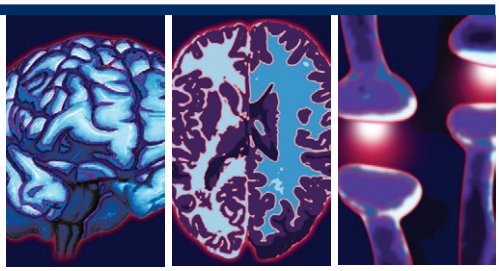
Case Report



Between Autistic Spectrum Disorder (ASD) and Childhood Onset Schizophrenia (COS): A Case Report

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Abstract

Background:

Even if childhood-onset of schizophrenia is described in the literature, and there are several case reports of concomitant autism spectrum disorders (ASD) and childhood-onset schizophrenia (COS), early diagnosis remains less the rule than the exception.

Method:

We report the detailed clinical history of a young woman with ASD and childhood onset schizophrenia from birth to the age of 26. The evolution of the state of the patient is reported together with the diagnosis provided by the caregivers and the pharmacological and psychological treatment.

Results:

The delay in formulating a diagnosis of concomitant ASD and COS as well as the pressure on academic achievement have contributed to the patient's sequel of crisis and relapses. The clinical status of the patient has presented a marked improvement when the comorbidity has been acknowledged and properly treated, both pharmacologically and via an appropriate reduction of the stressful proficiency requirements.

Conclusion:

Early diagnosis of psychiatric comorbidities in ASD allows a more effective therapeutic strategy and the adoption of a psychopedagogical approach adapted to the vulnerability of these patients with respect to stress.

Keywords

Children Onset Schizophrenia (COS), Autistic Spectrum Disorder (ASD), Psychopedagogical approach, Early diagnosis

Introduction

Even if childhood-onset of schizophrenia is described in the literature, and there are several case reports of patient with ASD and childhood-onset schizophrenia, difficulties persist to establish an early diagnosis. This may depend on the peculiar psychotic symptoms, easily confused with nightmares that are relatively common in infancy, as well as on the focalisation of the family environment and of the teachers on the

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school proficiency, which for these patients can be sufficient or even good in spite of the poverty of the social interactions.

The presence of psychotic symptoms is furtive, exposing for several years the young patient to a chronic situation before the "official" onset of the illness, without an identifiable acute phase [1,2].

The possible link between ASD and psychosis is subject of controversy [3-5]. This is possibly the reason for which Rapoport and colleagues [6] consider that the separation of autism and childhood-onset psychosis (COS), particularly schizophrenia, introduced an improvement in the understanding of childhood psychopathology. Watkins, *et al.* and Alaghband-Rad, *et al.* noted that age of onset, differential diagnosis, and treatment of the two conditions differ [7,8]. Some authors stress the clinical utility of this distinction, and they observe that systematic studies show high comorbidity between COS and ASD in correlation with the emergence of common family, genetic and imaging evidence [9,10]. Birth complications [11] and increased family risk of schizophrenia [12,13] are possible vulnerability factors of psychosis.

Recently, in a large review, Kiyoharu and colleagues [5] note that, although previous studies demonstrated a wide range (0% to 28%) of lifetime prevalence of schizophrenia in ASD subjects, most authors report a prevalence below 4%. In fact, according to studies in prodromal psychosis in subjects with ASD, neurocognitive impairments, such as executive dysfunction and deficits in the theory of mind, are considered vulnerability for future psychosis.

ASD was regarded as a risk factor for psychotic episodes or non-affective psychotic disorders in several cohort studies [11,14]. In the diagnosis, it is important to differentiate the onset of endogenous psychosis as comorbidity and psychotic reactions to a stressful situation in ASD individuals. Selten et al. [11] underline that in persons with ASD the difficulties to understand subtleties of social interactions could be erroneously attributed to psychosis and conversely the social impairment related to psychosis may be assumed as due to ASD. The attempt to distinguish the two different entities could result in a missed diagnosis of comorbidity. This suggests that clinicians should avoid "over diagnosis" of spontaneous psychotic disorders, including schizophrenia, and rather consider vulnerability to psychotic reaction in ASD individuals.

