Research in Developmental Disabilities 38 (2015) 242–255

Contents lists available at ScienceDirect

Research in Developmental Disabilities

Acute behavioral crises in psychiatric inpatients with autism spectrum disorder (ASD): Recognition of concomitant medical or non-ASD psychiatric conditions predicts enhanced improvement

Vincent Guinchat [a,1], Cora Cravero [a,1], Lautaro Diaz [a,1], Didier Périsse [a,1], Jean Xavier [a,1], Claire Amiet [a,1], Isabelle Gourfinkel-An [b], Nicolas Bodeau [a,1], Lee Wachtel [c], David Cohen [a,d,1,*], Angèle Consoli [a,e,1]

[a] Department of Child and Adolescent Psychiatry, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Université Pierre et Marie Curie, 47 bd de l'Hôpital, 75013 Paris, France
[b] Center of Epileptology, Reference Center for Rare Epilepsies and Department of Genetics, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Université Pierre et Marie Curie, 47 bd de l'Hôpital, 75013 Paris, France
[c] Kennedy Krieger Institute, Johns Hopkins School of Medicine, 707 North Broadway Street, Baltimore, MD 21205, USA
[d] Institut des Systèmes Intelligents et Robotiques, CNRS UMR 7222, Université Pierre et Marie Curie, 1 Place Jussieu, 75005 Paris, France
[e] INSERM U669, Maison de Solenn, 97 bd de Port Royal, 75014 Paris, France

ARTICLE INFO

Article history:
Received 20 October 2014
Received in revised form 10 December 2014
Accepted 11 December 2014
Available online

Keywords:
Autism
Adolescence
Acute behavioral state
Regression
Intellectual disability

ABSTRACT

During adolescence, some individuals with autism spectrum disorder (ASD) engage in severe challenging behaviors, such as aggression, self-injury, disruption, agitation and tantrums. We aimed to assess risk factors associated with very acute behavioral crises in adolescents with ASD admitted to a dedicated neurobehavioral unit. We included retrospectively in 2008 and 2009 29 adolescents and young adults with ASD hospitalized for severe challenging behaviors and proposed a guideline (Perisse et al., 2010) that we applied prospectively for 29 patients recruited for the same indications between 2010 and 2012. In total, 58 patients were admitted ($n = 70$ hospitalizations, mean age = 15.66 (±4.07) years, 76% male). We systematically collected data describing socio-demographic characteristics, clinical variables (severity, presence of language, cognitive level), comorbid organic conditions, etiologic diagnosis of the episode, and treatments. We explored predictors of Global Assessment Functioning Scale (GAFS) score and duration of hospitalization at discharge. All but 2 patients exhibited severe autistic symptoms and intellectual disability (ID), and two-thirds had no functional verbal language. During the inpatient stay (mean = 84.3 (±94.9) days), patients doubled on average their GAFS scores (mean = 17.66 (±9.05) at admission vs. mean = 31.4 (±9.48) at discharge). Most common etiologies for acute behavioral crises were organic causes [$n = 20$ (28%), including epilepsy: $n = 10$ (14%) and painful medical conditions: $n = 10$ (14%)], environmental causes [$n = 17$ (25%) including lack of treatment: $n = 11$ (16%) and adjustment disorder: $n = 6$ (9%)], and non-ASD psychiatric condition [$n = 33$ (48%) including catatonia: $n = 5$ (7%), major depressive episode: $n = 6$ (9%), bipolar disorder: $n = 4$ (6%),

* Corresponding author at: Department of Child and Adolescent Psychiatry, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Université Pierre et Marie Curie, 47-83 bd de l'Hôpital, F-75651 Paris Cedex 13, France. Tel.: +33 1 42 16 23 51; fax: +33 1 42 16 23 53.
E-mail address: david.cohen@psl.aphp.fr (D. Cohen).
[1] Address: Groupe Hospitalier Pitié-Salpêtrière, 47-83 bd de l'Hôpital, F-75651 Paris Cedex 13, France.

http://dx.doi.org/10.1016/j.ridd.2014.12.020
0891-4222/

schizophrenia: $n = 6$ (9%), other/unknown diagnosis: $n = 12$ (17%)]. We found no influence of age, gender, socio-economic status, migration, level of ID, or history of seizure on improvement of GAFS score at discharge. Severity of autism at admission was the only negative predictor ($p < .001$). Painful medical conditions ($p = .04$), non-ASD psychiatric diagnoses ($p = .001$), prior usage of specialized ASD care programs ($p = .004$), functional language ($p = .007$), as well as a higher number of challenging behaviors upon admission ($p = .001$) were associated with higher GAFS scores at discharge. Clinical severity at admission, based on the number of challenging behaviors ($r = .35$, $p = .003$) and GAFS score ($r = -.32$, $p = .008$) was correlated with a longer inpatient stay. Longer hospitalization was however correlated ($r = .27$, $p = .03$) with higher GAFS score at discharge even after adjustment for confounding factors. Challenging behaviors among adolescents with ASD may stem from diverse risk factors, including environmental problems, comorbid acute psychiatric conditions, or somatic illness such as epilepsy or acute pain. The management of these behavioral challenges requires a unified, multidisciplinary approach.

1. Introduction

Adolescence is a crucial period in human development. Regarding neuropsychiatric disorders, adolescence is the period of onset for schizophrenia, bipolar disorder, and catatonia (Cohen et al., 2005; Consoli et al., 2012). In the field of autism, most children navigate adolescence without manifesting major adult psychiatric disorders. Indeed, the core symptoms of autism – deficiencies in social interaction, language delay and communication disabilities, and restricted and stereotyped behavior – tend to show improvement over time (Darrou et al., 2010; Kobayashi & Murata, 1998; Seltzer et al., 2003).

However, some authors have observed that the onset of puberty is temporally associated with clinical deterioration and the occurrence of severe challenging disorders (Billstedt, Gillberg, & Gillberg, 2005; Gillberg & Schaumann, 1981). In a review of studies published before 1996, Nordin and Gillberg (1998) observed that cognitive or behavioral regression occurred in 12–22% of adolescents with autism. The largest study of this phenomenon, a survey conducted on 201 young adults with autism born in Japan, indicated that 32% showed marked clinical deterioration during adolescence (Kobayashi, Murata, & Yoshinaga, 1992). More recently, a prospective study conducted on 120 Swedish autistic subjects showed that behavioral and cognitive regression, catatonia, and "adult psychosis" occurred during adolescence in 16%, 12%, and 8% of those studied, respectively (Billstedt et al., 2005). This adolescent decline is significant in light of the known increased prevalence of all psychiatric disorders in children with ID as first demonstrated in the Isle of Wight studies four decades ago, as well as multiple international studies supporting increased psychiatric illness among adults with ID at an estimated 3–4 fold higher rate than the neurotypical population (Borthwick-Duffy, 1994; Rutter, Tizard, Yule, Graham, & Whitmore, 1976; White, Chant, Edwards, Townsend, & Waghorn, 2005).

During adulthood, comorbid psychopathology is frequent in ASD. In a large sample of 137 adults with ASD and ID, Tsakanikos, Sturmey, Costello, Holt, and Bouras (2007) found comorbid psychopathology in 42% of cases. The most frequently diagnosed disorder was schizophrenia, followed by depression, adjustment disorder, and anxiety. Another longitudinal clinical study showed that affective disorder was amongst the most common newly emerging psychiatric disorders in adults with autism (Hutton, Goode, Murphy, Le Couteur, & Rutter, 2008). This increase in comorbid conditions has important therapeutic implications as Mouridsen, Rich, Isager, and Nedergaard (2008) showed using a case-control method that adults with autism had a higher frequency of additional treatable psychiatric disorders than controls, in particular psychotic and affective disorders.

A key associated factor of deterioration, may be cognitive functioning and language skills. On one hand, among individuals with autism, those without ID experience less deterioration than those with ID (Ballaban-Gil, Rapin, Tuchman, & Shinnar, 1996; Venter, Lord, & Schopler, 1992). On the other, among individuals with ID, those with autism experience more deterioration than those without (Bradley & Bolton, 2006; Hill & Furniss, 2006; Rojahn, Wilkins, Matson, & Boisjoli, 2010). However, severe behavioral changes and mental health problems in adolescents with autism are poorly investigated and currently inadequately understood. In particular, no empirical guidelines are available regarding etiology and treatment, as there are very few studies concerning inpatient treatment of subjects with autism (Frazier et al., 2010; Perisse et al., 2010; Shattuck et al., 2007; Siegel & Gabriels, 2014). Some recent studies have investigated the use of risperidone and aripiprazole for behavioral disturbances associated with autism and/or ID in children and adolescents (age 6–17 years), resulting in two specific FDA approvals (Cohen et al., 2013) for these agents in self-injury, aggression and agitation in autistic individuals. Apart from psycho-pharmaceuticals, it is highly relevant to recognize the efficacy of applied behavioral analysis (ABA) and associated intensive behavioral interventions in relieving self-injurious and aggressive behaviors (Frazier et al., 2010). First-line combined treatment models, including tandem psychopharmacological and behavioral assessment and treatment development, are particularly effective in evaluating the contributing roles of environmental, or operant, functions of challenging behaviors, along with underlying psychotropic-responsive psychiatric conditions (Wachtel & Hagopian, 2006).

