

Egyptian children with autism spectrum disorders: risk factors and comorbidity in relation to disease severity

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Background

Autism spectrum disorders (ASDs) represent a group of neurodevelopmental disorders characterized by impaired reciprocal socialization and communication, often accompanied with stereotyped ritualistic behavior. To date, no clear data could explain the dramatic worldwide increase in the incidence of ASD during the last two decades. It is suggested that some environmental factors besides a genetic predisposition leads to the disease. In addition, the disease is known to be associated with other psychiatric comorbidities.

Aim

The current study aimed to assess the incidence of psychiatric comorbidity present in those children and to relate the findings to the severity of the disease.

Patients and methods

The current study included 40 children (27 boys and 13 girls), with ages ranging from 3 to 11 years, and diagnosed with ASDs on the basis of the DSM-IV-TR criteria. Patients were divided to three groups according to their score on Gilliam Autism Rating Scale: mild ASD (10 cases); moderate ASD (11 cases), and severe ASD (19 cases). Data were collected through clinical psychiatric interview, Mini International Neuropsychiatric Interview for children and adolescent (M.I.N.I. KID), the Gilliam Autism Rating Scale, Vineland Adaptive Behavior Scales, and a scale for measuring family socioeconomic status for health research in Egypt.

Results

The present study demonstrated that 72.5% of the cases presented in families with middle socioeconomic status, which are highly educated, the majority (80%) of parents of studied cases lacked consanguinity degree, while only 20% from them had consanguinity from first degree; the vast majorities (92.5%) of the cases were not presented with family history of autism. As regards comorbidity, 90% of the cases were associated with one or more comorbid conditions and the presence of more than one comorbidity usually associated with male sex and severe type of autism, 72.5% of studied cases suffered from comorbid tics (40% occurs in severe autism), 25% of cases presented with associated attention-deficit/hyperactivity disorder, 20% of cases suffered from oppositional defiant disorder (ODD) as comorbid conditions, 37.5% of studied cases had comorbid obsessive compulsive disorder (OCD), and 5% of cases suffered from comorbid general anxiety disorder.

Conclusion

From the current study it was concluded that boys, high and moderate socioeconomic states, consanguinity, positive family history represented conditions that are associated with an increased risk for autism and ASDs in Egyptian population. Presence of one or more of those risk factors in children with autism is usually associated with severe type of the disease and more associated comorbidities. Determining the contribution of these risk factors may improve detection, earlier treatment, and better prevention of the disease. Comorbid tics, attention-deficit/hyperactivity disorder, ODD, and OCD are most presented among boys, whereas comorbid general anxiety disorder is more presented in girls with autism. The most occurring coincidence of comorbidity is comorbid tics and OCD, followed by comorbid OCD and ODD. Those coincidences were associated with severe autism and male sex. We suggest future studies using large samples to confirm the finding of the present work.

Keywords:

autism, autism spectrum disorder-risk factors, autism spectrum disorders, comorbidity

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Introduction

Autism is a medical term that encompasses a broad spectrum of neurodevelopmental disorders characterized by impaired reciprocal socialization and

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communication, often accompanied with stereotyped ritualistic behavior (Levy *et al.*, 2009). Despite a strong genetic factor there are no clear-cut biological markers of autism and its diagnosis is purely based upon clinical observation, psychological tests, and employment of diagnostic instruments and standard checklist questionnaires, which are amenable to human bias (Le Couteur *et al.*, 2003). The clinical boundaries of autism spectrum disorder (ASD) have been changed over the years by the American Psychiatric Association, and at present are based on the 5th edition of the *Diagnosis and statistical manual of mental disorders* (DSM-V) (American Psychiatric Association, 2013). The dramatic worldwide increase in the incidence of ASD during the last two decades might be related to environmental factors, but is also a result of more permissive clinical criteria as well as increased worldwide awareness of ASD by both medical and educational personnel (Fombonne, 2005). This awareness has expanded throughout the whole world, including the Middle Eastern Arab world, where autism was rarely reported in the past (Hussein *et al.*, 2011).

Recent epidemiological studies have converged in findings that child autism and pervasive developmental disorders, collectively referred to as autistic spectrum disorders (ASDs), are more common than previously thought and have prevalence of 0.06–1% in child and adolescent population (Fombonne, 2005). From a public health point of view, ASD represents an important cause of morbidity and high service utilization. This is because of the early onset of the disease, its persistence along the patient life, the high level of the resulted impairment, and the absence of effective treatment for the disease. Impairment is mainly due to cognitive deficits, which are considered the core feature of autism. Other causes of impairment associated with the disease may be psychiatric comorbidities. Delineated psychiatric comorbidities may specify targets for specific intervention, which could reduce overall impairment and improve quality of life (McPartland and Volkmar, 2012). Previously, the only diagnosis of ASD was done through exclusion of any additional psychiatric symptoms and no further diagnostic approaches were made. Researchers have noted the necessity for further development in this area as ASD and other comorbidities are difficult to tease apart (Matson and Nebel-Schwalm, 2007). To our knowledge, in Egypt there has been few number of researches focused on this disease with no documented researches about epidemiology of autism among Egyptian children.

The current study aimed to assess the incidence of psychiatric comorbidity present in those children and to relate the findings to the severity of the disease.