Some authors referred that three underlying symptoms-unusual fears, thought disorders and bizarre anxiety reactions - are related to psychosis in ASD [15].

The precocious beginning of psychotic symptoms, often misleading because covered by withdrawal and relative "reassuring" school results, makes diagnosis difficult and delays treatment. Symptoms as withdrawal accompanied with aggressive outbursts are present both in autistic and psychotic behaviour and it is very difficult to distinguish if they are ASD or COS symptoms [1,16,17].

The clinical picture of paranoid schizophrenia is dominated by relatively stable, often persecutory, delusions, usually accompanied by hallucinations, particularly of the auditory kind (hearing voices), and perceptual disturbances. These symptoms can have a sizeable effect on functioning and can negatively affect a person's quality of life. Paranoid schizophrenia is a lifelong illness, but with proper treatment, patients can live a higher quality of life [18].

The psychiatric comorbidity is largely present in person with ASD and Intellectual Disability [19]. The Cabinet of Diagnosis and Care - Geneva has a population of 182 patients, 5 patients (approximately 3%), 3 girls and 2 boys, present the following specific clinical signs:

Starting from school age (5-8 year): "mild" developmental problems (poor comprehension of social situations without serious language impairment, difficulty to adapt to new situations).

From late childhood until early adolescence: "mild to severe" psychotic symptoms similar to the negative and positive symptoms of schizophrenia, withdrawal, loneliness, increasing social adaptive impairment but also delusion (above all paranoid) and hallucinations.

In early adulthood: few, if any, sexual relationships (hetero or homosexual).

In adulthood: persistence of psychotic symptoms, severe impairment of social interactions, low quality of life, progressive reduction of autonomy, presence of obsessive compulsive symptoms.

The goal of the present work is to propose an early diagnosis of COS and ASD comorbidity, or at least to open the possibility of such a diagnosis, in order to guide the cure as soon as possible to an individualised and moderate stimulation of

the scholastic activity, keeping in mind the toxic effect of stress on the mental development of these young and fragile patients. An appropriate schedule of studies, with, for example the split of a school year over two, introducing periods of rest in each day (music, calm, some quiet walk) allows a more harmonious cognitive evolution, avoiding to waste much more time because of crisis and relapses.

Case Report

The patient is a young woman of 26, with ASD and paranoid schizophrenia.

She is the first of two siblings, with a 3-years younger brother. There is an occurrence of alcoholism in the family of the mother, and a cousin of the father suffers from schizophrenia. The patient is born at full term by vaginal delivery after a normal pregnancy.

The child had several wraps of the umbilical cord around her neck and a broken collarbone. The Apgar score was not recorded.

From early infancy to two years of age, the patient shows little emotions when separated from her parents, alternatively crying and sleeping a lot. When awaken, she is hyperactive with agitation and some difficulties to stay in the arms of adults, with poor gaze fixation. She suffers of several otitis in her first year but then she enjoys an excellent health. She spends some months in a child care. No speech delay is recorded.

After the birth of her brother, she enjoys one year of calm. The patient attends kindergarten for 6 months.

At 4, frequently during familial strolls, she begins to show tantrums and fear without apparent reason.

Between 4 and 5 the patient attends another kindergarten where she begins to show some difficulties to develop social interactions and sometimes aggresses (scratching) other children.

In spite of that, she has good exchanges with her brother and other children of the family.

The patient is able to learn to ski and follows some courses of gymnastic and music. She shows a lack of concentration but also willingness to challenge her difficulties.

At 5 her family moves and she begins to attend preschool, where the teacher remarks a bizarre behaviour characterized by a lack of socialization with the other children and a lack of verbal communication. The patient studies with her mother and becomes a good reader, learning by heart several poems. In arithmetic, she presents a serious problem of comprehension.