Organic comorbidities may also contribute to behavioral impairments in ASD (Kohane et al., 2012). Epilepsy has been widely studied and is over represented in ASD with ID (Amiet et al., 2008, 2013). Other factors have been recently outlined in children with ASDs, such as sleep disturbances (Goldman, Richdale, Clemons, & Malow, 2012; Mayes & Calhoun, 2009), gastrointestinal problems (abdominal pain) (Buie et al., 2010), and sensory problems (Baker, Lane, Angley, & Young, 2008; Tseng, Fu, Cermak, Lu, & Shieh, 2011). Finally, some genetic conditions associated with ASD may be associated with both an increased risk of challenging behaviors within the syndrome's behavioral phenotype, as well as increased rates of psychiatric illness associated with certain syndromes, for example psychotic deterioration in adolescence such as 22q13 deletion, 22q11 deletion and 15q11 deletion syndromes (Denayer et al., 2012).

Unfortunately, challenging behavior may persist in some patients despite exhaustive interdisciplinary interventions (including symptomatic psychotropic drugs and behavioral interventions targeting demonstrable operant function), exposing both patient and caregiver to significant injury risk, and sharply curbing psychosocial functioning. Only case reports or series are currently available regarding other therapeutic approaches for extreme behavioral conditions, considered by some as highly controversial such as electroconvulsive therapy (ECT) (Consoli et al., 2013; Wachtel, Kahng, Dhossche, Cascella, & Reti, 2008) and/or packing[2] (Consoli et al., 2010; Lobry et al., 2011). In a previous retrospective study (Perisse et al., 2010), we showed that challenging behaviors among adolescent inpatients with autism may stem from diverse risk factors, including environmental problems, comorbid acute psychiatric conditions, or somatic diseases. We pursued a multimodal framework for the acute evaluation and treatment of these challenging conditions based on the multidisciplinary treatment approach. In terms of the optimal inpatient setting for these severely ill patients, our hospital developed a neurobehavioral unit for resistant acute situations associated with autism and/or ID, modeled after a similar unit in the USA (http://www.kennedykrieger.org/patient-care/patient-care-programs/inpatient-programs/neurobehavioral-unit-nbu, 2014-10-17).

The present study aimed (1) to describe a larger series of patients with autism hospitalized in a dedicated neurobehavioral unit who engaged in severe challenging behaviors and (2) to assess risk factors associated with these very acute states and with improvement at discharge.

2. Methods

2.1. Participants

Between 2008 and 2012, we included all patients with autism who were hospitalized for an acute episode of challenging behavior at the Pitié-Salpêtrière Hospital, a University teaching hospital that treats 30–40% of all child and adolescent psychiatry inpatients in the Paris area [10 million people]. It is the only hospital that has an adolescent Psychiatric Intensive Care Unit treating life-threatening treatment refusal (Jaunay et al., 2006), catatonic syndrome (Cohen et al., 2005; Cornic et al., 2009), severe mood disorders (Taieb et al., 2002), and severe behavioral regression (Perisse et al., 2010). At admission, parental informed consent was obtained for both care and research that was approved by the local ethical committee. In 2010, the Paris area health network opened an inpatient neurobehavioral unit for adolescents and young adults with autism and acute challenging behavior who were resistant to outpatient treatment. In 2008 and 2009, we included the patients retrospectively and proposed a guideline (Perisse et al., 2010) that we applied prospectively for the following 29 patients recruited in the same indications between 2010 and 2012. The study inclusion criteria were: (a) ICD-10 diagnosis of childhood autism confirmed by the Childhood Autism Rating Scale (CARS) (Schopler, Reichler, DeVellis, & Daly, 1980) and Autism Diagnostic Interview-Revised (Lord, Rutter, & Le Couteur, 1994); (b) the main reason for admission being challenging behavior or cognitive regression; (c) Clinical Global Impression-Severity score was 6, severely ill, or 7, extremely ill (Guy, 1976). No a priori exclusion criteria were used. The ICD-10 nosography is a criteria-based classification. For autism, the criteria are very similar to those used in the DSM-IV. It defines autism with three symptomatic domains (social interaction, communication, and restricted and stereotyped patterns of behavior/interests) and one developmental criterion (abnormal or impaired development is evident before the age of 3 years) (OMS, 1993).

2.2. Procedure

During the inpatient stay, clinicians followed the multimodal framework for evaluation and treatment of these challenging conditions we previously developed (Perisse et al., 2010). It was based on a multidisciplinary functional approach. Assessment procedure included systematic physical examinations by an internist, a geneticist, a neurologist with expertise in epilepsy, an ophthalmologist, an otorino-laryngologist and a dentist. We conducted this systematic assessment within each patient's first week of admission and such was repeated or completed with other specialists' consultation as needed. Clinical and para-clinical investigations to help determine the medical conditions potentially associated with acute behavioral crises in autism where based on our previous experience with similar patients (Perisse et al., 2010) as well as

[2] Packing therapy is based on multisensory (tactile, cenesthesic and proprioceptive) stimulations. The overall treatment encompasses a series of two sessions per week over a minimum one-month period. During sessions, the patient is wrapped in damp sheets, and the body spontaneously warms up. The head remains free from the wrapping, which allows for communication through visual and auditory channels.

young patients with catatonia (Sedel et al., 2007; Lahutte et al., 2008). Diagnosing a medical condition from somatic and psychiatric examinations does not always readily occur given that pathognomonic symptoms are rare and many patients with autism show poor cooperation during the physical examination. Some possible conditions must be aggressively and creatively sought, in particular epilepsy and painful medical conditions (Perisse et al., 2010). Although most para-clinical investigations were based on clinical examination findings, even in the absence of frank clinical symptoms (beyond challenging behaviors and autism), para-clinical investigations included: routine hematological and biochemical tests, antinuclear antibodies, serum prolactin, screening for coeliac disease, *Helicobacter pylori* serology, serum ammonia and homocysteine levels, plasma ceruloplasmin level and urinary drug screening, full dental panoramic X-ray, abdominal radiography, brain MRI and electroencephalography (EEG). When fever was present, we performed cerebrospinal fluid analysis. Other specific investigations (e.g. gastric fibroscopy) were performed under prescription when we found other signs suggestive of medical or neurological problems.

2.3. Organization of the inpatient admission (Table 1)

The inpatient admission is organized according to (1) two major domains of assessment, the medical and developmental/behavioral; and (2) three discrete phases including (1) baseline assessment after admission, (2) serial implementation of therapeutic interventions and evaluation of their efficacy and (3) preparation for safe discharge. In terms of practical organization, patients and families received (1) general non-specific supports including general physical care (e.g. advance healing bandages/wound care), protective and restrictive equipment when needed, autonomy and support for activities of daily living, risk assessment, and parental support (e.g. home visit; weekly parental consultation); (2) specific therapeutic approaches that are based on the multidisciplinary assessment. These included targeted prescription toward a specific cause (e.g. antiepileptic drugs in case of seizures); applied behavior therapy targeting challenging behaviors with operant functions within daily assessments; occupational therapy in small groups; sensory integrative approaches based on body mediated treatment; augmented communication facilities; protective and restrictive equipment along with environmental modifications when needed and particularly to mitigate against further acute injury, family interventions when needed (e.g. home visit with parental training).

2.4. Variables

At admission, we systematically assessed the following variables. (1) *Socio-demographic data*: we collected age, gender, socio-economic status of the family based on income and parental work activity [classified into three groups: low, middle, and high], and composition of the family at the time of admission (number of siblings and marital status of the parents). Special focus was placed on the type of care provided to the patients at the time of admission. The individuals were classified into three groups: those who received no special therapies, interventions or education (i.e., stayed at home all day), those who received care and education in non-specific institutions (mainly institutions dedicated to all types of ID), and those who received therapies care and education in institutions specifically dedicated to ASD. (2) *Medical history*: this was based on a semi-structured interview to evaluate patients' personal and family histories of psychiatric and medical disorders (detailed in Taieb et al., 2002). A particular emphasis was placed on associated pathologies (such as epilepsy, genetic disorders, and other chronic illnesses associated with autism), previous painful conditions, dental care, gastrointestinal motility dysfunction, medication received. (3) *Cognitive functioning*: due to the difficulties involved in testing individuals who exhibit such problematic behaviors, subjects were identified as having ID according to the definition of the American Association on Intellectual and Developmental Disabilities (2011). The estimates of *cognitive ability* were based on performance before the onset of the acute state that required hospitalization. Information was obtained from case records and interviews with parents and caregivers. For half of the patients, we were able to obtain an assessment of the adaptive functioning level with the Vineland Adaptive Behaviors Scales (VABS). The VABS is a semi-structured parental interview that evaluates adaptive functioning in four domains: communication, daily living skills, socialization, and motor skills. Age Equivalent Scores and Standard Scores are provided for each domain. Finally, individuals were classified into five groups: profound, severe, moderate, and mild ID, and borderline-normal cognitive ability. For the same reasons, a similar method was used to estimate the level of expressive *language* before the onset of the acute state. The individuals were classified into three groups: those with no expressive language at all, those with only a few words or with very impaired expressive language (a maximum of 15 words was chosen arbitrarily), and those with greater verbal abilities. (4) *Challenging behaviors*: a challenging behaviors check list based on the retrospective study (Perisse et al., 2010) was used to classify all challenging behavioral topographies as present or absent. The list included 9 groups of challenging behaviors: aggression or violence toward others, self-injurious behaviors, severe stereotypies, hyperactivity, tantrums, panic attacks, catatonia, akathisia and instinctual disorders (severe disturbance concerning sleep, alimentation, sexuality, or urinary/fecal control). (5) *Severity variables*: severity was measured using the CARS, the CGI-S, and the Global Assessment Functioning Scale (GAFS, Hall, 1995). For children ($\leq$13 years), we used the Children's Global Assessment Scale (C-GAS) (that was adapted from the GAFS, Shaffer et al., 1983).

