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Comorbid Psychiatric Disorders Associated with Asperger Syndrome/High-functioning Autism: A Community- and Clinic-based Study

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Abstract The present study identifies the prevalence and types of comorbid psychiatric disorders associated with Asperger syndrome (AS)/high-functioning autism (HFA) in a combined community- and clinic-based sample of fifty 9- to 16-year-old subjects using the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version. The level of functioning was estimated using the Children's Global Assessment Scale. The results support common (prevalence 74%) and often multiple comorbid psychiatric disorders in AS/HFA; behavioral disorders were shown in 44%, anxiety disorders in 42% and tic disorders in 26%. Oppositional defiant disorder, major depressive disorder and anxiety disorders as comorbid conditions indicated significantly lower levels of functioning. To target interventions, routine evaluation of psychiatric comorbidity in subjects with AS/HFA is emphasized.

Keywords Comorbidity · CGAS · Asperger syndrome · Autism · Pervasive developmental disorders · Autism spectrum disorders

Introduction

According to recent publications, there is growing acceptance that pervasive developmental disorders (PDDs) are not conditions with precise boundaries, and there are also a number of overlapping disorders and behavioral symptoms that are not accounted for by the diagnosis of PDD (Gadow

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et al. 2004; Ghaziuddin et al. 1998; Leyfer et al. 2006; Simonoff et al. 2008).

In the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; APA 2000), symptoms of inattention and hyperactivity are described as occurring frequently in children with PDD, but there is an exclusionary criterion concerning comorbid diagnosis of attention deficit/hyperactivity disorder (ADHD) with PDDs in both the DSM-IV-TR and the International Classification of Diseases (ICD-10; WHO 1993). In spite of this, many investigators have looked at the evidence linking PDDs and ADHD (Gadow et al. 2006; Goldstein and Schwebach 2004; Lee and Ousley 2006; Yoshida and Uchiyama 2004). Additionally, the coexistence of ADHD in children with PDDs may have important consequences as regards treatment (Posey et al. 2007) as well as genetics research (Ronald et al. 2008).

The symptomatology of obsessive–compulsive personality disorder (OCPD) according to the DSM-IV-TR seems to be strikingly similar to that of "autistic psychopathy" as described by Asperger (1944). Co-occurrence of anxiety and anxiety disorders including obsessive–compulsive disorder (OCD) has been demonstrated to be at greater than chance levels in high-functioning individuals with PDDs (Gillott et al. 2001; Kim et al. 2000; Kuusikko et al. 2008; Russell et al. 2005; Sukhodolsky et al. 2008; White et al. 2009b). However, the diagnostic criteria of Asperger syndrome (AS) according to the ICD-10 exclude OCD.

Autism was originally considered to be childhood schizophrenia, but later it was separated. In addition, AS diagnostic criteria in DSM-IV-TR and ICD-10 exclude schizophrenia. However, similarities and differential diagnostics concerning AS and schizophrenia have recently been studied (Da Fonseca et al. 2008; Murphy 2006). In contrast to ADHD, OCD and schizophrenia, tic disorders are not excluded from autism or AS diagnostic criteria. Again, Tourette's syndrome, motor and vocal tics are considered to be diagnoses overlapping with PDDs (Baron-Cohen et al. 1999; Ringman and Jankovic 2000).

In general, psychiatric patients are significantly more often smokers than the general population (Poirier et al. 2002). Clinically significant ADHD symptoms are also associated with levels of cigarette smoking (Tercyak et al. 2002). According to the results of a study by Bejerot and Nylander (2003) smoking is rare among adults with autism spectrum disorders (ASDs). However, the association between ASDs and substance-related disorders including smoking has not been much studied.

It has long been common knowledge among clinicians that subjects with ASDs suffer from insomnia and other sleep disturbances. During the past few years, researchers have also shown a growing interest in sleep disturbances in cases of ASDs (Allik et al. 2006; Krakowiak et al. 2008).

Studies concerning comorbid psychiatric disorders in PDDs have mainly revealed one or just a few comorbidities. Relatively few investigators have dealt with the whole spectrum of psychiatric comorbid disorders in PDDs or have used standardized instruments (Ghaziuddin et al. 1998; Leyfer et al. 2006; Simonoff et al. 2008). Several population-based PDD prevalence studies have been published (Baird et al. 2006; Baron-Cohen et al. 2009; Ehlers and Gillberg 1993; Mattila et al. 2007), but, to our knowledge, there is only one population-based study that has dealt with psychiatric comorbid disorders in subjects with PDDs, involving a population-derived sample (Simonoff et al. 2008).

The aims of our study were to identify the prevalence and types of comorbid psychiatric disorders associated with AS/high-functioning autism (HFA) in a combined community- and clinic-based sample using the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL; Kaufman et al. 1997) and to estimate the level of functioning in these children/adolescents using the Children's Global Assessment Scale (CGAS; Shaffer et al. 1983).

Methods

Participants

The Finnish population is homogeneous, mainly of Finnish extraction and Finno-Ugric origin. In Finland, everyone has an equal right to basic education, healthcare and social security. Mainstream comprehensive schooling is divided into two phases, primary school from 1st to 6th grade, with pupils aged 7–12 years, and secondary school from 7th to 9th grade, with pupils aged 13–16 years.

The participants comprised 12- to 13-year-old subjects with AS/HFA ($n = 18$) from a community-based study (Mattila et al. 2007) and 9- to 16-year-old subjects with AS/HFA ($n = 32$) from a clinic-based study (e.g., Jansson-Verkasalo et al. 2005; Korpilahti et al. 2007; Kuusikko et al. 2009; Loukusa et al. 2007; Weiss et al. 2009), making a combined sample of 50 (mean age 12.7, SD 1.5, age range 9.8–16.3; full-scale IQ [FSIQ] > 75) (Table 1; Fig. 1).