Patients and methods

Patients

The current study included 40 children (27 boys and 13 girls), with their ages ranging from 3 to 11 years, who were diagnosed with ASDs. The diagnosis was based on the DSM-IV-TR criteria. Patients were divided into three groups according to their score on Gilliam Autism Rating Scale, to differentiate the degree of severity of ASD. The groups were as follows: mild ASD (10 cases), for which GARS scale indicates very low and below average probability of autism; moderate ASD (11 cases), for which GARS scale indicates average probability of autism; and severe ASD (19 cases), for which GARS scale indicates above average, high, and very high probability of autism.

Methods

The instruments used to collect and analyze data related to the study were clinical psychiatric interview, Mini International Neuropsychiatric Interview for children and adolescent (M.I.N.I. KID), the Gilliam Autism Rating Scale, Vineland Adaptive Behavior Scales, and a scale for measuring family socioeconomic status (SES) for health research in Egypt. A structured interview sheet was designed on the basis of the previously mentioned instruments to obtain information. The sheet comprised questions about sociodemographic characteristics. Also, there were questions to demonstrate the presence of certain risk factors related to ASD in studied cases such as the presence of consanguinity between parents, family history of autism, obstetric history mother such as drugs used without doctors' prescription, rubella infection, gestational diabetes, exposure to X-ray during pregnancy, premature labor, delivery complications, medical history of the child including admission to incubator, congenital anomalies, exposure to infectious diseases such as meningitis or encephalitis, and a history of obligatory immunization. Parents were also interviewed regarding the child's daily living skills – for example, using the bathroom and feeding oneself, the communication skills such as understanding what is said and being able to answer, and social skills with peers and family members. The aim of the current study was explained to all participants. An informed consent from the parents of the children was obtained.

Statistical analysis

Descriptive statistics (frequencies, proportions, median, interquartile range) was carried out using computer program SPSS (version 22; IBM Corp., Armonk, NY). The Pearson χ^2 -test was used to compare differences in the distribution of frequencies among different groups.

One sample binomial test was used to find significant difference in certain variable in the same group. For quantitative analysis, the Mann–Whitney test was used to compare parameters in two different groups and the Kruskal–Wallis test was used to compare parameters in more than two groups. Cramer's V was used to assess the association between two nominal variables, whereas Spearman's correlation was used to determine the degree of association in case of ordinal variables and quantitative variables in groups.

Results

In the current work, 25% of studied cases were suffering from mild autism, 27.5% from moderate autism, while 47.5% of cases had the severe type. Co-morbid tics were found to be associated more with male sex (Male to female ratio was 1.9 : 1) also, males patient were found to have higher incidence of co-morbid attention-deficit/hyperactivity disorder (ADHD) compared to female patients male to female ratio was 1.5 : 1. Beside that, comorbid oppositional defiant disorder (ODD) and comorbid obsessive compulsive disorders (OCD) were found to occur more with autism among males than females (male to female ratio 7 : 1 and 6.5 : 1 respectively). There was a significant moderate association between sex and presence of comorbid OCD ($P = 0.045$, Cramer's $V = 0.317$). In contrast, a higher incidence of comorbid general anxiety disorder (GAD) was found in girls with autism rather than in boys (the two cases with comorbid GAD were females) with a significant moderate association between the incidence of comorbid GAD and sex ($P = 0.037$, Cramer's $V = 0.331$) (Table 1).

Occurrence of comorbid tics in cases from urban areas was six times those from rural areas; the incidence of comorbid ADHD in cases from urban areas was nine times those who were living in rural areas. In addition, comorbid ODD was detected in cases from urban areas seven times those in rural areas, comorbid OCD was found to occur in cases from urban areas six times those in rural areas. All cases with co-morbid were from urban areas (Table 1). In addition, there was a significant moderate association between presence of associated comorbid tics and SES ($P = 0.035$, Cramer's $V = 0.410$). It is presented mostly in middle level (57.5% of cases are in middle SES and presented with co-tics) (Table 1).

There was a significant moderate association between presence of comorbid OCD in studied cases and the history of both gestational complications ($P = 0.041$, Cramer's $V = 0.323$) and delivery complications ($P = 0.014$, Cramer's $V = 0.387$). Of the seven cases

associated with gestational complications, five were presented with OCD (Table 1).

A high significant association was found between comorbid ODD and consanguinity between parents ($P < 0.0001$, Cramer's $V = 0.688$). Of the eight cases for which there was consanguinity between their parents, six cases were presented with associated ODD. In addition, there was significant moderate association between comorbid OCD and consanguinity between parents ($P = 0.014$, Cramer's $V = 0.387$). Of the eight cases for which there was consanguinity between their parents, six cases were presented with associated OCD (Table 1). There was a significant association between presence of comorbid ODD in studied cases and the presence of autistic child in their relatives ($P = 0.036$, Cramer's $V = 0.332$) (Table 1).