Around this time, she learns to swim and to ride a bike, with some difficulties above all in biking.

The teacher suggests sending her to private school in order to make the most of a more individualized teaching.

Between 5 and 7 the tantrum episodes intensify and the patient rolls on the floor screaming. The tantrum crises are appeased with cuddly toys with which the child plays and talks. The gravity of the situation is underestimated. A diagnosis of ASD could be made with appropriate assessment tools. A verbal therapy of psychodynamic orientation is proposed for 6 months.

At the age of 7, the family of the patient leaves for the USA, where the mother works part time and the child attends a Waldorf-Montessori school. She studies English and her mother obtains the permission to stay with her during the mornings at school to translate the lessons from English to French in order to facilitate her learning. The child becomes bilingual and she learns to write poems, draw, paint and play piano. The child attends support courses in mathematics twice a week. Even if the integration in social groups continues to be difficult, the child finds a friend (a girl) who sleeps over at her home once a week.

After the first year of school, teachers propose to the patient to see cognitive behavioural and speech therapists to help her to integrate groups and develop a more appropriate social behavior.

At 9 the patient admits to the parents that she hears voices, in particular in the morning. The nature of voices is threatening; they call her by her name. The parents observe an alternation of "good moments" when the child is calm and acting normally, and "bad moments" filled with agitation and anxiety. After collecting different advices, they treat her with "St. John's wort", massages and acupuncture without a real amelioration.

Teachers recommend a psycho-educational evaluation. The diagnosis is "…semantic - pragmatic language disorder. During a comprehensive review of her intellectual skills, the child scores appear to be low, with both a language and visual attention disorders. The existence of an attention deficit (ADHD) remains unconfirmed and is not accepted as diagnosis."

The family consults a child psychiatrist, who pronounces a diagnosis of generalized anxiety disorder with depressed mood and attention difficulties. No diagnosis of ASD is proposed at this moment.

At 11 the child receives a treatment with Paroxetine (10 mg per day). The same year the family returns to Europe and the child reintegrates her old school with personalised help and psychomotricity. She attends the Bell School to pursue her English education. The evaluation specifies "Using DELF (Diploma of study in French – Diplôme d'étude en langue française) exercises and PEI-IEP (Individualized Educative Project), we note that the child shows good learning abilities by taking advantage of the available aid. In addition, she transfers spontaneously strategies learned across different situations. The identified weaknesses are lack of autonomy and self-confidence, impulsiveness when exercises seem easy to her, lack of strategy, lack of precision in solving tasks in communication and lack of control."

The child enjoys sport (ski, bike, swimming and horse riding) and plays piano but, despite the presence of her highly socially integrated brother, who often introduces games and activities in the neighborhood, she has no friends, and suffers increasingly from her social withdrawal.

Several treatments are proposed at different dosages: Paroxetine, Sertraline, Mirtazapine, Quetiapine.

At 12 an endocrinologic investigation shows a delayed puberty. The thyroidal functionality is normal.

At 13 the young girl successfully completes her preparatory classes and enters middle school. At this point she "buckles", alternating moments of mutism with moments of verbal and physical violence against all the members of her family, especially against her mother. At school, she is incontinent and incapable of writing even her name; she suffers from vomiting and she gets lost in the public transports. She cannot eat or sleep anymore. Four days after the beginning of the school the parents decide to stop normal schooling and the young girl is oriented to the Waldorf School, with an individualized program.

Here the behavior of the patient is discontinuous with disruption of schooling during periods of crisis. The disorders alternate with moments when she can integrate herself in the school activities. Otherwise, she is non-pragmatic, with thoughts' disorders. She is followed by a neurologist. He describes her as "distant, unreachable, and slow in her gestures with an aspect more catatonic than cataplexic. She is devoid of initiative and blocked or otherwise agitated with what, according to the description, can be tics or compulsions. Stereotypes appear with the development of rituals."