The community-based sample ($n = 18$; mean age 12.7, SD 0.3, age range 12.2–13.1; FSIQ > 75) consisted of all 18 subjects with AS/HFA from the community-based study, and the clinic-based sample ($n = 40$; mean age 12.7, SD 1.7, age range 9.8–16.3; FSIQ > 75) consisted of 32 subjects with AS/HFA from the clinic-based study plus 8 subjects who were in both groups. These eight participants were born in 1992 and belonged to the community-based population, but they were also registered as ASD patients

Table 1 Study subjects and condensed procedures

Study subjects	Combined sample	Community-based sample[a]	Clinic-based sample[a]
Participants (male/female)	50 (38/12)	18 (12/6)	40 (32/8)
Mean age/age range	12.7/9.8–16.3	12.7/12.2–13.1	12.7/9.8–16.3
FSIQ	>75	>75	>75
AS (male/female)	27 (20/7)	8 (5/3)	22 (17/5)
HFA (male/female)	23 (18/5)	10 (7/3)	18 (15/3)
Primary school-aged (male/female)	36 (26/10)	18 (12/6)	26 (20/6)
AS/HFA	17/19	8/10	12/14
Secondary school-aged (male/female)	14 (12/2)	–	14 (12/2)
AS/HFA	10/4	–	10/4

Condensed procedures	Community-based study	Clinic-based study
Participants [n (male/female)]	18 (12/6)	32 (26/6)
Measures		
1. AS/HFA diagnostics	x	x
ASSQ	x	
ADI-R	x	x
ADOS, module 3	x	x
WISC-III	x	x
Hospital records	x	x
School-day observations	x	
2. Comorbidity examinations	x	x
K-SADS-PL	x	x
CGAS	x	x

AS, Asperger syndrome; HFA, high-functioning autism; FSIQ, full-scale IQ; x, included in procedure; ASSQ, Autism Spectrum Screening Questionnaire; ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; WISC-III, Wechsler Intelligence Scale for Children-Third Revision; K-SADS-PL, Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version; CGAS, Children's Global Assessment Scale

[a] Eight participants were in both samples

in hospital records and belonged to the clinic-based sample (Table 1; Fig. 1).

Measures (See Table 1)

Measures in AS/HFA Diagnosis

The Autism Spectrum Screening Questionnaire (ASSQ; Ehlers et al. 1999) was translated from Swedish into Finnish according to official requirements. The validity of the Finnish ASSQ has been assessed (Mattila et al. 2009).

The Autism Diagnostic Interview-Revised (ADI-R; Lord et al. 1995) and the Autism Diagnostic Observation Schedule (ADOS; Lord et al. 2000), module 3, were translated from English into Finnish (Mattila et al. 2007; Dansk psykologisk Forlag 2009). The physicians (M.-L.M. and S.-L.L.), psychologist (K.J.) and Master of Education graduate (M.K.) who participated in the diagnostic process have been trained in use of the ADI-R and ADOS for research purposes. ADI-R and ADOS algorithms were not used in this study.

Intelligence (IQ) was measured by means of the Wechsler Intelligence Scale for Children-Third Revision (WISC-III; Wechsler 1991). In our samples, all subjects with autism were high-functioning (HFA) with FSIQ > 75. Early development was verified from University Hospital of Oulu records.

Measures in Comorbidity Examinations

The K-SADS-PL schedule is a semi-structured interview designed to assess current and past episodes of psychopathology in children and adolescents between the ages of 6–18, according to DSM-IV criteria via parent and child/adolescent interviews. The K-SADS-PL schedule has well-established reliability and validity (Kaufman et al. 1997). In this study, the primary K-SADS diagnoses (affective, psychotic, anxiety, behavioral, eating, tic and post-traumatic stress disorders as well as substance abuse and dependence) and the question on sleep disturbances, with several response options, concerned all participants.