In the current work, 90% of the cases were associated with one or more comorbid conditions, which were comorbid tics, comorbid ODD, comorbid ADHD, comorbid OCD, and comorbid GAD, but no cases was associated with dysthymia, mania, panic attacks, agoraphobia, anxiety, and specific or social phobia (Table 2). Comorbid tics were presented in 72.5% of the studied cases; 40% occurred in cases with severe autism, 20% in moderate type, and 12.5% in mild cases. Overall, 25% of the autistic cases presented with associated ADHD. ADHD is less presented in mild cases (5% of all cases) and equally presented in moderate and severe cases (10% of all cases in both groups). In addition, it was found that 20% of the cases suffered from ODD as comorbid conditions. Three (7.5%) cases had ADHD associated with ODD, five (12.5%) had tics associated with ODD, and six (15%) cases had both OCD and ODD as comorbid conditions with ASD. The occurrence of ODD was associated with severe autism (Table 3). There was a significant association between the presence of ODD as comorbid condition with autism and the presence of autistic child among relatives of cases ($P = 0.036$), and a significant high association between comorbid ODD and consanguinity between parents ($P < 0.0001$). Of the eight cases for which there was consanguinity between their parents, six cases were presented with associated ODD (Table 1). In the present work, 37.5% of the studied cases had comorbid OCD. OCD was not presented in mild cases. Severe autism was the type most associated with OCD (32.5% studied cases presented with severe autism and associated with OCD) (Table 3). A significant high association was found between the presence of OCD as comorbidity and the severe type of autism ($P < 0.0001$) (Table 1). In the current study, 5% of cases suffered from comorbid GAD, 1% in both mild and severe autism and no cases in moderate autism (Table 3).

Table 1 Correlation between different associated comorbidities and both descriptive and risk factors in studied cases

Descriptive data and associated risk factors	Comorbid tics		P value (Cramer's V)	Comorbid ADHD		P value (Cramer's V)	Comorbid ODD		P value (Cramer's V)	Comorbid OCD		P value (Cramer's V)	Comorbid GAD		P value (Cramer's V)	Total (N = 40)
	No [11 (27.5%)]	Yes [29 (72.5%)]		No [30 (75%)]	Yes [10 (25%)]		No [32 (80%)]	Yes [8 (20%)]		No [25 (62.5%)]	Yes [15 (37.5%)]		No [38 (95%)]	Yes [2 (5%)]		
Sex																
Male	8 (20)	19 (47.5)	0.664 (0.069)	6 (15)	6 (15)	0.559 (0.092)	7 (17.5)	7 (17.5)	0.177 (0.214)	14 (35)	13 (32.5)	0.045 (0.317)*	27 (67.5)	0	0.037 (0.331)*	27 (67.5)
Female	3 (7.5)	10 (25)		4 (10)	4 (10)		1 (2.5)	1 (2.5)		11 (27.5)	2 (5)		11 (27.5)	2 (5)		13 (32.5)
Residence																
Urban	11 (27.5)	25 (62.5)	0.194 (0.205)	9 (22.5)	9 (22.5)	1.000 (<0.0001)	7 (17.5)	7 (17.5)	0.792 (0.042)	23 (57.5)	13 (32.5)	0.586 (0.086)	34 (85)	2 (5)	0.629 (0.076)	36 (90)
Rural	0	4 (10)		1 (2.5)	1 (2.5)		1 (2.5)	1 (2.5)		2 (5)	2 (5)		4 (10)	0		4 (10)
Gestational complications																
No	8 (20)	25 (62.5)	0.316 (0.158)	8 (20)	8 (20)	0.810 (0.038)	5 (12.5)	5 (12.5)	0.096 (0.263)	23 (57.5)	10 (25)	0.041 (0.323)*	31 (77.5)	2 (5)	0.504 (0.106)	33 (82.5)
Yes	3 (7.5)	4 (10)		2 (5)	2 (5)		3 (7.5)	3 (7.5)		2 (5)	5 (12.5)		7 (17.5)	0		7 (17.5)
Delivery complications																
No	7 (17.5)	18 (45)	0.927 (0.014)	7 (17.5)	7 (17.5)	0.572 (0.089)	5 (12.5)	5 (12.5)	1.000 (<0.0001)	12 (30)	13 (32.5)	0.014 (0.387)*	23 (57.5)	2 (5)	0.261 (0.178)	25 (62.5)
Yes	4 (10)	11 (27.5)		3 (7.5)	3 (7.5)		3 (7.5)	3 (7.5)		13 (32.5)	2 (5)		15 (37.5)	0		15 (37.5)
Neonatal medical complications																
No	8 (20)	24 (60)	0.479 (0.112)	8 (20)	8 (20)	1.000 (<0.0001)	5 (12.5)	5 (12.5)	0.167 (0.219)	20 (50)	12 (30)	1 (<0.0001)	30 (75)	2 (5)	0.468 (0.115)	32 (80)
Yes	3 (7.5)	5 (12.5)		2 (5)	2 (5)		3 (7.5)	3 (7.5)		5 (12.5)	3 (7.5)		8 (20)	0		8 (20)
Consanguinity between parents																
No	9 (22.5)	23 (57.5)	0.859 (0.028)	8 (20)	8 (20)	1.000 (<0.0001)	2 (5)	2 (5)	<0.0001 (0.688)*	23 (57.5)	9 (22.5)	0.014 (0.387)*	30 (75)	2 (5)	0.468 (0.115)	32 (80)
Yes	2 (5)	6 (15)		2 (5)	2 (5)		6 (15)	6 (15)		2 (5)	6 (15)		8 (20)	0		8 (20)
Presence of autistic child in relatives																
No	11 (27.5)	26 (65)	0.267 (0.175)	8 (20)	8 (20)	0.083 (0.274)	6 (15)	6 (15)	0.036 (0.332)*	23 (57.5)	14 (35)	0.877 (0.025)	35 (87.5)	2 (5)	0.679 (0.065)	37 (92.5)
Yes	0	3 (7.5)		2 (5)	2 (5)		2 (5)	2 (5)		2 (5)	1 (2.5)		3 (7.5)	0		3 (7.5)
Socioeconomic status																
High	0	3 (7.5)	0.035 (0.410)*	0	0	0.138 (0.314)	0	0	0.511 (0.183)	3 (7.5)	0	0.370 (0.223)	3 (7.5)	0	0.671 (0.141)	3 (7.5)
Middle	6 (15)	23 (57.5)		6 (15)	6 (15)		7 (17.5)	7 (17.5)		17 (42.5)	12 (30)		27 (67.5)	2 (5)		29 (72.5)
Low	5 (12.5)	3 (7.5)		4 (10)	4 (10)		1 (2.5)	1 (2.5)		5 (12.5)	3 (7.5)		8 (20)	0		8 (20)