She starts to stutter with increased repetitive movements; she constantly skips. Her parents try to feed her with a spoon; her weight is now 36.4 kg for a height of 149 cm.

Treatments with Valproate 600 mg per day and Clomipramine 10 mg per day are briefly introduced and stopped because agitation.

At 14 the patient, according to the description of a consulting neuro-paediatrician, presents a developmental disorder, essentially with a semantic - pragmatic type of dysphasia and a generalized anxiety disorder, occurring in spurts, essentially characterized by thought disorders and a rich motor and psycho-affective symptomatology. A neurological examination reveals that blood, metabolic balance and EEG are within the standard, likely excluding a neuro-metabolic cause.

Due to the seriousness of the situation and to the presence of anorexia, the girl is hospitalized for investigations in a psychiatric unit for adolescent in Geneva. Genetic analyses are performed to search for a 22q11 microdeletion or a fragile X syndrome, but with negative results. A brain MRI fails to detect any abnormality. Medications are removed and the patient is fed via a nasogastric tube for 3 months.

The medical team introduces a new treatment: olanzapine associated with escitalopram, risperidone soon replaced and then stopped. At the discharge from the hospital the treatment is: amisulpride, olanzapine and escitalopram with biperidene 4 mg per day to correct the neurological side effects. A notable somatic side effect is the gain of weight. The patient is now 14 and she weighs 50 kg for a height of 160 cm; before puberty and in less than a year she has gained 10 kg.

The patient is discharged after 6 months. She can feed and hydrate her and has regained basic functions, while remaining completely secluded in her world. She resumes family life and is admitted during school hours to a Day Centre for teenagers (OMP). Transportation is put in place to allow her to attend the Day Center. The

patient regularly attends psychotherapy sessions with a psychologist 3 times per week (from age 14 to 21) and psychomotricity sessions with a horse twice a week (from age 14 to 18).

At the end of the hospitalization, two diagnoses are proposed. The first is Asperger's Disorder - Depressive Psychosis - Severe Anxiety accompanied by a physiological inability to cope with stress. The second is Schizophrenia.

Puberty appears at 15.

The evaluation of cognitive and psychological behaviour (WISC-III and CMS Memory Scale for Children) reads: "The comparison between the two evaluations at 14 and at 16 shows elements of improvement notably at the relational level. (...) In general, the second evaluation indicates a deterioration of cognitive performance, in particular at the visuospatial level. The symptomatology at 14 is compatible with catatonic psychosis, a condition quite exceptional in a child of this age. (...). At 16, from the clinical standpoint, the patient appears to have made considerable progress, especially in her ability to interact, and there is a reduction of the symptoms related to her sensation of persecution. (...) The patient presents auditory hallucinations (a voice speaks to her from inside her head, sometimes negatively) which she is not capable to stop, but that she can criticize. She presents sensory hallucinations (feeling of vibration) that she can criticize. The psychotic symptomatology is now dominated by negative rather than positive symptoms with flat affect, emotional and social withdrawal, a major difficulty of abstraction, lack of spontaneity and a decreased verbal flow. (...) the cognitive deterioration is correlated with an increase in the negative symptoms."

At 16, Aripiprazole is introduced (10 mg once a day) with Escitapopram 20 mg once a day, Clozapine 225 mg per day. The patient has lost weight and gained in height (50 kg for 166 cm).

At 17 the girl enters a more stable period. Her weight decreases and returns to normal; she can use public transports and is more independent.