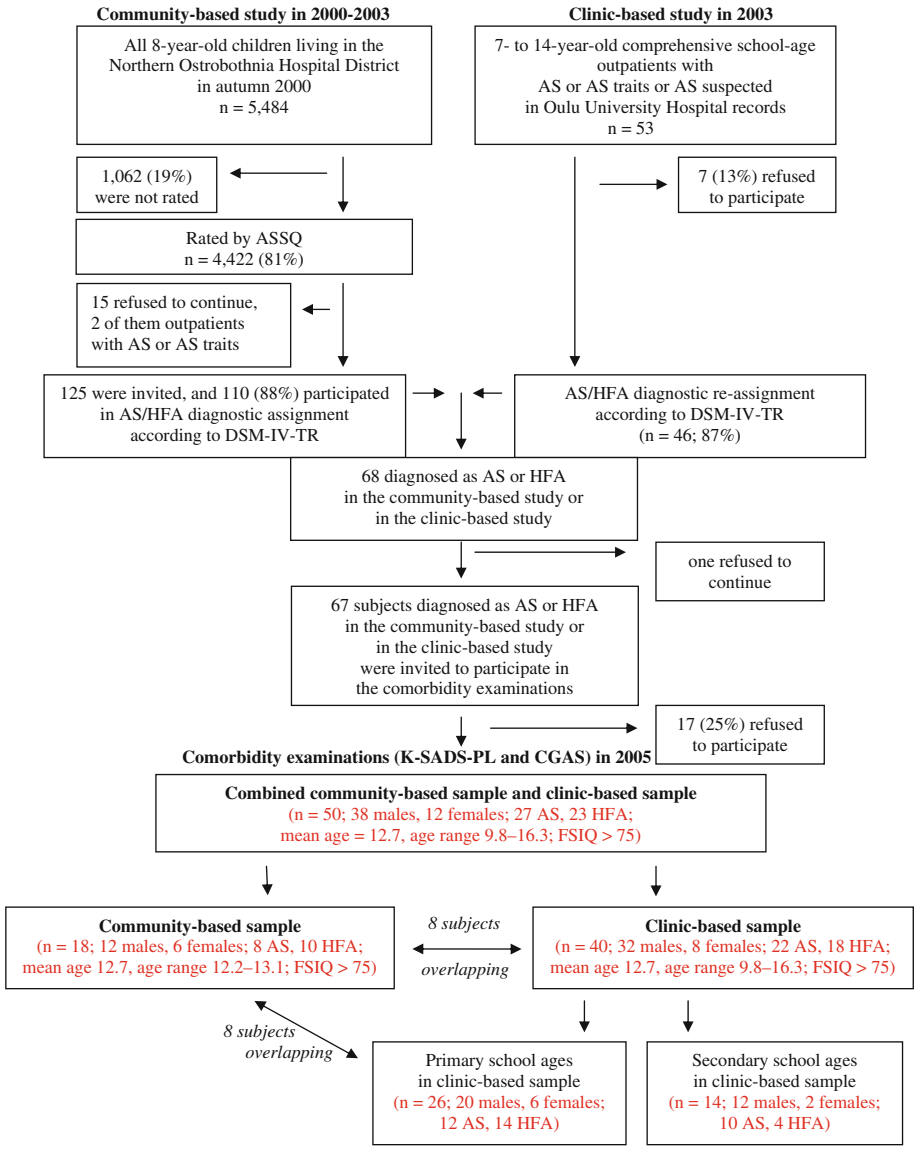

Fig. 1 Study design. AS, Asperger syndrome; ASSQ, Autism Spectrum Screening Questionnaire; HFA, high-functioning autism; K-SADS-PL, Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version; CGAS, Children's Global Assessment Scale; FSIQ, full-scale intelligence quotient

Definite current and past DSM-IV psychiatric diagnoses were assessed. Lifetime diagnosis included current and past diagnoses. Diagnostic endorsements did not involve use of the exclusionary rules in DSM-IV with regard to autism and AS.

The CGA scale was used to evaluate children's/adolescents' level of functioning in everyday life (e.g., at home, at school, with peers). CGAS scores range between 1 and 100, with higher scores indicating better functioning. CGAS scores below 70 are considered to indicate psychiatric disturbance and limited functioning. For subjects with no history of psychiatric disturbance, only a current CGAS score is assigned. For subjects with current and/or past psychiatric disorders, two CGAS scores can be estimated, one for current and one for worst lifetime functioning. In this study, the current and worst lifetime CGAS scores were used.

Procedures (See Table 1)

The study was carried out in the Northern Ostrobothnia Hospital District in the province of Oulu in Finland, and was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District. Written informed consent was obtained from all parents and from all children of 12 years of age or more. This study was performed in three phases: first, AS/HFA screening and diagnosis in the community-based study (Mattila et al. 2007), second, AS/HFA diagnosis in the clinic-based study (Kuusikko et al. 2009; Loukusa

et al. 2007; Weiss et al. 2009), and third, comorbidity examinations. The study design is shown in Fig. 1.

Diagnosis of AS/HFA in the Community-based Study

The community-based study has been described in detail elsewhere (Mattila et al. 2007). All 8-year-old children born in 1992 and living within this hospital area in autumn 2000 were chosen for the target population ($n = 5{,}484$; Statistics Finland 2000). The procedure included screening by ASSQ ($n = 4{,}422$; 81%) and AS/HFA diagnostics of the screened children ($n = 110$; 88%) using ADI-R (M.-L-M.), ADOS, module 3 (M.-L-M.), WISC-III (a clinical and a research psychologist), patient records (M.-L.M.), and school-day observations (M.K.). The ADI-R interviews and ADOS observations were videotaped. Early development was checked from the patient records of Oulu University Hospital in the case of subjects for whom verification was considered to be essential after the ADI-R interviews. School-day observations were carried out in the case of 24 subjects for whom verification was regarded as necessary, 22 of them completely, including observation of the child, and structured (ASSQ) and non-structured teacher interviews. After these examinations, 82 children remained for re-evaluation by reviewing all available data (ASSQs, ADI-R, ADOS tapes, patient records, school-day observations). DSM-IV-TR criteria (APA 2000) were used to construct clinical consensus diagnoses of AS or HFA, based on all gathered information, among a pediatrician (M.-L.M) with extensive clinical experience of PDDs and other developmental disorders and a child psychiatrist (S.-L.L.) with long-term clinical experience of PDDs and other psychiatric disorders.

Diagnosis of AS/HFA in the Clinic-based Study

The target population included all registered outpatients with AS or AS traits (features of AS or autism) or AS suspected at Oulu University Hospital. In our hospital district, all children with suspected PDD were referred to Oulu University Hospital at the time of this study. Thus, the outpatient participants were not selected (by socio-economic status for example) when the outpatient data were collected. All outpatients had been diagnosed in the child psychiatric clinic or in the child neurological department, supervised by a child psychiatrist or a child neurologist. Clinical diagnoses had then been assigned regarding current behavior (without regarding development during the first 3 years), and as a consequence, the subjects with normal intelligence had been diagnosed as having AS/AS traits/AS suspected.

Hospital records were evaluated during autumn 2002, originally for the genetic part of the clinic-based study in high-functioning children and adolescents with PDD (Weiss et al. 2009). All participants were high-functioning (FSIQ $\geq$ 80; WISC-III). The outpatients with AS or AS traits who had already participated in the community-based study (Mattila et al. 2007) were removed from the diagnostic phase in the clinic-based study. Finally, 53 outpatients with AS ($n = 43$), AS traits ($n = 8$) or AS suspected ($n = 2$), aged 7–14 years, were invited and 46 (87%) participated in defining the AS/HFA diagnosis more closely in 2003.

Diagnostic examinations included ADI-R (K.J.) and ADOS, module 3 (K.J.). The ADI-R interviews and ADOS observations were videotaped. Early development in all cases was verified from the patient records of Oulu University Hospital (K.J. and T.H.). After these investigations the clinical diagnoses of AS/AS traits/AS suspected were re-assigned by the psychologist (K.J.) on the basis of all gathered information, consulting the pediatrician (M.-L.M.) in the case of subjects for whom a second opinion was considered to be essential. DSM-IV-TR criteria (APA 2000) were used in detail to derive a diagnosis of AS or HFA.