ADHD, attention-deficit/hyperactivity disorder; GAD, general anxiety disorder; OCD, obsessive compulsive disorder; ODD, oppositional defiant disorder; *statistically significant.

Table 2 Numbers, types and coincidence of associated co-morbid conditions in relation to types of autism and sex in studied cases

Co-morbid disorders and their co-incidence	Autistic type [n (%)]			Sex		Total (N = 40)
	Mild autism (N = 10) (25%)	Moderate autism (N = 11) (27.5%)	Severe autism (N = 19) (47.5%)	Male	Female	
Number of cases with no associated comorbidity	4 (10)	0	0	3 (7.5)	1 (2.5)	4 (10)
Number of cases with one type of comorbidity						
Only comorbid tics	4 (10)	6 (15)	3 (7.5)	8 (20)	5 (12.5)	13 (32.5)
Only comorbid ADHD	0	1 (2.5)	0	0	1 (2.5)	1 (2.5)
Only comorbid ODD	0	0	0	0	0	0
Only comorbid OCD	0	1 (2.5)	0	1 (2.5)	0	1 (2.5)
Only comorbid GAD	0	0	0	0	0	0
Total cases	4 (10)	8 (20)	3 (7.5)	9 (22.5)	6 (15)	15 (37.5)
Number of cases with two types of comorbidity						
Comorbid tics and ADHD	1 (2.5)	1 (2.5)	1 (2.5)	2 (5)	1 (2.5)	3 (7.5)
Comorbid tics and OCD	0	0	6 (15)	4 (10)	2 (5)	6 (15)
Comorbid tics and GAD	0	0	1 (2.5)	0	1 (2.5)	1 (2.5)
Comorbid ADHD and OCD	0	1 (2.5)	0	1 (2.5)	0	1 (2.5)
Comorbid ADHD and GAD	1 (2.5)	0	0	0	1 (2.5)	1 (2.5)
Comorbid ODD and OCD	0	0	3 (7.5)	3 (7.5)	0	3 (7.5)
Total cases	2 (5)	2 (5)	11 (27.5)	10 (25)	5 (12.5)	15 (37.5)
Number of cases with three types of comorbidity						
Comorbid tics, ADHD, and ODD	0	1 (2.5)	1 (2.5)	1 (2.5)	1 (2.5)	2 (5)
Comorbid tics, ADHD, and OCD	0	0	1 (2.5)	1 (2.5)	0	1 (2.5)
Comorbid tics, ODD, and OCD	0	0	2 (5)	2 (5)	0	2 (5)
Total cases	0	1 (2.5)	4 (10)	4 (10)	1 (2.5)	5 (12.5)
Number of cases with four types of comorbidity						
Comorbid tics, ADHD, ODD, and OCD	0	0	1 (2.5)	1 (2.5)	0	1 (2.5)
Total cases	0	0	1 (2.5)	1 (2.5)	0	1 (2.5)

ADHD, attention-deficit/hyperactivity disorder; GAD, general anxiety disorder; OCD, obsessive compulsive disorder; ODD, oppositional defiant disorder.

Table 3 Frequency of associated comorbidity of autism among different autistic types

Comorbid disorders	Autistic type						Total (N = 40)	P value	Cramer's V
	Mild autism (N = 10) (25%)	P_1	Moderate autism (N = 11) (27.5%)	P_2	Severe autism (N = 19) (47.5%)	P_3			
Tics									
No	5 (12.5)	1.000	3 (7.5)	0.227	3 (7.5)	0.004*	11 (27.5)	0.146	0.310
Yes	5 (12.5)		8 (20)		16 (40)		29 (72.5)		
ADHD									
No	8 (20)	0.109	7 (17.5)	0.549	15 (37.5)	0.019*	30 (75)	0.592	0.162
Yes	2 (5)		4 (10)		4 (10)		10 (25)		
ODD									
No	10 (25)	–	10 (25)	0.012*	12 (30)	0.359	32 (80)	0.035*	0.409
Yes	0		1 (2.5)		7 (17.5)		8 (20)		
OCD									
No	10 (25)	–	9 (22.5)	0.065	6 (15)	0.167	25 (62.5)	<0.0001*	0.623
Yes	0		2 (5)		13 (32.5)		15 (37.5)		
GAD									
No	9 (22.5)	0.021*	11 (27.5)	–	18 (45)	<0.0001*	38 (95)	0.575	0.166
Yes	1 (2.5)		0		1 (2.5)		2 (5)		

ADHD, attention-deficit/hyperactivity disorder; GAD, general anxiety disorder; OCD, obsessive compulsive disorder; ODD, oppositional defiant disorder, P , statistically significant (χ^2 -test), significant difference between groups, P_1 , statistically significant (one sample binomial test), significant difference between variables in mild autism group, P_2 , statistically significant (one sample binomial test), significant difference between variables in moderate autism group, P_3 = statistically significant (one sample binomial test), significant difference between variables in severe autism group, *Statistically significant (χ^2 -test).