At 18 she is admitted to the Psychiatric Unit for Young Adults (JADE) of the Geneva University Hospital that accepts young people between 18 and 25 years with first onset of mental disorders. She lives at home, pursuing her verbal therapy 3 times per week and attending the JADE program. The patient is stable; she is able to manage her daily activities (personal hygiene, cleaning her room, attending therapies) and makes considerable progress toward maturity. She shows more autonomy when using public transportations. Nevertheless, when she feels less well, she stays at home and reduces the activities with JADE; she spends more time resting. Parents are suggested to be less present and less demanding. She is not asked to participate to all the family activities. She continues to join sports activities (hiking, skiing) but with decreased frequency. She can stay alone for short periods in the family flat, learning to do laundry and to go out shopping. In general aggression decreases but stressful situations still make her very aggressive and difficult for her entourage, so at home family members deploy an "avoidance policy" trying to skirt critical situations.

Concerning psychotropic medications, Clozapine is progressively increased to 400 mg per day with 25 mg to be added in case of need, up to a maximum of 3 times per day to calm anxiety and aggression.

At 19 she attends a 6-week part-time internship in gardening with poor results. At 20 she attends training at a workshop and visits specialised workshops for possible integration in their activities. The patient cannot not focus on one activity, she is agitated, standing up and disturbing others. She needs to be constantly with an educator to be sufficiently calm.

At 20 the patient gradually moves to the specialised institution Village d'Aigues-Vertes. The medical care is provided by the JADE team that suggests discontinuing verbal psychotherapy.

The treatment at this time is Clozapine 400 mg per day, up to 10 mg per day in case of agitation or aggression and Escitalopram 10 mg once per day,

The transition from the family house to the Village d'Aigues-Vertes proceeds well. The tranquillity of the Village d'Aigues-Vertes seems to suit her. She lives in an apartment with five other young persons under the supervision of teachers, who are on standby from 7h00 to 21h00 (at night here are watchmen). She attends textiles and ceramics workshops in the Village for a few hours in the morning and the afternoon. The integration is hindered by the fact that the patient cannot focus for long: she is constantly rising from her chair and disturbing other participants.

A few months later it is decided to remove the patient from the ceramic workshop because she

does not manage to complete artefacts for the baking phase and has to start over each time. She continues to work with the loom and she also attends the "polyvalent" workshop for leisure activities, but the outcome is not positive.

At 21 JADE ends its support because the patient has reached the age limits. The new psychiatrist decides to change the type of psychotherapy, seeing the patient only on a need basis instead than on a regular schedule.

At 22 the patient presents her first epileptic crisis with cranial trauma and short loss of consciousness, circumstantial amnesia, with a post critic status lasting for 20-30 minutes. Educators report almost regular episodes of absence evocating partial or minor epilepsy.

Hospitalisation is required and neurologists introduce Lamotrigine (100 mg per day), very quickly stopped because it causes severe aggressiveness.

During this year, the increase in the challenging behaviour requires another hospitalisation, this time in the psychiatric unit. An EEG is performed in June 2011 to evaluate the introduction of Levetiracetame. It shows "organic psychotic disorder associated with cerebral anoxia, behavioural disorders, intellectual disability. It also shows a history of generalized tonic-clonic epileptic crisis and a left temporal epileptic focus. The EEG has a normal rhythm with sporadic wave peaks in relation to precedent crisis." Levetiracetame is introduced (500 mg per day) but because of the poor response, it is replaced by Oxcarbazepine at 150 mg per day.

Because of the seriousness of the behavioural disorders, the hospitalisation lasts 4 months, and subsequently the patient is admitted in the Day Hospital of the psychiatric unit, dedicated to adults with psychiatric disorder and intellectual disability. The patient attends the unit 3 days a week, living in her institution the rest of the time. The clinical status of the patient improves very slowly.

The patient is logorrheic, with severe psychomotor agitation, rambling speech, anxiety, several obsessive compulsory disorders and distrust toward therapists. The educators report night-time awakenings.

Because of the persistence of severe anxiety, Lorazepam is introduced and Aripiprazole is stopped after a short period, due poor results.

One month after her admission in the Day Hospital, she is re-hospitalised, this time as an in-patient in the psychiatric unit dedicated to adults with psychiatric disorder and intellectual disability because of "a severe and persistent psychomotor agitation accompanied by verbal aggression, hetero aggressive gestures, anxiety and non-compliance."