During hospitalization, *treatment data* were also prospectively collected, including the duration of the hospitalization, the type and number of prescribed medications, adverse effects of medication leading to discontinuation, and all para-clinical investigations. At discharge, we determine for each case the main causal risk factor (see below) and the effectiveness of the hospitalization measured with the GAFS.

2.5. Causality assessment method

The *team consensus best-estimate diagnostic method*, which is usually used to ascertain clinical diagnoses or data, was used at discharge to determine the etiology of the acute behavioral decompensation (Klein, Ouimette, Kelly, Ferro, & Riso, 1994). The team included the three co-authors who were in charge of the patients (CC, VG, DP), two senior psychiatrists with a large amount of experience in inpatient care (DC, AC), and both a psychiatrist and a neurologist with expertise in epilepsy (CA, IAG). The etiology was the primary explanation retained for the behavioral regression. Postulated etiologies were based on all available information, including direct interviews, family history data, and treatment response (Klein et al., 1994). Each case received only one major postulated etiology, whereas several contributing factors were present in some cases. For medical conditions based on our experience in catatonia (Consoli et al., 2012), we systematically checked the following criteria: (1) the existence of similar cases in the literature; (2) the presence of supporting clinical symptoms; (3) the presence of supporting biological symptoms; (4) the presence of other para-clinical indicators (MRI, EEG findings); (5) response to a specific treatment related to the suspected medical condition (e.g., improvement of challenging behaviors after antiepileptic medication in case of seizures). Among environmental causes, we used lack or disruption of outpatient treatment only in case of: (1) absence of medical conditions; (2) absence of comorbid psychiatric diagnosis other than challenging behaviors and autism; (3) absence of recent stressors other than lack/disruption of outpatient treatment; (4) rapid ($\leq$3 weeks) patient's improvement with hospitalization and the adapted milieu therapy (see Table 1).

2.6. Statistical analysis

All analyses were performed using R software, version 2.12.2 (The R Foundation for Statistical Computing). The significance level (α) was set to 5% and tests were two-tailed. As for the description of our dataset, the whole dataset was first described in a classic way computing frequencies for factors and, for quantitative variables, means and standard deviations. To assess possible biases, we compared descriptive variables in patients recruited retrospectively and patients recruited prospectively. We found no significant difference for sex, GAFS score, and frequency of aggression or violence toward others, hyperactivity, tantrums, panic attacks, catatonia, akathisia and instinctual disorders. We found a significant difference regarding age (14.7 ($\pm$1.4) vs. 17.1 ($\pm$5.9), $p = 0.038$), CARS scores (42.2 ($\pm$3.1) vs. 37.4 ($\pm$5.2), $p < 0.001$), the frequency of

Table 1
Organization of the inpatient setting.

Medical domain	Developmental/behavioral domain
Assessment after admission	
Physical examination	Developmental assessment
Paraclinical screening and assessment	Applied behavioral analysis
Psychiatric evaluation	Search for reinforcing factors
Forensics as needed	Functional analysis
Socio-economic support as needed	
Definition of quantitative objectives by using specific scales (e.g. Catatonia scale) or counting targeted behaviors (number of self-injurious behaviors per day)	
Therapeutic proposals	
Physical treatment of complications	Behavioral therapy targeting challenging behaviors and associated operant functions
Treatment of causal medical condition when needed	Occupational therapy in small groups
Treatment of psychiatric comorbidity	Sensory integrative approaches based on body mediated treatment
Other medication (e.g. pain relievers)	Augmented communication facilities
	Ergonomic device when needed
Preparation of discharge	
Search for post-hospitalization adapted setting	Maintenance and generalization measures
Parental mediation and support	Home visit for parent training
Social worker when needed	Follow-up assessment
Follow-up medical assessment	
General nonspecific care	**Specific care**
Nonspecific physical care	Multidisciplinary assessment
Movement restriction and protection when needed	Crisis intervention (all staff is specifically trained and uses adapted tools (e.g. papoose board)
Parental visit including mediation when needed	Targeted prescription toward specific cause
Autonomy supports	Individual behavioral therapy
Daily activities supports	Occupational therapy (e.g. drawing, games, cooking, gardening, iPad)
Risk assessment	Assessment of evolution of target behaviors
Parental support	Facilitated communication
	Psychomotricity[a]
	Ergonomic device
	Parental mediation

[a] A *psychomotricien* is a therapist holding a French diploma in *psychomotricity* which is a specialized training in psychomotor disturbances within the Occupational Therapy course.

self-injurious behaviors (38% vs. 76%, $p < 0.001$), and the frequency of severe stereotypies (41% vs. 79%, $p < 0.001$). Secondly, we used a multiple correspondence analysis to visualize the relationships between the challenging behaviors and explore whether it was legitimate to perform predictive analysis taking into account any specific clustering of challenging behavioral symptoms.

Then, two short-term outcomes upon discharge were considered for the analysis: the change in GAFS score and the duration of hospitalization. The normality of the residuals, and their homoscedasticity, was checked graphically. For the hospitalization duration a log transformation was used to normalize this variable before analysis. Using the R "pwr" package, we calculated an a posteriori power. Using a medium effect size of 0.15, a regression with two predictors on our sample gives a power of 88%. The GAFS score was analyzed using a linear regression, with the GAFS score upon discharge as the dependent variable and the GAFS score at admission as an independent variable. Hence the effect of the following explicative variables: age, sex, socio-economic status, marital status, family ethnic origin, episode causes, degree of ID, history of an organic developmental disorder, type of previous treatment, number of challenging behaviors and CARS score at intake took into account the initial differences in GAFS scores. In the particular case of a binary predictor, like sex, this kind of regression is also called an ANOVA.

The duration of hospitalization (in days) was tested with the same set of explicative variables. The distribution of the duration of hospitalization was positively skewed and a log transformation was used to analyze this outcome. For quantitative variables Pearson's correlations were computed, for binary variables *t*-tests were performed (using Welch's correction in case of heteroscedasticity) and for other qualitative variables ANOVAs were conducted.

3. Results

3.1. Socio-demographic, personal history, and clinical characteristics at admission (Table 2)

We collected 70 inpatient admissions corresponding to 58 patients (44 males, 14 females). The male-female ratio was 3.1/1. The mean age was 15.66 (±4.07) years (range 10.9–37). Socio-demographics are summarized in Table 2. All subjects had severe autistic syndrome (CARS score: mean (±SD) = 40.18 (±4.76)) associated (except for two) with ID: 40 (71%) patients had severe or profound ID. The majority had poor language abilities: 40 (69%) patients had no language or a few words.

Twenty two patients (38%) had a history of one or more comorbid organic conditions affecting neurodevelopment: epileptic encephalopathy ($N = 5$; West syndrome, continuous spikes and waves during slow sleep (CSWSS), Lennox–Gastaut syndrome), seizures ($N = 12$), cerebral palsy due to neonatal anoxia ($N = 3$), Fragile X syndrome ($N = 1$), tuberous sclerosis ($N = 1$), FG syndrome (a multiple congenital anomaly/ID syndrome; $N = 1$), Cornelia de Lange syndrome ($N = 1$), mucopolysaccharidosis type IIIA ($N = 1$), oligophrenin-1 (OPHN-1) gene mutation ($N = 1$), Down syndrome ($N = 1$), Attention Deficit Hyperactivity Disorder ($N = 1$), fetal alcohol syndrome ($N = 1$), twin-to-twin transfusion syndrome ($N = 1$), and measles encephalitis ($N = 1$).

Fourteen (24%) patients had a history of other serious organic conditions: obesity ($N = 5$), skin conditions ($N = 5$: acnea, vitiligo, Ehlers–Danlos syndrome, psoriasis, atopic dermatitis), diabetes mellitus ($N = 1$), asthma ($N = 1$), anal fissure ($N = 1$), growth retardation ($N = 1$), cardiac malformation ($N = 1$), testicular cancer ($N = 1$), anemia ($N = 1$), alpha thalassemia ($N = 1$), hydrocele ($N = 1$), Barrett's Esophagus ($N = 1$), and choroidosis ($N = 1$).

Prior to admission to the hospital, only half of the patients ($N = 35$; 50%) received care in a specialized facility for individuals with ASD. Fifteen patients (21%) received outpatient care in nonspecific psychiatric settings or in special programs for youths with ID. Twenty patients (29%) received no specialized or outpatient care and stayed at home. Reasons for referral are listed in Table 2. The mean number of challenging behaviors was 3.47 (±1.59). The most frequent challenging behaviors were aggression, instinctual disorder, severe stereotypies, self-injury and hyperactivity. Multiple correspondence analysis (MCA) of challenging behaviors showed that 2 dimensions explained 70% of the variance. Patients' representation on the MCA factor map evidenced no subgroups and no need for clustering analysis (Fig. 1). Therefore, in the predictive analysis (see below), we only considered the number of challenging behaviors at admission. The mean GAFS score at the time of admission was 17.66 (±9.05). The mean number of psychotropic drugs prior to admission was 1.83 [range: no medication to 5 compounds].