Comorbidity Examinations

Of the 68 subjects diagnosed as having AS or HFA in the community-based study or in the clinic-based study, one had earlier announced refusal to continue. Thus, 67 subjects with AS/HFA were invited to take part in the comorbidity examinations in 2005, and 50 (75%) participated. The parents and children/adolescents were interviewed, using the K-SADS-PL schedule, and the level of functioning was estimated in these children/adolescents, using the CGA scale. When both parents were available, they were interviewed together. The interviews were videotaped. The graduate-level interviewers (T.H. and H.H.) were trained in administration of the K-SADS-PL schedule and the CGA scale. First, a senior child and adolescent psychiatrist (I.M.) and an educational psychologist (T.H.) were trained by a highly qualified child and adolescent psychiatrist, James J. McGough, MD, from the University of Los Angeles, California, US (Smalley et al. 2007). Second, the senior interviewer (T.H.) trained the junior interviewer (H.H.) in the administration of the K-SADS-PL schedule and the CGA scale. A best-estimate procedure described by Leckman et al. (1982) and all the information available was used to make clinical psychiatric diagnoses and CGAS assessments. The interviewers (T.H. and H.H.) and the senior child and adolescent psychiatrist (I.M.) had consensus meetings to confirm diagnostic assessments and CGAS scores, if needed. In addition, the senior interviewer (T.H.), experienced in the use of K-SADS administration and coding (Hurtig et al. 2007), reviewed every tenth

interview by the junior interviewer (H.H.) to ensure consistency between the raters. Inter-rater reliability was assessed by means of Cohen's κ (κ for diagnoses 0.94, SD 0.06) and percentage agreement between the interviewers (percentage mean for diagnoses 99.7%).

Data Analysis

The prevalences of current and lifetime comorbid conditions were determined. Confidence Intervals (CIs) for comorbid psychiatric disorders were calculated by using Confidence Interval Analysis (CIA) for Windows, Version 2.0.0. 2000 (London: BMJ Publishing Group). Co-occurring disorders and the effect of age (primary school vs. secondary school age) on comorbid conditions were analyzed by using Chi-square tests (Pearson Chi-Square or Fisher's Exact Test). Differences between mean current CGAS scores among AS/HFA subjects with and without psychiatric comorbid disorders were assessed by using the *t*-test. The influences of comorbid psychiatric disorders on CGAS scores were analyzed by using multiway analysis of variance (multiway ANOVA), having the CGAS score as response variable and comorbid psychiatric disorders as explanatory variables. No statistical comparison between the community-based sample and the clinic-based sample was carried out because there were eight overlapping participants. Statistical significance was evaluated using two-tailed 0.05 level tests. Analyses were performed with SPSS for Windows, Rel. 16.0. 2008 (Chicago: SPSS Inc.).

Results

Prevalence of Comorbid Psychiatric Disorders (See Tables 2, 3)

Combined Community- and Clinic-based Sample

One or more comorbid psychiatric disorders (current/lifetime) were diagnosed in 74%/84% of the cases. The most common disorders (current/lifetime) were behavioral (44%/50%), anxiety (42%/56%) and tic disorders (26%/38%). Of current comorbid psychiatric disorders, one disorder was diagnosed in 32%, two in 20%, three in 14% and four or more in 8% of the subjects with AS/HFA.

Current behavioral disorders ($n = 22$) often co-occurred ($n = 13$; p = 0.030, *df* 1) with current anxiety disorders ($n = 21$). Of current behavioral disorders, oppositional defiant disorder (ODD; $n = 8$) co-occurred ($n = 7$; $p = 0.007$) significantly with current anxiety disorders ($n = 21$), especially ($n = 4$; $p = 0.037$, $df = 1$) with OCD ($n = 11$). About half of the 19 cases with current ADHD and about half of the 21 cases with current anxiety disorder had both disorders simultaneously ($n = 11$; $p = 0.075$, *df* 1), although this was not statistically significant.

Current psychiatric disorders were more common in primary school-age ($n = 30/36$) than in secondary school-age ($n = 7/14$) participants ($p = 0.029$). Of all current comorbid psychiatric disorders, tic disorders ($n = 13/36$ vs. $n = 0/14$; $p = 0.010$) and behavioral disorders ($n = 19/36$ vs. $n = 3/14$; $p = 0.045$, $df = 1$) were more common in primary school-age ($n = 36$) than in secondary school-age ($n = 14$) participants. No secondary school-age participants had current tic disorders, but four of them recalled having had motor and/or vocal tics in the past.

A significant number of ADHD features indicating lifelong comorbid diagnosis of combined, inattentive or hyperactive-impulsive types of ADHD was shown in 44% of the subjects. In turn, 38% met a current diagnosis of ADHD (68% of them combined type, 32% inattentive type, and none hyperactive, impulsive type). In 21% of the current cases, ADHD type had changed over the years. All ODD diagnoses ($n = 8$) were current; thus, no past ODD was diagnosed. The most common current anxiety disorders were specific phobias (28%; fear of animals [dogs, bees], darkness, heights, confined spaces, bridges, and needles or injections), and OCD (22%). Two or three different current anxiety disorders were diagnosed in 14% of the participants.

None met the criteria for schizophrenia or related disorders, eating disorders or substance abuse disorders, and none had ever smoked.

Community-based Sample and Clinic-based Sample

One or more current comorbid psychiatric disorders were diagnosed in 78% of cases in the community-based sample and in 75% of cases in the clinic-based sample. In the community-based sample, the prevalence of behavioral disorders (current/lifetime) was 39%/44%, that of anxiety disorders 39%/50% and that of tic disorders 44%/50%, while in the clinic-based sample, the corresponding figures were 48%/55%, 45%/58%, and 23%/35%.

In the clinic-based sample, current psychiatric disorders were more common in primary school-age ($n = 23/26$) than in secondary school-age ($n = 7/14$) participants ($p = 0.018$). Of all current comorbid psychiatric disorders, tic disorders ($n = 9/26$ vs. $n = 0/14$; $p = 0.016$) and behavioral disorders ($n = 16/26$ vs. $n = 3/14$; $p = 0.015$, $df = 1$) were more common in primary school-age ($n = 26$) than in secondary school-age ($n = 14$) participants.