In December 2012, the patient experiences a convulsive episode with oculomotor disturbances and upward gaze associated with significant anxiety, sensation of "impending doom" and tremor of the extremities. This indicates an atypical crisis and several diagnoses are proposed, amongst which Levetiracetame withdrawal syndrome or a panic episode. Investigations are performed to exclude somatic disorders, such as intermittent porphyria or celiac disease, but with negative results.

An EEG, performed a few days after this episode (December 2012), shows "poor collaboration during the EEG due to the patient's severe anxiety and tendency to persecution delusion. The EEG is normal, except for the presence of posterior intermittent slow waves. Compared to the June EEG, there is an improvement with the disappearance of paroxysmal elements."

Medication now consists of Baclofene 20 mg, Biperidene 2 mg, Clozapine 325 mg, Haloperidole 3 mg, Oxcarbazepine 300 mg, Macrogol 3350 1 dose per day, Diphénhydramine 50 mg in case of insomnia, Clotiapine 20 mg 3 times per day in case of agitation and Clozapine 25 mg 4 times per day in second intention if agitation.

Contraception is taken care of with Medroxiprogesterone IM 150 mg 1x/3 months

In January 2013, there is an "Aggravation of EEG results compared to December 2012 with paroxysmal elements spikes, sometimes fast polyspikes followed by slow waves, multifocal or generalized. The posterior slow waves present in previous EEG had disappeared. There are further anxiety disorders, accompanied by a rigid akinesis or extrapyramidal syndromes with oculogyric elements. This along with the presence of tachycardia (sinus without QT elongation), attributed to her neuroleptic medication, potentially modifies the EEG (posterior slow waves) and increases the paroxysmal elements.

In February 2013, the EEG reveals "a diffuse moderate encephalopathy with paroxysmal epileptiform bursts, probably linked to the treatment. Part of this neurological consultation is dedicated to the investigation of possible collagen pathologies."

After 5 months the patient is discharged with the following treatment: Oxcarbazepine cp 150 mg per day per os (progressively reduced until complete stop within a month), Biperidene retard 4 mg per day, Valproate-Chrono 1000 mg per day per os, Baclofene 75 mg per day, Clozapine 500 mg per day, Haloperidole Haldol 0,5 mg per day, Macrogol 3350 1 dose per day, Vitamine B12 cp 1000 micrograms per day, Clozapine 25 mg up to 4 times per day in case of agitation, Biperidene 2 mg once per day in case of extrapyramidal side effects, Hydroxyzine 25 mg 2x day max in case of anxiety, Diphénhydramine 50 mg, in case of insomnia, Macrogol 3350 1 dose in case of constipation.

Medroxiprogesterone IM 150 mg once every 3 months is used for contraception.

The discharge from the hospital is prepared by introducing changes in her accommodation at Village d'Aigues-Vertes. The young lady is moved to an apartment dedicated to persons with Autistic Spectrum Disorders (ASD). The day activities are structured and tailored to her needs.

She no longer attends the Village workshops and follows tailored organized activities, often alone with an educator or sport teacher or in small groups with a few residents. She works few hours per day in the Village's grocery to arrange yogurt pots, taking care of recycling, participating in meal preparation and laying out the table. Progressively she takes part to more outings with other residents (movies, restaurant, nature walks, shopping in molls, skating or swimming at the pool). She performs several activities accompanied by one educator outside the Village. She goes to riding school and to the animal center La Gavotte, picking fruits and vegetables at the farm, performing various sports activities.

Every day is precisely organized and she knows exactly what her program is going to be.