3.2. Inpatient care and retained diagnosis

The mean duration of hospitalization was 84 (±95) days. The distribution of the duration was not unimodal. Treatments included milieu therapy, intensive behavioral intervention, regular family visits and consultations, social support when necessary, and medication. At the end of the hospitalization, the mean GAFS score was 31.4 (±9.48), representing on average a doubling of the GAFS score at discharge. The mean number of psychiatric medications at discharge was 1.94, and 56 (80%) patients were prescribed an antipsychotic. Compared with the number of psychotropic medications taken at admission, 15 (21%) patients had fewer psychotropics at discharge, 40 (57%) the same number, 13 (19%) had one more and 1 (1.4%) had two more. Fifteen patients received an anti-epileptic drug, and most of these patients had only one antiepileptic medication ($N = 8$). Two patients took more than two drugs but had epileptic encephalopathy [Lennox–Gastaut syndrome or CSWSS]. Short-term adverse effects of prescription medications were observed in 43 (61%) hospitalizations. These included extra-pyramidal effects ($N = 17$), adverse endocrine effects ($N = 10$), weight gain ($N = 4$), paradoxical effects of benzodiazepine ($N = 10$), constipation ($N = 15$), and seizures ($N = 3$). Finally, 4 patients received electroconvulsive therapy (ECT). Paraclinical examinations, such as EEG and neuroimaging, were prescribed in 53 (76%) cases and 34 (49%) cases, respectively. In many cases, however, behavioral disturbances prevented

Table 2
Socio-demographic and clinical characteristics at admission of 70 acute hospitalizations for adolescents and young adults with autism spectrum disorder and severe disruptive behavior.

Socio-demographics	
Sex (% male)*	14 F, 44 M (76)
Age: mean ± SD [range]	15.66 ± 4.07 [10.9–37]
Number of siblings*	2.91 ± 1.43 [1–9]
SES: *n* (%) low/middle/good*	20 (34)/18 (31)/20 (34)
Parental origin: *n* (%) migrants*	36 (62)
Family: *n* (%) single parent/living with both parents*	25 (43)/33 (57)
Personal history	
ADI-R, 4–5 years, mean (±SD)**	
Social impairment score	24.3 (±8.2)
Communication score	17.3 (±5.3)
Repetitive interest score	6.5 (±2.5)
Developmental score	3.83 (±1.47)
Vineland Adaptive Behaviors Scales**	
Developmental age: mean ± SD [range]	20.7 months (±5.9) [13.8–37]
Comorbid intellectual disability: *n* (%)*	
No	2 (3)
Mild	7 (12
Moderate	9 (16)
Severe	27 (47)
Profound	13 (22)
Language: *n* (%)*	
No language	19 (33)
Few words (<15)	21 (36)
Functional language	18 (31)
History of developmental comorbidity*	22 (38)
History of medical comorbidity*	14 (24)
Clinical characteristics at admission	
Type of care prior admission	
No care	20 (29)
Unspecific educative/therapeutic approach	15 (21)
Specific ASD therapeutic approach	35 (50)
Current medical comorbidity	9 (13)
Recent disruption of the treatment setting: yes/no	32 (46)/38 (54)
Disruptive symptoms: mean ± SD [range]	3.47 ± 1.59 [1–9]
Hetero-aggressivity: *n* (%)	54 (77)
Hyperactivity: *n* (%)	29 (41)
Instinctual disorder: *n* (%)***	44 (63)
Stereotypies: *n* (%)	35 (50)
Self-injurious behaviors: *n* (%)	33 (47)
Tantrums: *n* (%)	19 (27)
Panic attacks: *n* (%)	9 (13)
Catatonia: *n* (%)	12 (17)
Akathisia: *n* (%)	8 (11)
GAFS-Admission: mean ± SD [range]	17.66 ± 9.05 [5–40]
CARS-Admission: mean ± SD [range]	40.18 ± 4.76 [25–47]
Psychotropic drugs: mean ± SD [range]	1.83 ± 1.2 [0–5]
Including antipsychotics: mean ± SD [range]	1.21 ± 0.64 [0–3]

* *N* = 58 since several patients were admitted more than once.
** *N* = 24 due to missing data.
*** Instinctual disorder includes severe disturbance in sleep, alimentation, urinary/fecal control or sexuality.
ADI-R, Autism Diagnostic Interview-Revised; ASD, autism spectrum disorder; CARS, Children Autism Rating Scale; F, female; GAFS, global assessment functioning scale; M, male; SD, standard deviation; SES, socio-economic status.

technicians from performing these examinations or made the results unusable, and the risk-benefit ratio of general anesthesia for such imaging was carefully discussed. In total, forty one (59%) patients underwent an EEG and 25 (36%) patients underwent neuro-imaging.

The most common etiologies of the behavioral crises are listed in Table 3. For each patient, only the principal etiology was retained. In summary, the acute state was caused by environmental causes in 17 patients (25%), an organic cause in 20 patients (28%), and a psychiatric cause in 33 patients (47%). In 8 cases, despite being sent to the inpatient unit from specific facilities dedicated to ASD, no apparent cause was found for the acute episode. For these patients, we can hypothesize that they presented with a psychiatric diagnosis that was misdiagnosed due to their absence of language, or other environmental factors that could not be fully evaluated from an applied behavioral standpoint in our unit.

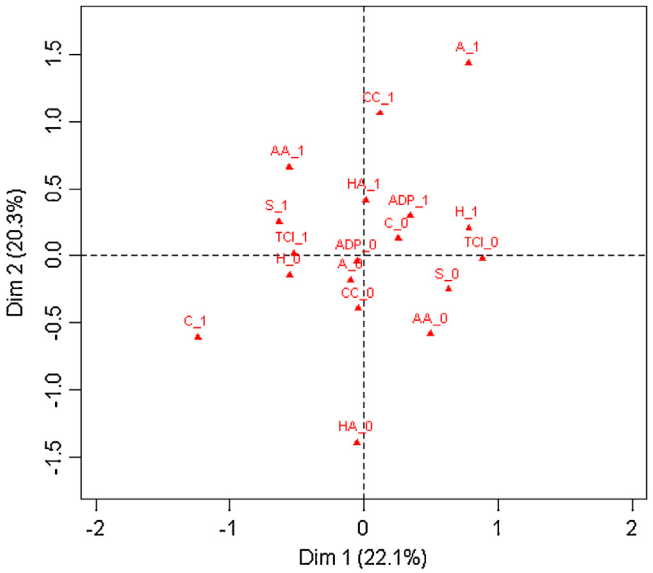

Fig. 1. Multiple correspondence analysis (MCA) factor map. MCA of challenging behaviors showing 2 dimensions explaining 70% of the variance. Auto-(AA); Hetero-aggression (HA); Hyperactivity (H); Instinctual disorders (TCI); Stereotypies (S); Tantrums (CC); Panic attacks (ADP); Catatonia (C); Akathisia (A). HA_1 means Hetero-aggression present; HA_0 means Hetero-aggression absent.

Table 3
Clinical characteristics at discharge and best retained diagnosis for 70 acute hospitalizations for adolescents and young adults with autism spectrum disorder and severe disruptive behavior.

Clinical characteristics at discharge	
Days of hospitalization: mean ± SD [range]	84.33 ± 94.91 [2–599]
GAFS-Discharge: mean ± SD [range]	31.4 ± 9.48 [10–50]
Psychotropic drugs: mean ± SD [range]	1.94 ± 0.87 [0–4]
Including antipsychotics: mean ± SD [range]	1.1 ± 0.51 [0–3]
Best retained etiology for the acute state	
Environmental causes: *n* (%)	
Lack/disruption of treatment	11 (16)
Adjustment disorder	6 (9)
Organic causes: *n* (%)	
Seizure	10 (14)
Other organic condition	10 (14)
Psychiatric causes: *n* (%)	
Catatonia	5 (7)
Major depressive episode	6 (9)
Bipolar disorder	4 (6)
Schizophrenia/schizo-affective disorder	6 (9)
Unknown/other	12 (17)

GAFS, global assessment functioning scale; SD, standard deviation.

Regarding psychiatric disorders, the diagnoses were made according to the ICD-10 criteria (OMS, 1993). In the current series, we listed five psychiatric comorbid conditions with acute states in autism (catatonia, major depression, bipolar disorder, and schizophrenia/schizoaffective disorder and adjustment disorder). Although adjustment disorder is a psychiatric diagnosis according to the ICD-10 and DSM-IV, we considered it as an environmental cause that should be differentiated from the other specific psychiatric disorders. As explained in the Methods section, we did not consider adjustment problems associated with a simple change of daily routine in patients with autism. An adjustment disorder was diagnosed when a major modification or a breakdown of the patient's environment was the explanation for the disruptive symptoms ($N = 6$, 9%). Such included severe abuse for one patient, the recent death of one patient's father, the psychiatric hospitalization of two patients' mothers, the hospitalization for cancer of one patient's mother, and an unanticipated change of treatment facility for one patient. A lack of specific treatment was considered as the cause when both (a) a lack of appropriate care (including no care at all) was considered responsible for the acute state and (b) the inpatient setting was sufficient to reduce behavioral symptoms. This occurred in 11 (16%) hospitalizations.