Table 2 Current and lifetime comorbid psychiatric disorders in subjects with AS/HFA

	Combined sample[a] [*n*/males = 50/38 (mean age 12.7, range 9.8–16.3)]		Community-based sample[a] [*n*/males = 18/12 (mean age 12.7, range 12.2–13.1)]		Clinic-based sample[a] [*n*/males = 40/32 (mean age 12.7, range 9.8–16.3)]	
	Current/lifetime (*n*/*n*)	CI (%)	Current/lifetime (*n*/*n*)	CI (%)	Current/lifetime (*n*/*n*)	CI (%)
Behavioral disorders	22 (44%)/25 (50%)	31–58/37–63	7 (39%)/8 (44%)	20–61/25–66	19 (48%)/22 (55%)	33–62/40–69
Attention deficit/hyperactive disorder	19 (38%)[b,c,d]/22 (44%)	26–52/31–58	6 (33%)[b]/7 (39%)	16–56/20–61	16 (40%)[c,d]/19 (48%)	26–55/33–62
Combined type (current)	13 (68%)[b]/15		5 (83%)[b]/5		10 (62.5%)/12	
Inattentive type (current)	6 (32%)[c, d]/8		1 (17%)/2		6 (37.5%)[c,d]/7	
Hyperactive type (current)	0 (0%)/3		0/1		0/3	
Conduct disorder	1 (2%)/1 (2%)	0.4–10/0.4–10	1 (6%)/1 (6%)	1–26/1–26	1 (2.5%)/1 (2.5%)	0.4–13/0.4–13
Oppositional defiant disorder	8 (16%)/8 (16%)	8–28/8–28	3 (17%)/3 (17%)	6–39/6–39	8 (20%)/8 (20%)	10–35/10–35
Anxiety disorders	21 (42%)/28 (56%)	29–56/42–69	7 (39%)/9 (50%)	20–61/29–71	18 (45%)/23 (58%)	31–60/42–72
Separation anxiety disorder	1 (2%)/4 (8%)	0.4–10/3–19	1 (6%)/3 (17%)	1–26/6–39	1 (2.5%)/2 (5%)	0.4–13/1–16
Panic disorder with agoraphobia	1 (2%)/1 (2%)	0.4–10/0.4–10	1 (6%)/1 (6%)	1–26/1–26	1 (2.5%)/1 (2.5%)	0.4–13/0.4–13
Agoraphobia	1 (2%)/1 (2%)	0.4–10/0.4–10	0/0	0–18/1–18	1 (2.5%)/1 (2.5%)	0.4–13/0.4–13
Social phobia	2 (4%)/3 (6%)	1–14/2–16	1 (6%)/1 (6%)	1–26/1–26	1 (2.5%)/2 (5%)	0.4–13/1–16
Specific phobia	14 (28%)/17 (34%)	18–42/22–48	6 (33%)/7 (39%)	16–56/20–61	11 (28%)/13 (33%)	16–43/20–48
Obsessive–compulsive disorder	11 (22%)/14 (28%)	13–35/18–42	2 (11%)/2 (11%)	3–33/3–33	10 (25%)/13 (33%)	14–40/20–48
Tic disorders	13 (26%)/19 (38%)	16–40/26–52	8 (44%)/9 (50%)	25–66/29–71	9 (23%)/14 (35%)	12–38/22–50
Tourette's syndrome	7 (14%)/7 (14%)	7–26/7–26	5 (28%)/5 (28%)	12–51/12–51	5 (13%)/5 (13%)	6–26/6–26
Motor tics	3 (6%)/5 (10%)	2–16/4–21	1 (6%)/1 (6%)	1–26/1–26	3 (8%)/5 (13%)	3–20/6–26
Vocal tics	3 (6%)/8 (16%)	2–16/8–28	2 (11%)/3 (17%)	3–33/6–39	1 (2.5%)/5 (13%)	0.4–13/6–26
Mood and related disorders	3 (6%)/7 (14%)	2–16/7–26	1 (6%)/1 (6%)	1–26/1–26	3 (8%)/7 (18%)	3–20/9–32
Major depressive disorder	3 (6%)/7 (14%)	2–16/7–26	1 (6%)/1 (6%)	1–26/1–26	3 (8%)/7 (18%)	3–20/9–32
Enuresis	1 (2%)/8 (16%)	0.4–10/8–28	1 (6%)/4 (22%)	1–26/9–45	1 (2.5%)/7 (18%)	0.4–13/9–32
Encopresis	1 (2%)/3 (6%)	0.4–10/2–16	1 (6%)/1 (6%)	1–26/1–26	1 (2.5%)/3 (8%)	0.4–13/3–20
Insomnia (current)[e]	18 (36%)	24–50	5 (28%)	12–51	15 (38%)	24–53
Initial	17 (34%)[f]	22–48	5 (28%)	12–51	14 (35%)	22–50
Middle	2 (4%)[f]	1–14	0	0–18	2 (5%)	1–16
Circadian	1 (2%)[f]	0.4–10	0	0–18	1 (2.5%)	0.4–13
Nonresto	1 (2%)[f]	0.4–10	0	0–18	1 (2.5%)	0.4–13

AS, Asperger syndrome; HFA, high-functioning autism; CI, confidence interval; ADHD, attention deficit/hyperactive disorder

[a] Combined sample = community-based sample + clinic-based sample; eight outpatients overlapping between the community-based and the clinic-based sample

[b] One has changed from past ADHD inattentive type into current ADHD combined type

[c] Two have changed from past ADHD combined type into current ADHD inattentive type

[d] One has changed from past ADHD hyperactive type into current ADHD inattentive type