A great association was found between the presence of more than one comorbidity and both male sex and severe type of autism. This coincidence occurred in severe types, almost more in boys. The most

occurring coincident comorbidity was comorbid tics and OCD, which represented 25% of all cases. Presence of comorbid ODD associated with comorbid OCD in the studied cases represented the

second coincident comorbidity, and represented 15% of all cases. This coincidence occurred also in cases with severe autism, almost more in boys. Comorbid ODD and comorbid ADHD represented 7.5% of all studied cases (Table 2).

Discussion

ASD is a syndrome that is presented with impairment features in social interaction and communication. It is also known to be associated with restricted interests and presence of repetitive and stereotypic activities. Both genetic and environmental factors have been described as predisposing factors of autism (Matson and Nebel-Schwalm, 2007).

Autism is a lifelong disability that needs continuous treatment and education in residential settings. Thus, studying the risk factors and comorbid conditions of ASD is very essential in helping to protect and in perfect diagnosis and management (Rozga *et al.*, 2011).

In the current work, the comorbidity of psychiatric disorders presented in children was assessed. Furthermore, the association between consanguinity and family history of other psychiatric disorders in ASD patients was examined.

In the current study, boys with autism represented by higher incidence of comorbid tics (about twice that in girls; boy to girl ratio was 1.9 : 1), a higher incidence of comorbid ADHD (about one and half that in girls; boy to girl ratio was 1.5 : 1), a higher incidence of comorbid ODD (about seventh time that in girls; boy to girl ratio was 7 : 1), a higher incidence of comorbid OCD (about sixth times that in girls; boy to girl ratio was 6.5 : 1, with significant moderate association between sex and presence of comorbid OCD ($P = 0.045$, Cramer's $V = 0.317$). In contrast, a higher incidence of comorbid GAD was founded in females with autism rather than in males (the two cases with comorbid GAD were presented in females and not presented at all male cases) with a significant moderate association between the incidence of comorbid GAD and sex ($P = 0.037$, Cramer's $V = 0.331$).

In their study, Halladay *et al.* (2015) reported greater prevalence of ADHD and other developmental conditions in males compared with females, which is in agreement with the findings of the present work.

Comorbidity of autism spectrum disorder

Children with ASD were classified as having a comorbid disorder if they met KID-SCID criteria for at least one

comorbid disorder, which is in line with the CBCL manual (Achenbach, 1991). The current study demonstrated that all studied cases were not associated with dysthymia, mania, panic attacks, agoraphobia, anxiety, and specific or social phobia. In the current work, it was also found that 10% of the cases were not associated with comorbid conditions and were among mild cases of autism. Those cases with no associated comorbidity were more males with a male to female sex ratio was 3 : 1.

Van Steensel *et al.* (2013) in their study reported that 57.5% of the children with autism in their study associated with comorbid disorders for ASDs. The 90% of the cases in the current study, which were associated with comorbid conditions, were distributed as follow: 37.5% associated with one comorbid condition (10% in mild, 20% moderate, and 7.5% with severe cases among boys; boy to girl sex ratio was 1.5 : 1), 37.5% associated with two comorbid conditions (5% in mild, 5% moderate, and 27.5% with severe cases; boy to girl sex ratio was 2 : 1), 12.5% associated with three comorbid conditions (2.5% moderate and 10% with severe cases; boy to girl sex ratio was 4 : 1), and 2.5% associated with four comorbid conditions and were present in severe autism cases and only among boys. Presence of more than one comorbidity usually associated with male sex and severe type of autism.

Comorbid tics

In the current work, 72.5% of the studied cases suffered from tics as comorbidity with autism; 40% occurred in cases with severe autism, 20% in moderate type, and 12.5% in mild type. Comorbid tics were more prevalent among severe cases compared with mild and moderate autism ($P = 0.004$). The incidence of tics as comorbidity is higher in males with autism than that in females (male to female ratio was 1.9 : 1) and in patients living in urban areas than in those from rural areas (six times those in rural areas). There was a significant moderate association between the presence of associated co-tics and SES ($P = 0.035$, Cramer's $V = 0.410$). It was presented mostly in middle level (57.5% of cases are in middle SES and presented with co-tics). No significant association was found between the occurrence of comorbid tics with autistic cases in the study and the presence of either gestational, delivery, or neonatal medical complications or with consanguinity between parents and presence of autistic child relative. The most occurring coincidence of comorbidity was comorbid tics and OCD, which represented 25% of all cases (15% presented with only the two conditions, 5% with associated ODD, 2.5% with associated ADHD, and 2.5% with associated ODD and ADHD). This coincident occurred in severe types, almost more in male sex.