Finally, we also observed organic conditions. The acute state was caused by uncontrolled seizures in 10 patients, and antiepileptic medications led to significant improvement. For 6 of them, the behavioral crisis marked their first diagnosis of seizures. Other non-neurological organic causes were observed in 10 cases, and most of these conditions were painful, including *Helicobacter pylori* gastritis, tooth decay, urinary tract infection, anemia, bilateral cataracts, skin burn lesions after domestic accident, acute otitis, chronic constipation complicated with occlusive syndrome, chronic pain due to severe self-injurious behavior (a highly unusual case of an adolescent showing a Cornelia de Lange syndrome comorbid with an Ehlers–Danlos syndrome). In these cases, the specific treatment of the condition led to a significant decrease in the challenging behaviors.

3.3. Explicative variables of GAFS score improvement at discharge and length of hospitalization

We assessed whether independent variables (age, sex, socio-economic status, marital status, family ethnicity, ID severity, history of an organic developmental disorder, history of seizure, type of previous treatment, number of challenging behaviors, episode causes (no treatment/maladaptive/seizure/painful medical condition/psychiatric), and CARS and GAFS scores at intake) were associated with GAFS score improvement at discharge and length of hospitalization using linear regression models. Regarding improvement of GAFS score at discharge, we found no influence of age, gender, socio-economic status, migration, level of ID, or history of seizure. Severity of autism (CARS score) at admission was the only negative predictor ($\beta = 7.43$, $R^2 = 0.24$, $p < .001$). Painful medical conditions ($\beta = 8.23$, $R^2 = 0.25$, $p = .04$), non-ASD psychiatric diagnoses ($\beta = 9.49$, $R^2 = 0.25$, $p = .001$), the existence of prior specialized ASD care program ($\beta = 7.43$, $R^2 = 0.21$, $p = .004$), functional language ($\beta = 8.34$, $R^2 = 0.15$, $p = .007$), and a higher number of challenging behaviors at admission ($\beta = 2.59$, $R^2 = 0.19$, $p = .001$) were associated with higher GAFS score at discharge.

Regarding length of hospitalization, severity at admission based on the number of challenging behaviors ($r = .35$, $p = .003$) and GAFS score ($r = -.32$, $p = .008$) were correlated with longer inpatient stay. Longer hospitalization was correlated ($r = .27$, $p = .03$) with higher GAFS score at discharge even after adjustment for confounding factors. Since we found significant correlations with the number of challenging behaviors and GAFS score at admission, we used these variables as dependent variables and the length of hospitalization as the variable to be explained in the context of a regression. The number of challenging behaviors remains significant ($\beta = .22$, $p = 0.016$) while there is a strong tendency for the GAFS score ($\beta = -.03$, $p = 0.063$). The R^2 of the model is 0.22.

4. Discussion

The current study provides a detailed clinical picture of a population of adolescents and young adults with autism hospitalized in a psychiatric setting with a dedicated neurobehavioral unit for acute behavioral impairment, and documents the factors influencing their short-term outcome. Meaningful interpretation of the study requires consideration of its limitations and strengths. First, generalizability to other autistic patients may be limited by the extreme nature of the cases described here, given the recruitment bias related to acute hospitalization. Second, although some efforts were made to use standardized instruments, patients' clinical severity and irregular family availability limited their utility in better delineating patients' degree of ID and language function. Similarly, imaging was not performed in all patients due to behavioral disturbances. We may expect more adapted preparation procedures to improve the rates (Johnson et al., 2014). Third, given the sample size, we used a limited number of clinical variables [GAFS, CARS, behavior symptoms checklist]. Finally, some differences emerged between patients recruited retrospectively and patients recruited prospectively. Age was expected as we opened specifically an adult unit in 2010. Other differences were minor in terms of clinical relevance and did not involve GAFS our main outcome variable. The strengths of the study include the prospective design since end 2009; the multidisciplinary approach in the context of guideline proposal based on a previous study (Perisse et al., 2010); the use of experts in epilepsy, internal medicine, dental care and genetic/metabolic disease; the free access to inpatient care in France; and the use of long inpatient stay to monitor outcomes of multiple therapeutic techniques for behavioral improvement.

4.1. Comments on acute state causality

The current study confirms our previous data on a much smaller sample (Perisse et al., 2010). Etiologies for behavioral deterioration can be classified in three groups: environmental, psychiatric and organic causes. Among environmental causes, absence of care was frequent, highlighting two important facts. First, adolescence is a period with higher risk of a break in the continuity of care (Fombonne, Du Mazaubrun, Cans, & Grandjean, 1997; Smith, Greenberg, & Mailick, 2012). Second, since the major risk factor for the absence of appropriate care in France is a high degree of behavioral impairment (Thevenot, Philippe, & Casadebaig, 2008), both adolescence and behavioral impairment may serve as exclusion criteria for outside services in individuals with ASD. As a result, a vicious circle occurs in several cases as the absence of care may increase behavioral impairment, and the behavioral impairment makes it even more difficult to access care in the future. In addition, the importance of family support is demonstrated by cases in which behavioral deterioration occurred after major family events. In these cases, a diagnosis of adjustment disorder was retained for the acute behavioral exacerbation.

In nearly half of the sample, a psychiatric illness was diagnosed. If we accept the hypothesis that some subjects with a diagnosis of adjustment disorder were, in fact, depressed, the most common diagnosis was major depressive disorder. There

is emerging evidence that depression is probably the most common comorbid psychiatric disorder occurring in autistic people (Hutton et al., 2008), but this disorder can be difficult to recognize in subjects with autism with ID and poor communication skills (Ghaziuddin, Ghaziuddin, & Greden, 2002; Kobayashi et al., 1992). Four patients had bipolar disorder, a comorbidity that has been reported in association with complex differential diagnosis issues in ASD and ID (Atlas & Gerbino-Rosen, 1995; Brunelle et al., 2009). Five adolescents exhibited catatonia. Classically associated with schizophrenia when it occurs in youths (Cohen et al., 2005; Cornic et al., 2009), catatonia can be associated with bipolar disorders (Brunelle et al., 2009), somatic illness (Lahutte et al., 2008), and also autism (Cohen et al., 2009; Consoli et al., 2012; Ohta, Kano, & Nagai, 2006; Wing & Shah, 2000). Finally, six patients had schizophrenia or schizo-affective disorder. The occurrence of schizophrenia during the course of ASD encompasses several issues: (i) the assessment is sometimes difficult because of communication disorders and ID; (ii) recent advances in genetics have identified common risk factors that are not easy to interpret (Bassett, Scherer, & Brzustowicz, 2010). (iii) Several retrospective studies (e.g. Alaghband-Rad et al., 1995; Waris, Lindberg, Kettunen, & Tani, 2013) that included patients with early onset schizophrenia have found a high occurrence of comorbidity with ASD. But longitudinal studies have indicated that the rate of schizophrenia in ASD cohorts was very rare during follow-up (e.g. Mouridsen, Rich, & Isager, 1999).

The importance of somatic illnesses is probably the most significant result. For nearly one third of the cases, we found a treatable medical illness. This high frequency and the variety of possible conditions confirm the importance of our systematic and diligent search for organic factors. Uncontrolled epilepsy should be the first-line hypothesis. Epilepsy was found to be causal in ten of our cases. Six of these patients received a diagnosis of epilepsy for the first time during hospitalization. The high prevalence is not surprising, given that epilepsy in autism is associated with ID (Amiet et al., 2008, 2013) and that adolescence have been reported to be one of the two peak periods for seizure onset (Myers & Johnson, 2007; Tuchman & Rapin, 2002). However, the relationship between autism and epilepsy is complex, and their association may have different origins. Various seizure types and epileptic syndromes have been described in association with autism. Moreover, epileptic anomalies are frequently observed on the EEGs of autistic patients despite an absence of seizures, suggesting at least a low epileptic threshold (Tuchman & Rapin, 2002). Indeed, three patients without known epilepsy seized during a gradual discontinuation of benzodiazepines. It may also be true that autism and epilepsy share a genetic and/or neurodevelopmental cause (Amiet et al., 2013). Epilepsy by itself may induce the development of autistic symptoms (e.g. West syndrome; Ouss et al., 2014). In terms of the diagnostic and therapeutic approach, we, like others, consider collaboration with an experienced neurologist to be crucial (Tuchman & Rapin, 2002).