Aggressiveness has disappeared almost completely despite irregular crisis episodes that still persist. In particular, when the patient "rolls her eyes" (oculogyric crisis), she experiences serious difficulties to communicate. She then presses her eyes with her fingers while experiencing moments of deep distress and anxiety. This usually happens in the second part of the afternoon and lasts from one to three hours. Once the crisis passed, the patient returns to feel well, and she appears nice and smiling. The oculogyric crisis can be attributed to an extrapyramidal effect or to an anxiety status. In the impossibility of excluding one of the two causes, and since an epileptic origin of these crises could not be ruled out, the treatment with Biperidene 2 mg and Lorazepam 1 mg in case of crisis, is maintained. No evidence of epileptic disorder is found in correlation with the oculogyric crisis.

The psychiatrist visits the patient once a week, and they regularly take a walk and have a refreshment in the small tea room of the Village. The psychiatrist then exchanges briefly with the educators to enquire about her during past week.

At the age of 23 (April 3013) a short hospitalisation is needed to perform a lumbar puncture to exclude organic reason for the oculogyric crises. No abnormalities or specificity is detected and the neurological examination confirms the absence of epileptic disorders linked to these crises. Drug levels are found to be below therapeutic thresholds.

The treatment is readjusted with the introduction of Hydroxyzine 50 mg 2 times per day (before it was administered only in case of anxiety) and the reintroduction of Lorazepam 1 mg with the usual posology of 1 per day in the afternoon and 1 mg up to 3 times per day during the "oculogyric crises".

The patient expresses pleasure in her activities. She enjoys weekends with her family during which she spends good time. She settles into her new apartment also thanks to the establishment of social contacts with the other residents. She feels safe. Even if she experiences anxiety accompanied by verbal aggression when leaving her apartment to spend time with her family, she manages to control herself. She is able to describe her auditory hallucinations. In spite of a gain of weight (65 kg for 166 cm) side effects are minor and the treatment is well tolerated. Regular meetings are organized with the family, the therapists and the socio-educational team to determine a common plan of care adapted to the patient needs.

At 26 the patient appears well stabilized. Today her treatment is: Biperidene retard 4 mg per day, Valproate- Chrono 750 mg per day per os, Hydroxyzine 100 mg per day, Atenolol 25 mg 1 times per day, Clozapine 250 mg per day, Haloperidole 1 mg once per day, Baclofene 25 mg per day, Lorazepam 1 mg in the usual dose once per day in the afternoon and 1 mg up to 3 times per day during the "oculogyric

crisis", Macrogol 3350 1 dose 2 times per day. Contraception is assured by Desogestrel 1 cp per day.

Valproate hematic level was measured once a year: 546 µMol/l in 2016, 441 µMol/l in 2017.

Discussion

The lifetime prevalence of schizophrenia in ASD subjects can be estimated to be under 4%. In our private practice experience, we seem to confirm this figure since in a population of 182 adults and young adults we find 5 patients (3%) with ASD and COS [5].

In this population, psychotic symptoms are precocious, but they are often misleading. Diagnosis is difficult and often late, and this delays treatment. As reported by some authors [20,21], the person with COS can present developmental impairment, above all in speech. In our patient, no delay in speech was reported and the social interaction has been the central problem since the age of 3. Extreme tantrum crises started in early childhood and persisted during the whole life of the patient. If we consider these as COS symptoms, they were more precocious than reported by Rapoport. On the other hand, contrary to what is reported by Vourdas, in our patient there was no speech impairment preceding the COS onset.

The goal of this paper is to attract the attention of psychiatrists, also in private practice, to the presence of this comorbidity ASD and COS, in order to enhance the possibility of early diagnosis. At the time of the infancy of our patient this was done with tools such as CARS or PEP [22-24]. Now this could be achieved with ADOS [25] and ADI-R [26]. We also want to point out the importance of individualized therapies and care, including a reduction of the stimulation to achieve results in school. Any stress, included the strive to achieve academic proficiency, has a toxic effect on the mental development of these young and fragile patients. A reduction of the academic demands and a managed delay in the study curriculum (e.g. splitting a school year in two by repeating a class) allows a more harmonious and complete cognitive development.