[e] None had terminal insomnia

[f] One had initial, middle, circadian and nonresto insomnia

Table 3 Current comorbid psychiatric disorders in subjects with AS/HFA

Gender	Group	CGAS	AS/HFA	MDD	ADs	Adsad	Adpd1	Adago	Adsop	Adspph	Adocd	BehDis	ADHD	CD	ODD	TicDis	Tourette	MT	VT	Enur	Encopr	SleepDis
Male[a]	1	77	AS																			x
Male[a]	1	61	AS									X	x								x	
Male[a]	1	73	HFA													X	x					x
Male[a]	1	59	HFA		X					x												
Male[a]	1	58	HFA													X	x					
Male[a]	1	61	HFA		X	x				x		X	x		x	X	x					
Male	1	55	AS									X	x			X			x			
Male	1	70	AS		X					x		X	x									
Male	1	68	AS		X					x	x					X			x			
Male	1	70	HFA													X	x					
Male	1	79	HFA																			
Male	1	62	HFA																			
Female	1	59	AS													X	x					x
Female	1	69	AS									X	x									x
Female	1	65	HFA																			x
Female	1	45	HFA		X				x	x												
Female[a]	1	39	AS	x	X		x				x	X		x	x	X		x				
Female[a]	1	51	HFA		X					x		X	x		x					x		
Male	2	65	AS													X	x					
Male	2	61	AS		X					x		X	x			X			x			
Male	2	65	AS		X						x											x
Male	2	69	AS									X	x									x
Male	2	56	AS		X					x		X	x		x							
Male	2	61	AS													X		x				
Male	2	69	AS									X	x									
Male	2	55	HFA									X	x									x
Male	2	64	HFA		X						x	X	x			X		x				
Male	2	65	HFA									X	x									
Male	2	41	HFA		X						x	X	x		x							
Male	2	59	HFA													X	x					
Male	2	54	HFA																			x
Male	2	59	HFA									X			x							x
Female	2	65	AS		X					x		X	x									x
Female	2	51	AS		X						x	X			x							x
Female	2	61	HFA		X					x		X	x									
Female	2	69	HFA																			

Table 3 continued

Gender	Group	CGAS	AS/HFA	MDD	ADs	Adsad	Adpd1	Adago	Adsop	Adspph	Adocd	BehDis	ADHD	CD	ODD	TicDis	Tourette	MT	VT	Enur	Encopr	SleepDis
Male	3	85	AS																			
Male	3	79	AS																			
Male	3	62	AS																			
Male	3	79	AS																			x
Male	3	55	AS		X						x											x
Male	3	59	AS		X				x	x	x											
Male	3	61	AS																			
Male	3	69	AS																			x
Male	3	55	HFA	x	X					x												
Male	3	59	HFA		X			x		x	x	X	x									x
Male	3	75	HFA																			x
Male	3	49	HFA	x								X	x									
Female	3	73	AS		X					x	x											
Female	3	39	AS		X						x	X	x		x							x
Total				3	21	1	1	1	2	14	11	22	19	1	8	13	7	3	3	1	1	18

CGAS, Children's Global Assessment Scale; AS, Asperger syndrome; HFA, high-functioning autism; MDD, major depressive disorder; ADs, anxiety disorders; Adsad, separation anxiety disorder; Adpd1, panic disorder with agoraphobia; Adago, agoraphobia; Adsop, social phobia; Adspph, specific phobia; Adocd, obsessive–compulsive disorder; BehDis, behavioral disorders; ADHD, attention deficit/hyperactive disorder; ODD, oppositional defiant disorder; CD, conduct disorder; TicDis, tic disorders; MT, motor tics; VT, Vocal tics; Enur, enuresis; Encopr, encopresis; SleepDis, sleep disturbances

Group: 1 = community-based study, primary school-aged; 2 = clinic-based study, primary school-aged; 3 = clinic-based study, secondary school-aged

[a] Overlapping subjects belonging to the community-based sample and the clinic-based sample

Level of Functioning

Combined Community- and Clinic-based Sample

The mean current CGAS score was 62 (SD 10.2; range 39–85), and the mean worst lifetime CGAS score was 58 (SD 9.6; range 35–79) in the combined sample ($n = 50$). The current CGAS score was below 70 in 80% ($n = 40$), and worst lifetime CGAS score was below 70 in 88% ($n = 44$) of the participants. The mean current CGAS score was significantly lower ($p = 0.049$, $t = 2.021$, $df = 48$) in females (57, SD 11.9; $n = 12$) compared with males (64, SD 9.2; $n = 38$), and the mean worst lifetime CGAS score was also significantly lower ($p = 0.040$, $t = 2.116$, $df = 48$) in females (53, SD 12.0; $n = 12$) than in males (60, SD 8.3; $n = 38$). Mean CGAS scores did not differ significantly according to school level or as regards AS versus HFA. CGAS scores decreased significantly along with the number of comorbid psychiatric disorders (Table 4).

AS/HFA associated with current anxiety disorders ($p = 0.014$, $n = 21$, SSq = 472.3, $df = 1$, MSSq = 472.3, $F = 6.6$), current mood disorders ($p = 0.021$, $n = 3$, SSq = 411.6, $df = 1$, MSSq = 411.6, $F = 5.7$) or current behavioral disorders ($p = 0.038$, $n = 22$, SSq = 330.4, $df = 1$, MSSq = 330.4, $F = 4.6$) decreased the current CGAS score significantly, and AS/HFA associated with two individual disorders, current ODD ($p = 0.002$, $n = 8$, SSq = 689.7, $df = 1$, MSSq = 689.7, $F = 10.7$), or current major depressive disorder (MDD) ($p = 0.009$, $n = 3$, SSq = 478.7, $df = 1$, MSSq = 478.7, $F = 7.4$), also decreased the current CGAS score significantly. In addition, a trend towards a decreased CGAS score was found when AS/HFA was associated with current OCD ($p = 0.085$, $n = 11$, SSq = 200.8, $df = 1$, MSSq = 200.8, $F = 3.1$).