Mattila *et al.* (2010) reported that tic disorders represent comorbid condition in 26% of the cases with autism included in their study, which is less than that in the current study. Furthermore, Mazzone *et al.* (2012) in their study mentioned that tic disorders have been found in comorbidity with ASD. A Swedish study showed that 20% of all school-age children with AS met full criteria for tics disorders. However, some authors consider this comorbidity as a predictor of a better outcome for autistic symptoms, even if the data collected to date are not sufficient to confirm this hypothesis.

Comorbid attention-deficit/hyperactivity disorder

In the present study 25% of the autistic cases presented with associated ADHD. ADHD was less presented in mild cases (5% of all cases) and equally presented in moderate and severe cases (10% of all cases in both groups). The incidence of ADHD as a comorbidity in males with autism was found to be about one and half of that in females (male to female ratio was 1.5 : 1) and occurs more in cases from urban areas (nine times those in rural areas). No significant association was found between the occurrence of comorbid ADHD with autistic cases in the study and SES, presence of either gestational, delivery, or neonatal medical complications or with consanguinity between parents and presence of autistic child among relatives.

Gadow *et al.* (2005) studied 182 cases with ASD in the age group 3–5 years and reported that the ratio of comorbid ADHD was 42.1% of the cases, which is higher than the results of the current work. Studies on sex ratios for ADHD show estimates ranging from 1.9: 1 to 5 : 1 (male : female) (Whiteley *et al.*, 2010). This is higher ratio between male and female than presented in the current work.

A study by Leyfer *et al.* (2006) reported that 55% of the children with autism had a significantly impairing ADHD syndrome, which is also higher than the findings of the present study. Leyfer *et al.* (2006) also mentioned that 31% of the autistic children met DSM-IV criteria for ADHD. An additional 24% fell just short of meeting DSM-IV criteria. Two-thirds of the children who met DSM-IV criteria for ADHD had the inattentive type and 23% had the combined type. Children with autism who fell just short of meeting DSM-IV criteria had long attention spans for their preferred activity but impaired attention in other situations. It is well known that some children with autism can attend almost indefinitely to a stimulus that they find interesting, be it functional or nonfunctional. Impaired attention is particularly obvious when children with autism are engaged in school and homework and

other cognitively demanding activities. It has not been clear in the past how to diagnose ADHD in persons with autism because of these unusual and idiosyncratic attention-inattention patterns (Dawson and Lewy, 1989).

The study by Leyfer *et al.* (2006) reported that children with autism, even those who have relatively high IQs, frequently suffer from impairing inattention. The rate of ADHD in autism reported by other investigators has varied from 29 to 73%, the variability likely due to the factors mentioned previously (Wozniak *et al.*, 1997; Ghaziuddin and Greden, 1998). The convergent findings of our study and the studies of other investigators suggest that impairing ADHD syndromes are common, but not universal phenomena, in autism. A study by Simonoff *et al.* (2008) reported that 70.8% of the ASD children had at least one current psychiatric disorder. The most common comorbidities were social anxiety (29.2%), ADHD (28.1%), and ODD (28.1%). In their study, Van Steensel *et al.* (2013) studied 40 cases of children with ASD and found that ADHD occurs as comorbidity in 22.5% of the cases, which is coincident with the frequency in the current study. Leitner (2014) mentioned that there are many hypotheses that were suggested to explain the co-occurrence of ASD and ADHD, but the most likely explanation may be that the two are independent disorders occurring together by association with a third independent factor, or alternatively they share a common underlying etiology. The authors believe the latter is the most likely model and that both disorders share a common genetic basis. Their view is supported by several family, twin, and molecular genetic studies that proved that ADHD and ASD originate from partly similar familial/genetic factors. About 50–72% of the contributing genetic factors in both disorders show overlap. These shared genetic and neurobiological underpinnings form an explanation why both disorders occur so frequently within the same patient and family.

A study by Mazzone *et al.* (2012) reported an association between Asperger Syndrome (AS)/High Functioning Autism (HFA) and ADHD. According to DSM-IV criteria, it is not possible to perform the diagnosis of ADHD in the context of an ASD. However, the debate about ADHD comorbidity in ASDs is still open in the DSM-V proposal and clinical opinion, research practice, and theoretical models seem to suggest that comorbidity between these disorders is a real, relevant, and a frequent occurrence (Gargaro *et al.*, 2011). Furthermore, a phenotypic overlap between the AS/HFA and ADHD has been recently discussed and the controversy whether these two conditions take part of a spectrum of symptoms is still also open. Even though an option being considered on DSM-V regarding

exclusion criteria for ADHD may be to remove ASD from the exclusion criteria, whether DSM-V will allow a comorbid ASD/ADHD diagnosis remains uncertain. Indeed, there is no evidence that ADHD is inconsistent with ASDs and when an association between ADHD and these disorders exists, it responds to treatment similar to ADHD without ASD. In the clinical practice it is often possible to recognize ADHD-like symptoms such as inattentive symptoms in children with AS/HFA, and neuropsychological studies have reported that children with AS/HFA show the same inattention pattern of children with ADHD in terms of type and degree. However, other studies showed that inattention symptoms in school settings among children with ASD were more likely to be attributed to low IQ (Mazzone *et al.*, 2012).