Among other frequent and easily treatable organic conditions, we found a list of painful condition among which gastrointestinal disorders were the most frequent. A recent meta-analysis confirmed that children with ASD experience more gastrointestinal symptoms than general population (McElhanon, McCracken, Karpen, & Sharp, 2014). Regarding *Helicobacter pylori* infections, we did not find any study reporting increased prevalence in ASD. However, it seems unlikely that our findings occurred by chance since (1) individuals with ID have an approximately two-fold higher risk of *Helicobacter pylori* than healthy people (Wallace, Webb, & Schluter, 2002), and (2) 20–50% of the French adult population is infected, with most contamination during childhood (Santé, 2010). The conjunction of symptomatic treatments such as antipsychotics and ASD gastro-intestinal susceptibility could have favored chronic constipation complicated with occlusive syndrome. After appropriate treatment, an improvement was noticed on tantrums and aggression, with improvement of food conducts and the progress of meals. These painful etiologies must be systematically looked for, especially in absence of functional language.Comments on predictors of discharge outcome

Low IQ, absence of communication skills, comorbid epilepsy and severity of autism at age 5 are well-known factors leading to a poor prognosis, including an impaired course of development during adolescence (Baghdadli et al., 2012; Ballaban-Gil et al., 1996; Gillberg & Steffenburg, 1987; Howlin, Goode, Hutton, & Rutter, 2004; Rapin, 1997; Venter et al., 1992). In the current sample, all individuals were severely impaired and had multiple challenging behaviors. This point is not surprising, as it has been shown in adults that these behaviors often co-occur (Matson, Cooper, Malone, & Moskow, 2008). All except two had ID; 50/58 (86%) had severe autism as measured by the CARS; less than a third had functional language; more than half of them had "syndromal or complex autism" (Cohen et al., 2005; Miles et al., 2005). However, other factors, including specific care, family support, socio-economic factors and migration, appear to also be crucial in the occurrence of these acute states. The proportion of patients from migrant families was noteworthy despite the known increased rates of ASD among children of immigrant or foreign born mothers (Bolton, McDonald, Curtis, Kelly, & Gallagher, 2014; Guinchat et al., 2012). However, in this severe inpatient sample, we found no influence of age, gender, socio-economic status, migration, level of ID, or history of seizure on improvement of GAFS score at discharge. Severity of autism at admission, measured by CARS score, was the only negative predictor, and the presence of a functional language was a positive predictor. Regarding improvement of GAFS score at discharge, a specialized ASD care program prior to admission and longer hospital duration were both positive predictive factors. In our study, after three months of hospitalization on average, our patients doubled their GAFS score. Consistent with the findings from previous studies (Gabriels et al., 2012), our results support the development of specialized psychiatric care practices within this population to positively impact their health care outcomes. Finally, the most important positive predictors were painful medical conditions and non-ASD psychiatric comorbidities. This finding demonstrates the crucial nature of investigating, diagnosing and treating the range of etiologies rather than limiting care to symptomatic treatments.

Regarding psychotropic interventions, we advocate caution in antipsychotic prescription in patients with ASD, both in terms of number of drugs and dosage, given the prevalence and severity of adverse events in this population (Perisse,

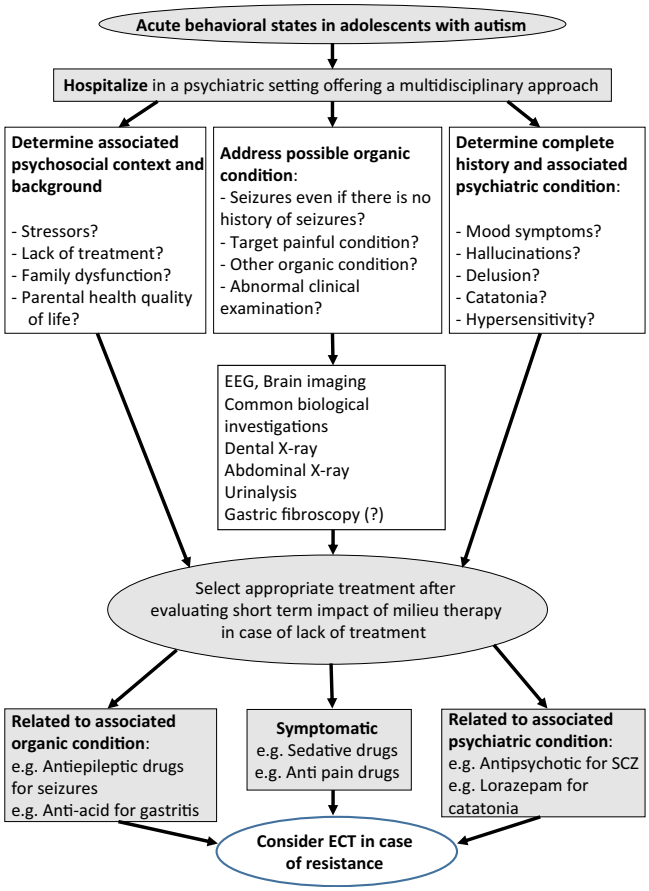

Fig. 2. Acute behavioral states in adolescents with autism: a multimodal framework for evaluation and treatment. ECT, electroconvulsive therapy; EEG, electroencephalography; SCZ, schizophrenia.

Guinchat, Hellings, & Baghdadli, 2012), and high rates of adverse effects noted in our study. This fact is crucial given the tendency toward polypharmacy despite the minimal evidence available regarding its effectiveness for challenging behavior associated with autism (Abadie, Balan, Chretien, & Simard, 2013; Matson & Neal, 2009; Rosenberg et al., 2010). Finally, it is highly salient that our study demonstrated that actually a *higher* number of challenging behaviors at time of admission were associated with a higher GAFS at discharge. This may be explained, at least in part, by the increased likelihood of concomitant psychiatric diagnoses in the presence of challenging behaviors, with implications for treatment of those underlying diagnoses and subsequent behavioral benefit (Moss et al., 2000; Myrbakk & von Tetzchner, 2008). This finding is also relevant from the perspective of retained hope for these challenged youth, and support allocation of appropriate resources for this population.

We summarize in Fig. 2 our current guideline proposal for the diagnosis and treatment of acute challenging behaviors or regression in adolescents or young adults with autism. We hope this integrative approach can assist clinicians in treatment decision-making. The guidelines are based on our previous proposal (Perisse et al., 2010) and on the current experience. Given the diversity of psychopathologies found in this study, we recommend a systematic integrative multidisciplinary approach that should include (a) a careful social and family evaluation, (b) a systematic search for comorbid medical conditions with a systematic focus on seizures and frequent painful conditions, and (c) a psychiatric evaluation, taking into account the particular profile of these patients [poor language skills, ID] and using adapted rating tools when available. This process should lead to a functional evaluation of each individual case and the formulation of a principal hypothesis regarding the cause of the acute behavioral state. As demonstrated, correct diagnosis of a painful medical condition or a comorbid psychiatric disorder improves the overall level of functioning at discharge.

5. Conclusion

Adolescents with autism who present with acute behavioral regression and challenging behaviors that compromise safety need to be examined with a multidisciplinary approach that includes organic, social, and psychiatric investigations, as these acute behavioral conditions may stem from diverse risk factors, including environmental factors, comorbid acute

psychiatric conditions, or somatic diseases such as epilepsy or painful conditions. Given the complexity of these situations and despite the cost of inpatient care, hospitalization on a designated neurobehavioral unit with interdisciplinary collaboration is indicated. The treating psychiatrist plays a key role in coordinating investigations, developing a proper differential diagnosis, and serially initiating interventions targeting the acute behavioral state.

Conflict of interest

During the last two years, Dr Cohen reported past consultation for or the receipt of honoraria from Bristol-Myers Squibb, Otsuka, Shire, Lundbeck and IntegraGen. Dr Consoli reported receiving travel support from BMS. No other author reported financial disclosure or conflict of interest.

Acknowledgements

We kindly thank all families and patients recruited in this study. We also thank the *Assistance Publique des Hôpitaux de Paris* and the *Agence Régionale de Santé d'Ile de France* for funding the neurobehavioral unit (*USIDATU*) at the Pitié-Salpêtrière hospital and for supporting this research.

References

Abadie, P., Balan, B., Chretien, M., & Simard, C. (2013). Suicidalité chez les adolescents appartenant au spectre de l'autisme. *Neuropsychiatrie de l'Enfance et de l'Adolescence, 61*(7–8), 409–414.

Alaghband-Rad, J., McKenna, K., Gordon, C. T., Albus, K. E., Hamburger, S. D., Rumsey, J. M., et al. (1995). Childhood-onset schizophrenia: The severity of premorbid course. *Journal of the American Academy of Child and Adolescent Psychiatry, 34*(10), 1273–1283.

American Association on Intellectual and Developmental Disabilities (2011). *Intellectual disability: Definition, classification, and systems of supports* (11th ed.). Washington, DC: American Association on Intellectual and Developmental Disabilities.

Amiet, C., Gourfinkel-An, I., Bouzamondo, A., Tordjman, S., Baulac, M., Lechat, P., et al. (2008). Epilepsy in autism is associated with intellectual disability and gender: Evidence from a meta-analysis. *Biological Psychiatry, 64*(7), 577–582.

Amiet, C., Gourfinkel-An, I., Laurent, C., Bodeau, N., Genin, B., Leguern, E., et al. (2013). Does epilepsy in multiplex autism pedigrees define a different subgroup in terms of clinical characteristics and genetic risk? *Molecular Autism, 4*(1), 47.

Atlas, J. A., & Gerbino-Rosen, G. (1995). Differential diagnostics and treatment of an inpatient adolescent showing pervasive developmental disorder and mania. *Psychological Reports, 77*(1), 207–210.

Baghdadli, A., Assouline, B., Sonie, S., Pernon, E., Darrou, C., Michelon, C., et al. (2012). Developmental trajectories of adaptive behaviors from early childhood to adolescence in a cohort of 152 children with autism spectrum disorders. *Journal of Autism and Developmental Disorders, 42*(7), 1314–1325.

Baker, A. E., Lane, A., Angley, M. T., & Young, R. L. (2008). The relationship between sensory processing patterns and behavioural responsiveness in autistic disorder: A pilot study. *Journal of Autism and Developmental Disorders, 38*(5), 867–875.

