 900 mg/day

Risperidone

- Recently approved by the FDA for schizophrenia for the age range 13-17 years.
- Based on two short-term (6 to 8 weeks), double-blind, controlled trials for patients with acute episode of schizophrenia
- 417 subjects in the two studies treated with Risperidone ranging from 0.15 mg/day to 6 mg/day

Risperidone

- Treated patients had significantly greater reduction decrease in PANSS scores
- Treated patients had significant decrease in hallucinations, delusional thinking, and other symptoms of their illness.
- Drowsiness, fatigue, increase in appetite, anxiety, nausea, dizziness, dry mouth, tremor, and rash were the most common side effects noted in the studies

Risperidone: Side Effects

- EPS: 5 of 16 patients in the series by Grcevich's group (1996)
- TD
- Weight gain (3.6-6.3 Kg)
- Fatigue/sedation
- Galactorrhea
- Hepatotoxicity: Association of weight gain, increased LFT and liver fatty infiltration?
- Others: photophobia, headache, insomnia, depression, anxiety, lightheadedness

Olanzapine

- 8-week open-label trial (Kumra et al., 1998)
  - 8 youths with treatment resistant EOS
  - Results based on CGI:
    - 3 much improved
    - 1 minimally improved
- 15 children with VEOS (Sholevar et al., 2000)
  - 6 to 13 years of age
  - Results
    - 5 “great improvement”
    - 5 “moderate improvement”

Olanzapine

- Pharmacokinetics:
  - Ages 10-18 years
  - Dose received 2.5-20 mg/day
  - Elimination half-life 37.2± 5.1 hours
- Adverse effects:
  - Increased appetite: average weight gain 3.4 ± 4.1 kg
  - Constipation
  - Nausea/vomiting
  - Headache
  - Somnolence
  - Transient elevation of liver function tests

Olanzapine

- 1-year open-label trial of olanzapine for the treatment of COS: Positive symptoms improved after 6 weeks and negative symptoms showed improvement after 1 year of treatment. (Ross 2003)
- Adverse effects reported in various studies: Increased appetite and weight gain, sedation, GI symptoms, headaches, agitation, liver function abnormalities, and sustained tachycardia

Quetiapine

- No published controlled trials
- Pharmacokinetic study (McConville et al., 2000):
  - well tolerated up to the dose of 400 mg bid
  - No unexpected and serious side effects observed
  - Most common SE: insomnia, tachycardia, and decreased total thyroxine
  - No emergence of EPS
- Single case reports:
  - 14-year-old boy with schizophrenia (Szigethy et al., 1998)
  - 15-year-old girl with an acute psychotic episode (Healy et al., 1999)

Ziprasidone

- Retrospective analysis in a State Hospital
- Children and adolescent who received ziprasidone for at least 10 days
- Chart reviewed for diagnoses, dose/duration, response, vital signs, EKGs, and side effects
- CGI-S were assigned retrospectively by the investigators
- Endpoint was defined as:
  - patient discharge from the hospital
  - discontinuation of ziprasidone therapy

» Patel et al., 2002

Ziprasidone

- 8 males and 5 females; age range: 13 to 18 yo
- Diagnoses: MDD (4); schizophrenia (4); bipolar disorder (3); Psychotic disorder, NOS (2)
- Average endpoint dose was 53.31 ± 25.22 mg/day
- 10 patients were considered as responders
- Limited side effects:
  - akathisia; agitation
  - gastrointestinal upset, sedation, and dizziness
  - EKGs
- Conclusion: Ziprasidone maybe effective and well tolerated as an acute treatment for children and adolescents

Ziprasidone

- Sikich 2006: Ziprasidone beneficial in 13/40 patients with COS after 12 weeks of treatment
- Mean final dosage 118 mg/d.
- Over 1 year: 50% patients gained weight but no significant ECG changes occurred.
- Preliminary data suggest that ziprasidone may be useful in the treatment of COS.

Aripiprazole

- October 2007: FDA approved aripiprazole for the treatment of childhood schizophrenia in patients aged 13-17 years.
- Initiation of treatment at 2mg/d and then titrated upwards for 5 days to a target dose of 10 mg/d
- Approval based on a randomized double-blind study of 302 ethnically diverse adolescents with an acute episode of schizophrenia requiring hospitalization at 101 centers in 13 countries.