Comorbid oppositional defiant disorders

In the current study, 20% of the cases were found to suffer from ODD as comorbid conditions. Three (7.5%) cases had also associated ADHD with ODD, five (12.5%) cases had tics associated with ODD, and six (15%) cases had OCD associated with ODD as comorbid conditions with ASD. The occurrence of ODD was associated with severe autism as from the eight cases (20% of all the cases) presented with autism, seven of them (17.5% of whole cases) were severe type. All cases with mild autism and about all cases of moderate type were not associated with ODD. The incidence of ODD as comorbidity in boys with autism was about seven times that in girls (boy to girl ratio was 7 : 1). Moreover, comorbid ODD occurs more in cases from urban areas (seven times of that in rural areas).

The current work also showed that there was significant association between the presence of comorbid ODD in the studied cases and the presence of autistic child among their relatives ($P=0.036$ and Cramer's $V=0.332$) and a significant high association between comorbid ODD and consanguinity between parents ($P < 0.0001$, Cramer's $V = 0.688$). Of the eight cases that there was consanguinity between their parents, six cases were presented with associated ODD. No other significant association was found between the occurrence of comorbid ODD with autistic cases in the study and SES or the presence of either gestational, delivery, or neonatal medical complications. Presence of comorbid ODD associated with c-morbid OCD in the studied cases represented the second occurring coincidence of comorbidity in the present study, after coincidence of comorbid tics and OCD, and represented 15% of all cases (7.5% presented with only the two conditions, 5% with associated tics and 2.5% with associated tics and ADHD). This coincidence occurred in severe types,

almost more in boys. Comorbid ODD and comorbid ADHD represented 7.5% of the studied cases.

Van Steensel *et al.* (2013) in their study examined 40 children with ASD and found that ODD occurs as comorbidity in 22.5% of cases, which is coincident with the adjacent percentage in the current study. In their study, Gadow *et al.* (2005) studied 197 cases between age 3 and 5 years with ASD and reported that the ratio of comorbid ODD was 12.7% of cases compared with 20% in the current work, and that 10.6% of cases had both ODD and ADHD as comorbid conditions with ASD compared with 7.5% in the current work. Gadow *et al.* (2008) also mentioned that the most common co-occurring psychiatric disorder with ODD was ADHD. In their study, Simonoff *et al.* (2008) reported that 70.8% of ASD children had at least one current psychiatric disorder. The most common comorbidities were social anxiety (29.2%), ADHD (28.1%), and ODD (28.1%).

A study by Leyfer *et al.* (2006) stated that although children with autism frequently have difficulty with following directions, being cooperative, and doing things on other people's terms, the frequency of DSM-IV defined ODD was not high in our sample. Only 7% of the children with autism met DSM-IV criteria for ODD. Cognitive and other factors associated with ODD in children with autism may be different than the factors reported in children without autism. We found that many children with autism do not even understand the concepts of spitefulness, vindictiveness, and intentionality, including deliberately annoying others and blaming others for one's behavior and mistakes. The relationship between oppositional behaviors in autism and cognitive impairments in autism, such as lack of appreciation of the mental states of others and problems with executive function such as rigid, inflexible thinking and behavior, need further study (Baron-Cohen, 1988, 1989, 1991, 1993; Ozonoff *et al.*, 1991).

Comorbid obsessive compulsive disorders

The current work represented that 37.5% of the studied cases had comorbid OCD. OCD is not present in mild cases. Severe autism is the most type associated with OCD in the current study (32.5% the studied cases presented with severe autism and associated with OCD). There was a significant moderate association between the incidence of OCD as comorbidity and sex ($P = 0.045$, Cramer's $V = 0.317$); more presented in males with autism, about sixth time that in females (male to female ratio was 6.5 : 1). Furthermore, comorbid OCD occurs more in cases from urban areas (sixth times those in rural areas). A significant association was found between presence comorbid

OCD in studied cases and the presence of gestational complications ($P = 0.041$, Cramer's $V = 0.323$). Of the seven cases associated with gestational complications, five were presented with OCD. In addition, there was a significant moderate association between comorbid OCD and delivery complications ($P = 0.014$, Cramer's $V = 0.387$). A significant high association was reported in the current study between comorbid OCD and consanguinity between parents ($P = 0.014$, Cramer's $V = 0.387$). Of the eight cases in which there was consanguinity between parents, six were presented with associated OCD. No other significant association was found between the occurrence of comorbid ODD with autistic cases in the study and SES or the presence of neonatal medical complications or presence of autistic child among relatives.

The most occurring coincidence of comorbidity was comorbid tics and OCD, which represented 25% of all cases (15% presented with only the two conditions, 5% with associated ODD, 2.5% with associated ADHD, and 2.5% with associated ODD and ADHD). This coincidence occurred in severe types, almost more in boys. The next occurring coincidence of comorbidity was comorbid ODD and OCD, which represented 15% of all cases (7.5% presented with only the two conditions, 5% with associated tics, and 2.5% with associated tics and ADHD). This coincidence occurred in severe types, almost more in boys.

Van Steensel *et al.* (2013) studied 40 cases of children with ASD and found that OCD occurs as comorbidity in only 7.5% of the cases compared with 37% in the current work. Van Steensel *et al.* (2011) in a previous study reported that 17% of children with ASD also meet the criteria of OCD. Lugnegård *et al.* (2011) stated that 7% of cases with autism in their study had comorbid OCD. The rate of OCD in individuals with autism reported by other investigators has varied from 1.5 to 81% (Rumsey *et al.*, 1985; Le Couteur *et al.*, 1989; Ghaziuddin *et al.*, 1992; Muris *et al.*, 1998).