Considering the diagnostic history of our patient, the presence of birth complications was probably underestimated as a possible vulnerability factor for psychosis [11]. No ASD diagnosis was proposed even when the tantrum crises were very far from normality in intensity and persisted and indeed increased well beyond the "terrible two". At 9 the diagnosis of generalized anxiety disorder with depressed mood and attention difficulties did not consider the possible presence of ASD. At 13 the psychical disorders largely affected eating and sleeping, mutism and stereotypes appeared evoking the psychotic withdrawal typical of COS. At 14 the treatment is compatible with a schizophrenia diagnosis and in fact two diagnoses are proposed: Asperger syndrome and schizophrenia.

Considering the violent tantrum crises as the expression of a psychotic anguish, schizophrenia onset is too precocious even for a COS. The absence of a serious impairment in verbal communication and the difficulty in the social contact are relatively mild and late for a classical ASD.

Parents and educators are often concerned, in the interest of the patient, by this "loss of time". However, it is our experience that an undue pressure on academic performance may cause a much greater loss of time and a high degree of suffering because of crisis and relapses. The presence of ASD and some difficulties in social communication make the appreciation of the pathology very difficult, because the patient does not complain and often refuses to communicate with the therapists.

Furthermore, late diagnosis often introduces a delay in pharmacological treatment that probably impairs social insertion of these patients, which end up in psychiatric adult units after a long, exhausting and often chaotic process with different pedopsychiatric approaches. In our patient, a left temporal epileptic focus was detected. In ASD the prevalence of epileptic disorder is large and often difficult to characterize also due to the lack of compliance of the patient for simple EEG or more complex imagery investigations. In our patient, the anti-epileptic medication was used to prevent the epileptogenic effect of the anti-psychotic treatment [27].

In our case report, we describe the long and complicated process of a young woman during a large part of her childhood, adolescence and early adult life, and of her family, confronted to a form of "reticence" to pose a complete diagnosis of ASD and COS comorbidity.

In our opinion this reticence was more motivated by a "philosophical attitude" than by a lack of knowledge or competence of the carers. The long-standing controversy on the possible link between ASD and psychoses and the established

separation of ASD from childhood-onset psychoses (COS), particularly schizophrenia, result in a reluctance by the caregivers to consider that there is a 3-4% prevalence of cases with a high comorbidity between COS and ASD.

When present, early recognition and diagnosis of this psychiatric comorbidity in ASD is important in adapting the therapeutic strategy, in particular tailoring the psychopedagogic approach to the vulnerability of these patients with respect to stress.

As the COS and ASD comorbidity is a very serious condition, the families of the patients should benefit of family therapy and interdisciplinary exchanges to find a common strategy in caring.

Conclusions

The present case report is a modest contribution to the wide field of COS and ASD comorbidity. We want to attract the attention to the fact that the price of a late or incomplete diagnosis is a poor quality of life for the patients and their families, often causing a diagnostic odyssey and exhausting uphill battles for everybody, including the caretakers.

Early diagnosis of psychiatric comorbidities in ASD allows a more effective therapeutic strategy and the adoption of a psychopedagogical approach adapted to the vulnerability of these patients with respect to stress.

Although situations similar to the one presented in this case report are described in the literature as cases of COS and ASD comorbidity, we have noticed that they present a peculiar and regular pattern that goes beyond the simple superposition of two known syndromes. The timing of the onset, early appearance of COS symptoms, followed by ASD manifestation at a later age, is typical and repetitive, and it is one of the causes of the difficulties encountered to diagnose and treat properly and timely these situations. We therefore wonder whether it would not be more appropriate, or at least clinically effective, to introduce the notion of a specific Syndrome characterized by the above pattern, that we could call "Passerella Syndrome" to indicate the specificity of the pathological profile.

It would be important to report this comorbidity in case reports and further studies would be necessary to better understand this disorder.

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