Aripiprazole

- Aripiprazole started at 2 mg/d and then up-titrated for 5 days to 10 mg/d or uptitrated for 11 days to 30 mg/d. Approximately 85% of patients completed the study
- At 6 weeks: Both doses achieved significant improvements from baseline relative to placebo
- 30 mg/d didn’t show improved efficacy vs. 10 mg/d
- Adverse reactions: Incidence ≥ 5% ; at least twice that of placebo
- A/E were dose related and included extrapyramidal symptoms, somnolence and tremor.

Comparisons of Antipsychotics in COS

Antipsychotic	Type of study	N	Outcome	Mean daily dose ranges	Adverse effects
Olanzapine vs risperidone vs haloperidol[18]	Double-blind, randomized, 8 weeks	50	3 agents equally efficacious	Olanzapine: 12.3 ± 3.5 mg Risperidone: 4 ± 1.2 mg Haloperidol: 5 ± 2 mg	Atypicals: Parkinsonian symptoms, EPS Haloperidol: EPS, headache, blurred vision All: weight gain
Risperidone[19]	Open-label prospective study	11	Significant improvement on total PANSS score (28%), BPRS score (30%), and CGI severity score (31%)	Risperidone 3.14 ± 1.6 mg/d	EPS, somnolence, weight gain, depression
Risperidone vs olanzapine[20]	Open-label, randomized, comparative 12-week study	259	Both agents equally efficacious	Risperidone: 1.62 ± 1.02 mg/d Olanzapine: 8.18 ± 4.41 mg/d	EPS and weight gain; no difference between 2 groups
Olanzapine vs risperidone vs haloperidol[21]	8 weeks, open clinical trial	43	Significant improvement in both positive and negative symptoms in all 3 groups using PANSS	Olanzapine: 12.9 ± 3.1 mg/d Risperidone: 3.3 ± 1.1 mg/d Haloperidol: 8.3 ± 3.8 mg/d	Haloperidol: more severe EPS and depression Olanzapine and haloperidol: fatigability, sedation, and increased sleep duration
Haloperidol vs clozapine[16]	6-week double-blind trial	21	Clozapine: better efficacy	Haloperidol: 16 ± 8 mg/d Clozapine: 176 ± 149 mg/d	Clozapine: neutropenia, seizures, cardiac complications
Clozapine vs olanzapine[17]	Double-blind, randomized 8-week trial	25	Clozapine: significant improvement compared with olanzapine using medication-free baseline	Clozapine: 327 mg/d Olanzapine: 19.1 mg/d	Both groups: weight gain Clozapine: seizures, lipid abnormalities

COS, childhood-onset schizophrenia; EPS, extrapyramidal syndrome; PANSS, positive and negative symptom scale; BPRS, brief psychiatric rating scale; CGI, clinical global impression.

Khurana et al 2007

Treatment of Early Onset Schizophrenia Spectrum Disorders Study (TEOSS)

- Publicly funded clinical trial
- To compare efficacy, safety and tolerability of risperidone, olanzapine, and molindone in youth
- Randomized, double-blind, parallel-group design at four sites
- Youth with EOSS (8-19 years): 8-week acute trial of risperidone (0.5-6.0 mg/d), olanzapine (2.5-20 mg/d), or molindone (10-140 mg/d)

McClellan, et al. JAACAP 2007

Treatment of Early Onset Schizophrenia Spectrum Disorders Study (TEOSS)

- Primary outcome measure: Responder status at 8 weeks (20% reduction in baseline PANSS scores + significant improvement on CGI
- 476 youths screened, 173 further evaluated, and 119 randomized.
- Responders continued double-blind treatment for 44 weeks.
- Results awaited

Frazier, et al. JAACAP 2007

Other Treatment approaches

- Evidence from the adult literature:
  - Lithium
  - Benzodiazepines
  - Anticonvulsants
  - ECT
- No data in children for Schizophrenia

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Answers

1) C
2) E
3) C
4) D
5) A