Community-based Sample and Clinic-based Sample

The mean current CGAS score was 62 (SD 10.5, range 39–79) and the worst lifetime CGAS score was 59 (SD 11.3, range 35–79) in the community-based sample ($n = 18$); the corresponding figures in the clinic-based sample ($n = 40$) were 62 (SD 10.4, range 39–85); and 58 (SD 9.0, range 39–77).

Discussion

To our knowledge, this is the first study involving community- and clinic-based data sets and a standardized interview instrument to determine the prevalence of comorbid psychiatric disorders in high-functioning subjects with AS/autism defined according to DSM-IV. Comorbid psychiatric disorders seemed to be common and often multiple in AS/HFA, decreasing the level of functioning significantly. Behavioral disorders, specifically ODD, co-occurred with anxiety disorders, specifically with OCD. Current psychiatric comorbidity was more common in primary school-age than in secondary school-age participants. In particular, tic disorders and behavioral disorders decreased with age; as a consequence, no tic disorders were diagnosed in secondary school-age participants. The high number of tic disorders in primary school-age participants and non-existence in secondary school-age participants led to the somewhat surprising result of more psychiatric disorders (78% with a disorder) in the primary school-age community-based sample than in the clinic-based sample (75% with a disorder) with primary- and secondary school-age participants. However, the presence of tic disorders did not decrease the CGAS scores significantly and might not be considered to be very impairing psychiatrically. In conclusion, concerning psychiatric comorbidity, the prevalence of current psychiatric disorders (74%) in children and adolescents with AS/HFA in our study was in concordance with the prevalence of psychiatric disorders (70%) in children with ASDs in a study by Simonoff et al. (2008) in a population-derived sample.

In Finnish population-based studies, the prevalence of ADHD has been reported to be 7.1% in children according to DSM-III-R criteria (Almqvist et al. 1999) and 8.5% in adolescents according to DSM-IV criteria (Smalley et al. 2007), whereas in our study, the prevalence of current ADHD was much higher (38%). Many investigators have

Table 4 Mean current CGAS scores among AS/HFA subjects with and without psychiatric comorbid disorders

Comorbid psychiatric disorder (*n*)	Mean current CGAS	SD	Range	*t*	*df*	*p* Value
No psychiatric disorder (13)	70.5	9.3	54–85			
Any psychiatric disorder(s) (37)	59.3	8.9	39–73	3.873	48	<0.001
One psychiatric disorder (16)	63.1	5.7	55–73	2.618	27	0.014
Two psychiatric disorders (10)	58.5	9.1	45–73	3.087	21	0.006
Three psychiatric disorders (7)	55.4	11.2	39–68	3.220	18	0.005
Four or more psychiatric disorders (4)	52.5	10.0	39–61	3.336	15	0.005

CGAS, Children's Global Assessment Scale; AS, Asperger syndrome; HFA, high-functioning autism

demonstrated even higher prevalences of ADHD associated with PDDs (Gadow et al. 2004; Goldstein and Schwebach 2004; Lee and Ousley 2006).

According to the DSM-IV data, aggression, often found in ODD or in conduct disorder (CD), is also regarded as being common in children with PDDs. None of the subjects in our study had recovered from ODD and no ODD diagnosis had changed into CD over the years, even if recovery from other comorbid psychiatric disorders, e.g., ADHD and tic disorders, had taken place. The prevalence of ODD in otherwise typically developing children usually decreases with age or the condition changes into CD, but on the basis of our results, the symptoms of ODD seem to be permanent during childhood in subjects with AS/HFA. However, recall bias may be possible in ODD past diagnoses. The symptoms of ODD might partly be a manifestation of the stubbornness and difficulties in compliance that are often typical in PDDs. Based on our result of co-occurrence of ODD and anxiety disorders, ODD may also be a behavioral manifestation of anxiety. However, this suggestion needs more research among PDD subjects and other clinical groups. Importantly, AS/HFA associated with ODD was reflected in significantly decreased CGAS scores.

In the light of the results of our study, children and adolescents with AS/HFA are at greater risk of anxiety disorders than the general child and adolescent population. The prevalence of current anxiety disorders was 39% in our community-based sample, while in a Finnish national study of 8- to 9-year-old children based on diagnostic interviews with the parents the corresponding prevalence (according to DSM-III-R) was 5.2% (Almqvist et al. 1999). Moreover, in that national study the prevalence of specific fears was 2.4%, while in our community-based sample, 33% suffered from current specific phobia.

A figure of 1% would be appropriate for the overall international prevalence figure for Gilles de la Tourette syndrome (Robertson 2008). In turn, a minimum prevalence of 8.1% for Tourette's syndrome in children with autism has been shown (Baron-Cohen et al. 1999). In our clinic-based sample, a concordant prevalence of 13% for Tourette's syndrome was assigned, but in our community-based sample the prevalence was more than twice as high (28%). Coincidence may play a part when the number of cases is small, but the primary diagnosis, Tourette's syndrome versus AS/HFA, might depend on the behavioral traits that are dominant at the time the diagnosis is made. As a consequence, not all ASD diagnoses might have been registered in patient records (and thus not have been included in our study). This might have biased the prevalence of Tourette's syndrome in the clinic-based sample.

A high prevalence of depression problems has been demonstrated in subjects with AS (37%; $n = 35$, age range = 8–51 years; Ghaziuddin et al. 1998) and a raised prevalence in children and adolescents with AS/HFA (17%; $n = 59$, age range = 9–14 years; Kim et al. 2000), while the prevalence of current MDD in our study was low (6%), being at the same level as depressive disorder (6.2%) in the Finnish national study of 8- to 9-year-old children (Almqvist et al. 1999). The participants in our study seemed to have good and close relationships with their parents, which may have prevented the development of depression and contributed to recovery from it. However, the presence of MDD was associated with significantly lowered CGAS scores, although the number of MDD cases was low. Therefore, depression associated with AS/HFA has to be taken seriously by professionals.