Ballaban-Gil, K., Rapin, I., Tuchman, R., & Shinnar, S. (1996). Longitudinal examination of the behavioral, language, and social changes in a population of adolescents and young adults with autistic disorder. *Pediatric Neurology, 15*(3), 217–223.

Bassett, A. S., Scherer, S. W., & Brzustowicz, L. M. (2010). Copy number variations in schizophrenia: Critical review and new perspectives on concepts of genetics and disease. *American Journal of Psychiatry, 167*(8), 899–914.

Billstedt, E., Gillberg, I. C., & Gillberg, C. (2005). Autism after adolescence: Population-based 13- to 22-year follow-up study of 120 individuals with autism diagnosed in childhood. *Journal of Autism and Developmental Disorders, 35*(3), 351–360.

Bolton, S., McDonald, D., Curtis, E., Kelly, S., & Gallagher, L. (2014). Autism in a recently arrived immigrant population. *European Journal of Pediatrics, 173*(3), 337–343.

Borthwick-Duffy, S. A. (1994). Epidemiology and prevalence of psychopathology in people with mental retardation. *Journal of Consulting and Clinical Psychology, 62*(1), 17–27.

Bradley, E., & Bolton, P. (2006). Episodic psychiatric disorders in teenagers with learning disabilities with and without autism. *British Journal of Psychiatry, 189*, 361–366.

Brunelle, J., Consoli, A., Tanguy, M. L., Huynh, C., Perisse, D., Deniau, E., et al. (2009). Phenomenology, socio-demographic factors and outcome upon discharge of manic and mixed episodes in hospitalized adolescents: A chart review. *European Child and Adolescent Psychiatry, 18*(3), 185–193.

Buie, T., Campbell, D. B., Fuchs, G. J., 3rd, Furuta, G. T., Levy, J., Vandewater, J., et al. (2010). Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: A consensus report. *Pediatrics, 125*(Suppl. 1), S1–S18.

Cohen, D., Nicolas, J. D., Flament, M. F., Perisse, D., Dubos, P. F., Bonnot, O., et al. (2005). Clinical relevance of chronic catatonic schizophrenia in children and adolescents: Evidence from a prospective naturalistic study. *Schizophrenia Research, 76*(2–3), 301–308.

Cohen, D., Nicoulaud, L., Maturana, A., Danziger, N., Périsse, D., Duverger, L., et al. (2009). The use of packing in adolescents with catatonia: A retrospective study with an inside view. *Clinical Neuropsychiatry, 6*, 1–6.

Cohen, D., Raffin, M., Bodeau, N., Canitano, R., Bonnot, O., Périsse, D., et al. (2013). Risperidone and aripiprazole in children and adolescents with autism and/or intellectual disability: A Bayesian meta-analysis. *Research in Autism Spectrum Disorders, 7*, 167–175.

Consoli, A., Gheorghiev, C., Jutard, C., Bodeau, N., Kloeckner, A., Pitron, V., et al. (2010). Lorazepam, fluoxetine and packing therapy in an adolescent with pervasive developmental disorder and catatonia. *Journal of Physiology, Paris, 104*(6), 309–314.

Consoli, A., Raffin, M., Laurent, C., Bodeau, N., Campion, D., Amoura, Z., et al. (2012). Medical and developmental risk factors of catatonia in children and adolescents: A prospective case–control study. *Schizophrenia Research, 137*(1–3), 151–158.

Consoli, A., Cohen, J., Bodeau, N., Guinchat, V., Wachtel, L., & Cohen, D. (2013). Electroconvulsive therapy in adolescents with intellectual disability and severe self-injurious behavior and aggression: A retrospective study. *European Child and Adolescent Psychiatry, 22*(1), 55–62.

Cornic, F., Consoli, A., Tanguy, M. L., Bonnot, O., Perisse, D., Tordjman, S., et al. (2009). Association of adolescent catatonia with increased mortality and morbidity: Evidence from a prospective follow-up study. *Schizophrenia Research, 113*(2–3), 233–240.

Darrou, C., Pry, R., Pernon, E., Michelon, C., Aussilloux, C., & Baghdadli, A. (2010). Outcome of young children with autism: Does the amount of intervention influence developmental trajectories? *Autism, 14*(6), 663–677.

Denayer, A., Van Esch, H., de Ravel, T., Frijns, J. P., Van Buggenhout, G., Vogels, A., et al. (2012). Neuropsychopathology in 7 patients with the 22q13 deletion syndrome: Presence of bipolar disorder and progressive loss of skills. *Molecular Syndromology, 3*(1), 14–20.

Fombonne, E., Du Mazaubrun, C., Cans, C., & Grandjean, H. (1997). Autism and associated medical disorders in a French epidemiological survey. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*(11), 1561–1569.

Frazier, T. W., Youngstrom, E. A., Haycook, T., Sinoff, A., Dimitriou, F., Knapp, J., et al. (2010). Effectiveness of medication combined with intensive behavioral intervention for reducing aggression in youth with autism spectrum disorder. *Journal of Child and Adolescent Psychopharmacology, 20*(3), 167–177.