In the light of a few existing studies, the co-occurrence of schizophrenia does not appear to be common in subjects with AS (Asperger 1944; Ghaziuddin et al. 1998). However, a relatively high prevalence of schizophrenia has been determined in the relatives of subjects with AS/HFA (Ghaziuddin 2005). Schizophrenia usually becomes manifest after 15 years of age, at the age of 15–25 years in males and 20–30 years in females. According to the results of a study by Nilsson et al. (1999), ASDs are overrepresented in subjects who have suffered from anorexia nervosa in their youth. Anorexia nervosa most often becomes manifest in youth or early adulthood. Therefore, the participants in our study were mostly too young to allow assessment of the prevalence of schizophrenia or anorexia nervosa. Additionally, the number of secondary school-age participants may have been too low to find them, owing to the fact of low prevalence in the general population.

Experiments with smoking are more obvious at secondary school age. In a Finnish survey among 14- to 16-year-old teenagers, 48% had never smoked (Statistics Finland Website 2006a), whereas there had been no smoking among the subjects with AS/HFA in our study. This may partly be due to lack of social contacts, because the first experiments often take place with peers. In the K-SADS interviews the subjects with AS/HFA also seemed to have a negative attitude towards smoking. It remains to be seen whether a comorbid diagnosis of ADHD would increase the incidence of smoking in subjects with AS/HFA.

Insomnia is a common and worsening problem. In a Finnish survey among 14- to 16-year-old teenagers, the prevalence of almost daily initial and middle insomnia was 11% (Statistics Finland Website 2006b). Based on our results, the prevalence of initial insomnia was, however, much higher (34%) in subjects with AS/HFA, being in concordance with the results of a study by Allik et al. (2006). Therefore, identification and treatment of sleep disturbances, e.g., with melatonin (Paavonen et al. 2003), should be a routine part of the treatment plan of children/adolescents with AS/HFA.

The CGAS scores reflected dysfunction in domains such as social interaction, but there was also a linear relationship between the number of comorbid psychiatric disorders and lower CGAS scores. AS/HFA associated with anxiety disorders or behavioral disorders, and with ODD or MDD, was reflected in significantly lowered CGAS scores. Anxiety disorders and behavioral disorders were more common in the clinic-based sample than in the community-based sample, possibly indicating that the subjects with a lower level of functioning had more often been referred to the hospital or had been more carefully diagnosed. The level of functioning (mean CGAS score) among girls was significantly lower than among boys, while mean CGAS scores did not differ significantly between primary- and secondary school-age participants or between participants with AS versus HFA. However, larger research groups might be needed to study CGAS score differences between younger and older subjects and between those with AS and HFA to establish or disprove these results. Subjects with PDD are considered to differ from each other and each of them is taken to be an individual with a variety of symptoms and traits. Importantly, this study raised a comment caused by individually variable comorbid psychiatric disorders: comorbidity influenced the clinical picture of the subjects with AS/HFA and the severity of the level of their functioning.

Limitations concerning the diagnostic instruments used in this study merit note. When we initiated this study, the time simultaneously also marked the beginning of the importation of international instruments, ADI-R and ADOS, to Finland. Therefore, we had to start from scratch with these, including official translations into Finnish and training courses in Finland. We thus decided to use these instruments in a clinical manner. By using multi-informant sources and basing the AS/HFA diagnoses on consensus and in detail on DSM-IV-TR diagnostic criteria, we compensated well for the drawback. In addition, there are no algorithms precisely for AS. In K-SADS-PL past diagnosis, the retrospective assessment by the parents and children/adolescents may have resulted in some recall bias. Because of the possible recall bias, we mainly reported current diagnoses. Recently, a modification of K-SADS-PL (Autism Comorbidity Interview-Present and Lifetime Version; ACI-PL; Leyfer et al. 2006) for children and adolescents with autism and a CGAS modification (Developmental Disability-Child Global Assessment Scale; DD-CGAS; Wagner et al. 2007) for children with PDDs have been developed. However, this study was drawn up and performed before these modified instruments were available. In addition, the K-SADS-PL schedule and CGA scale can be used in all children irrespective of diagnosis. Our results with the original K-SADS-PL and CGAS may thus be more comparable with the results of non-PDD studies.

Familiarity in the etiology of ADHD may also result in bias if parents with ADHD symptoms either under- or overreport these symptoms in their offspring. However, Faraone et al. (2003) reported that parental ADHD symptoms do not bias maternal reports of ADHD symptoms in their children. Also, it is possible that parental anxiety may influence parental reporting trends and/or biases (Bernstein et al. 2005). However, most participants with a specific phobia in our study seemed to be very stuck in their phobias.

All three study samples, combined, community- and clinic-based samples, can be regarded as being comparable according to ethnic and socioeconomic status, mean age and gender, but the age range in the community-based sample is narrower than in the clinic-based and combined samples. However, statistical comparison of the characteristics cannot be performed between the study samples because of the eight overlapping participants.

Comparison between primary- and secondary school-age participants to find out whether the comorbid psychiatric disorder spectra and CGAS scores change along with age involves a risk of bias. In this kind of comparison, we assume that the current primary school-age participants will turn into the same kind of secondary school-age adolescents as the current secondary school-age participants. Longitudinal studies are needed to show the trajectory of the comorbid psychiatric disorder spectrum and the trajectory of the impairment based on CGAS scores.

This study was carried out in a democratic Western country that provides almost free health care for all inhabitants. Therefore, the results are generalizable to developed countries that have a cultural context similar to that in Finland. Clinicians are reminded not to forget PDDs when evaluating children/adolescents with psychiatric diagnoses and neuropsychiatric disorders (e.g., ADHD, Tourette's syndrome). The significant number of ADHD and anxiety symptoms in subjects with AS/HFA indicates that the current exclusionary DSM-IV-TR and/or ICD-10 criteria concerning comorbid diagnosis of ADHD and/or OCD with PDDs should be re-considered. It should be possible to diagnose AS/HFA and ADHD and/or OCD simultaneously in order to target rehabilitation (White et al. 2009a) and treatment (Posey et al. 2007). In conclusion, we emphasize the importance of routine comprehensive comorbid psychiatric evaluation in children and adolescents with AS/HFA in order to select the best means of intervention and their combinations.

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