Gabriels, R. L., Agnew, J. A., Beresford, C., Morrow, M. A., Mesibov, G., & Wamboldt, M. (2012). Improving psychiatric hospital care for pediatric patients with autism spectrum disorders and intellectual disabilities. *Autism Research and Treatment, 2012*, 685053.
Ghaziuddin, M., Ghaziuddin, N., & Greden, J. (2002). Depression in persons with autism: Implications for research and clinical care. *Journal of Autism and Developmental Disorders, 32*(4), 299–306.
Gillberg, C., & Schaumann, H. (1981). Infantile autism and puberty. *Journal of Autism and Developmental Disorders, 11*(4), 365–371.
Gillberg, C., & Steffenburg, S. (1987). Outcome and prognostic factors in infantile autism and similar conditions: A population-based study of 46 cases followed through puberty. *Journal of Autism and Developmental Disorders, 17*(2), 273–287.
Goldman, S. E., Richdale, A. L., Clemons, T., & Malow, B. A. (2012). Parental sleep concerns in autism spectrum disorders: Variations from childhood to adolescence. *Journal of Autism and Developmental Disorders, 42*(4), 531–538.
Guinchat, V., Thorsen, P., Laurent, C., Cans, C., Bodeau, N., & Cohen, D. (2012). Pre-, peri- and neonatal risk factors for autism. *Acta Obstetricia et Gynecologica Scandinavica, 91*(3), 287–300.
Guy, W. (1976). *ECDEU Assessment Manual for Psychopharmacology*. Rockville, MD: US Department of Heath, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration.
Hall, R. C. (1995). Global assessment of functioning. A modified scale. *Psychosomatics, 36*(3), 267–275.
Hill, J., & Furniss, F. (2006). Patterns of emotional and behavioural disturbance associated with autistic traits in young people with severe intellectual disabilities and challenging behaviours. *Research in Developmental Disabilities, 27*(5), 517–528.
Howlin, P., Goode, S., Hutton, J., & Rutter, M. (2004). Adult outcome for children with autism. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 45*(2), 212–229.
Hutton, J., Goode, S., Murphy, M., Le Couteur, A., & Rutter, M. (2008). New-onset psychiatric disorders in individuals with autism. *Autism, 12*(4), 373–390.
Jaunay, E., Consoli, A., Greenfield, B., Guile, J. M., Mazet, P., & Cohen, D. (2006). Treatment refusal in adolescents with severe chronic illness and borderline personality disorder. *Journal of the Canadian Academy of Child and Adolescent, 15*(3), 135–142.
Johnson, N., Bree, O., Lalley, E., Rettler, K., Grande, P., Gani, Md, & Ahamed, S. I. (2014). Effect of an iPAD application for medical imaging procedure preparation for children with autism spectrum disorder. *Journal of Pediatric Nursing, 29*(6), 651–659.
Klein, D. N., Ouimette, P. C., Kelly, H. S., Ferro, T., & Riso, L. P. (1994). Test-retest reliability of team consensus best-estimate diagnoses of axis I and II disorders in a family study. *American Journal of Psychiatry, 151*(7), 1043–1047.
Kobayashi, R., & Murata, T. (1998). Behavioral characteristics of 187 young adults with autism. *Psychiatry and Clinical Neurosciences, 52*(4), 383–390.
Kobayashi, R., Murata, T., & Yoshinaga, K. (1992). A follow-up study of 201 children with autism in Kyushu and Yamaguchi areas, Japan. *Journal of Autism and Developmental Disorders, 22*(3), 395–411.
Kohane, I. S., McMurry, A., Weber, G., MacFadden, D., Rappaport, L., Kunkel, L., et al. (2012). The co-morbidity burden of children and young adults with autism spectrum disorders. *PLoS ONE, 7*(4), e33224.
Lahutte, B., Cornic, F., Bonnot, O., Consoli, A., An-Gourfinkel, I., Amoura, Z., et al. (2008). Multidisciplinary approach of organic catatonia in children and adolescents may improve treatment decision making. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 32*(6), 1393–1398.
Lobry, A., Jutard, C., Bodeau, N., Kloeckner, A., Consoli, A., & Cohen, D. (2011). Effectiveness of wet sheet packs in children and adolescents with severe auto/hetero aggressive behaviors: An exploratory approach. *Adolescent Psychiatry, 1*, 163–168.
Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders, 24*(5), 659–685.
Matson, J. L., Cooper, C., Malone, C. J., & Moskow, S. L. (2008). The relationship of self-injurious behavior and other maladaptive behaviors among individuals with severe and profound intellectual disability. *Research in Developmental Disabilities, 29*(2), 141–148.
Matson, J. L., & Neal, D. (2009). Psychotropic medication use for challenging behaviors in persons with intellectual disabilities: An overview. *Research in Developmental Disabilities, 30*(3), 572–586.
Mayes, S. D., & Calhoun, S. L. (2009). Variable related to sleep problems in children with autism. *Research in Autism Spectrum Disorders, 3*, 931–941.
McElhanon, B. O., McCracken, C., Karpen, S., & Sharp, W. G. (2014). Gastrointestinal symptoms in autism spectrum disorder: A meta-analysis. *Pediatrics, 133*, 874–883.
Miles, J. H., Takahashi, T. N., Bagby, S., Sahota, P. K., Vaslow, D. F., Wang, C. H., et al. (2005). Essential versus complex autism: Definition of fundamental prognostic subtypes. *American Journal of Medical Genetics Part A, 135*(2), 171–180.
Moss, S., Emerson, E., Kiernan, C., Turner, S., Hatton, C., & Alborz, A. (2000). Psychiatric symptoms in adults with learning disability and challenging behaviour. *British Journal of Psychiatry, 177*, 452–456.
Mouridsen, S. E., Rich, B., & Isager, T. (1999). Psychiatric morbidity in disintegrative psychosis and infantile autism: A long-term follow-up study. *Psychopathology, 32*(4), 177–183.
Mouridsen, S. E., Rich, B., Isager, T., & Nedergaard, N. J. (2008). Psychiatric disorders in individuals diagnosed with infantile autism as children: A case control study. *Journal of Psychiatric Practice, 14*(1), 5–12.
Myers, S. M., & Johnson, C. P. (2007). Management of children with autism spectrum disorders. *Pediatrics, 120*(5), 1162–1182.
Myrbakk, E., & von Tetzchner, S. (2008). Psychiatric disorders and behavior problems in people with intellectual disability. *Research in Developmental Disabilities, 29*(4), 316–332.
Nordin, V., & Gillberg, C. (1998). The long-term course of autistic disorders: Update on follow-up studies. *Acta Psychiatrica Scandinavica, 97*(2), 99–108.
Ohta, M., Kano, Y., & Nagai, Y. (2006). Catatonia in individuals with autism spectrum disorders in adolescence and early adulthood: A long-term prospective study. *International Review of Neurobiology, 72*, 41–54.
OMS (1993). *Classification statistique internationale des maladies et des problèmes de santé connexes. Dixième Révision (Vol. 1)*.
Ouss, L., Saint-Georges, C., Robel, L., Bodeau, N., Laznik, M. C., Crespin, G. C., et al. (2014). Infant's engagement and emotion as predictors of autism or intellectual disability in West syndrome. *European Child and Adolescent Psychiatry, 23*(3), 143–149.
Perisse, D., Amiet, C., Consoli, A., Thorel, M. V., Gourfinkel-An, I., Bodeau, N., et al. (2010). Risk factors of acute behavioral regression in psychiatrically hospitalized adolescents with autism. *Journal of the Canadian Academy of Child and Adolescent Psychiatry, 19*(2), 100–108.
Perisse, D., Guinchat, V., Hellings, J., & Baghdadli, A. (2012). Traitement pharmacologique des comportements problématiques associés aux troubles du spectre autistique: Revue de la littérature. *Neuropsychiatrie de l'Enfance et de l'Adolescence, 60*, 42–61.
Rapin, I. (1997). Autism. *New England Journal of Medicine, 337*(2), 97–104.
Rojahn, J., Wilkins, J., Matson, J. L., & Boisjoli, J. (2010). A comparison of adults with intellectual disabilities with and without ASD on parallel measures of challenging behaviour: The Behavior Problems Inventory-01 (BPI-01) and Autism Spectrum Disorders-Behavior Problems for intellectually disabled adults (ASD-BPA). *Journal of Applied Research in Intellectual Disabilities, 23*(2), 179–185.
Rosenberg, R. E., Mandell, D. S., Farmer, J. E., Law, J. K., Marvin, A. R., & Law, P. A. (2010). Psychotropic medication use among children with autism spectrum disorders enrolled in a national registry, 2007–2008. *Journal of Autism and Developmental Disorders, 40*(3), 342–351.
Rutter, M., Tizard, J., Yule, W., Graham, P., & Whitmore, K. (1976). Research report: Isle of Wight Studies, 1964–1974. *Psychological Medicine, 6*(2), 313–332.
Santé, H. A. d. *Recommandations HAS 2010. Dépistage de l'infection à Helicobacter pylori. Pertinence et populations concernées*..
Shaffer, D., Gould, M. S., Brasic, J., Ambrosini, P., Fisher, P., Bird, H., et al. (1983). A children's global assessment scale (CGAS). *Archives of General Psychiatry, 40*(11), 1228–1231.
Schopler, E., Reichler, R. J., DeVellis, R. F., & Daly, K. (1980). Toward objective classification of childhood autism: Childhood Autism Rating Scale (CARS). *Journal of Autism and Developmental Disorders, 10*(1), 91–103.
Sedel, F., Baumann, N., Turpin, J. C., Lyon-Caen, O., Saudubray, J. M., & Cohen, D. (2007). Psychiatric manifestations revealing inborn errors of metabolism in adolescents and adults. *Journal of Inherited Metabolic Disease, 30*(5), 631–641.
Seltzer, M. M., Krauss, M. W., Shattuck, P. T., Orsmond, G., Swe, A., & Lord, C. (2003). The symptoms of autism spectrum disorders in adolescence and adulthood. *Journal of Autism and Developmental Disorders, 33*(6), 565–581.

Shattuck, P. T., Seltzer, M. M., Greenberg, J. S., Orsmond, G. I., Bolt, D., Kring, S., et al. (2007). Change in autism symptoms and maladaptive behaviors in adolescents and adults with an autism spectrum disorder. *Journal of Autism and Developmental Disorders, 37*(9), 1735–1747.
Siegel, M., & Gabriels, R. L. (2014). Psychiatric hospital treatment of children with autism and serious behavioral disturbance. *Child and Adolescent Psychiatric Clinics of North America, 23*(1), 125–142.
Smith, L. E., Greenberg, J. S., & Mailick, M. R. (2012). Adults with autism: Outcomes, family effects, and the multi-family group psychoeducation model. *Current Psychiatry Reports, 14*(6), 732–738.
Taieb, O., Flament, M. F., Chevret, S., Jeammet, P., Allilaire, J. F., Mazet, P., et al. (2002). Clinical relevance of electroconvulsive therapy (ECT) in adolescents with severe mood disorder: Evidence from a follow-up study. *Eur Psychiatry, 17*(4), 206–212.
Thevenot, J., Philippe, A., & Casadebaig, F. (2008). *Suivi d'une cohorte d'enfants porteurs de troubles autistiques et apparentés en Ile-de-France de 2002 à 2007: Situation des enfants lors de l'inclusion*. Available online at http://psydoc-fr.broca.inserm.fr/Recherche/Rapports/InclusionAutistes.pdf
Tsakanikos, E., Sturmey, P., Costello, H., Holt, G., & Bouras, N. (2007). Referral trends in mental health services for adults with intellectual disability and autism spectrum disorders. *Autism, 11*(1), 9–17.
Tseng, M.-H., Fu, C.-P., Cermak, S. A., Lu, L., & Shieh, J.-Y. (2011). Emotional and behavioral problems in preschool children with autism: Relationship with sensory processing dysfunction. *Research in Autism Spectrum Disorders, 5*(4), 1441–1450.
Tuchman, R., & Rapin, I. (2002). Epilepsy in autism. *Lancet Neurology, 1*(6), 352–358.
Venter, A., Lord, C., & Schopler, E. (1992). A follow-up study of high-functioning autistic children. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 33*(3), 489–507.
Wachtel, L. E., & Hagopian, L. P. (2006). Psychopharmacology and applied behavioral analysis: Tandem treatment of severe problem behaviors in intellectual disability and a case series. *Israel Journal of Psychiatry and Related Sciences, 43*(4), 265–274.
Wachtel, L. E., Kahng, S., Dhossche, D. M., Cascella, N., & Reti, I. M. (2008). ECT for catatonia in an autistic girl. *American Journal of Psychiatry, 165*(3), 329–333.
Wallace, R. A., Webb, P. M., & Schluter, P. J. (2002). Environmental, medical, behavioural and disability factors associated with Helicobacter pylori infection in adults with intellectual disability. *Journal of Intellectual Disability Research, 46*(Pt 1), 51L 60.
Waris, P., Lindberg, N., Kettunen, K., & Tani, P. (2013). The relationship between Asperger's syndrome and schizophrenia in adolescence. *European Child and Adolescent Psychiatry, 22*(4), 217–223.
White, P., Chant, D., Edwards, N., Townsend, C., & Waghorn, G. (2005). Prevalence of intellectual disability and comorbid mental illness in an Australian community sample. *Australian and New Zealand Journal of Psychiatry, 39*(5), 395–400.
Wing, L., & Shah, A. (2000). Catatonia in autistic spectrum disorders. *British Journal of Psychiatry, 176*, 357–362.