The wide variation is likely due to the different assessment methods and criteria used, including criteria for impairment. Our findings about the association between autism and OCD are in agreement with the findings of an epidemiologic study of intellectually disabled children. Using the DISC-IV and lay interviewers, intellectually disabled children who had a positive screen for Pervasive Developmental disorders (PDD) were found to be 14 times more likely to meet Diagnostic Interview Schedule for Children Version IV (DISC-IV) criteria for OCD (Dekker and Koot, 2003).

A study by Leyfer *et al.* (2006) stated that 37% of the children with autism met DSM-IV criteria for OCD,

which is in agreement with the adjacent percentage of the current work. In their study, Leyfer *et al.* (2006) mentioned that the most common type of compulsion was a ritual involving other individuals. Nearly half of the children diagnosed with OCD had compulsions that involved others having to do things a certain way. Examples included the parents having to perform certain daily routines and greeting and separation rituals, or having to act or respond in a certain way. Another frequent compulsive behavior was the 'need to tell/ask', which mostly involved repeatedly having to ask the same question in extensive question-asking rituals or having to repeat the same statement over and over again. Interestingly, the diagnosis of autism involves deficits in social reciprocity and the two most frequent compulsions in the autism group involve dysfunctional interaction with other people in a compulsive manner.

A study by Mazzone *et al.* (2012) reported that indirect evidence for an association between ASDs and OCD comes from the studies of serotonin dysfunction in psychiatric disorders. Various studies have suggested that serotonergic abnormalities occur in both ASDs and OCD. In addition, medications that are effective in the treatment of OCD in the general population have been found to be useful in some patients with ASDs, especially in the control of ritualistic behaviors. The association between ASDs and OCD as well as other psychiatric symptoms including anxiety seems to be further supported by the observations that some brain regions such as the amygdala play a crucial role in ASDs, in relation to abnormal fears, compulsive behaviors, and increased anxiety.

Comorbid general anxiety disorders

In the current study, 5% of cases suffered from comorbid GAD, 1% in both mild and severe autism and no cases in moderate autism. The two cases with comorbid GAD were present in girls and not in boys. Furthermore, comorbid GAD occurs more in cases from urban areas (the two cases with comorbid GAD were from urban areas and no cases with comorbid GAD were from rural areas). There was no significant association between the occurrence of comorbid GAD with autistic cases in the study and SES, presence of either gestational, delivery, or neonatal medical complications, or with consanguinity between parents and presence of autistic child among relatives.

A study by Lugnegård *et al.* (2011) reported that 22% participants had generalized anxiety disorder compared with 5% in the current work. In their study, Van Steensel *et al.* (2011) reported that 15% of children with ASD also suffer from generalized anxiety disorders. Van Steensel *et al.* (2013) studied 40 cases of children with

ASD and found that GAD occurs as comorbidity in only 5% of the cases, which is in agreement with the results of the current study. Leyfer *et al.* (2006) stated that GAD represented comorbidity of autism in 2.4% of cases. White *et al.* (2009) have compared anxiety levels in different subtypes of ASD and they suggested that anxiety varies with ASD severity. Children with less severe ASD symptoms would endorse more anxiety. However, other studies reported that no differences are present in anxiety levels between ASD subtypes studies (Gadow *et al.*, 2004; Pearson *et al.*, 2006; Sukhodolsky *et al.*, 2008).

Leyfer *et al.* (2006) found that DSM-IV criteria for generalized anxiety disorder (GAD) usually did not capture the essential aspects of anxiety found in children with autism.

Aspects not captured included the manifestations of anxiety, the contexts in which anxiety occurred, and the environmental precipitants of anxiety. They mentioned that their observations must be considered tentative because the GAD section of the interview was completed on only 41 of the 109 children. One of the 41 (2%) children with autism, whose parents completed the GAD section, met DSM-IV criteria for GAD. While some of the children with autism were anxious about many things, the anxiety did not usually vary over time – that is, it appeared more trait-related rather than state-related. Anxiety in the children with autism, over and above this chronic anxiety trait, was usually focused on one rather than multiple things or it was related to transitions or changes in the environment. Their findings do not support the DSM-IV exclusion of a diagnosis of generalized anxiety disorder in individuals with autism.

In their study, Leyfer *et al.* (2006) found out that anxiety trait is common in autism. The findings also suggest that impairing anxiety syndromes, other than GAD, may occur alone or be superimposed on anxiety trait in patients with autism.

Conclusion

From the current study it was concluded that boys, high and moderate socioeconomic states, and positive family history represented conditions associated with an increased risk for autism and ASDs in Egyptian population. Comorbid tics, ADHD, ODD, and OCD are most presented among male sex, whereas comorbid GAD is more presented in females with autism. The most occurring coincidence of comorbidity is comorbid tics and OCD, followed by comorbid OCD and ODD. Those coincidences could be associated

with severe autism and male sex. Future studies are suggested using large samples to confirm the finding of the present work.

Recommendations

From the current study it is recommended to increase public awareness about risk factors and symptoms of ASD and about the hazards of marriage between the members from the same family and its proved risk in increasing the incidence of ASD. In addition, establishing specialized units in hospitals concerned with early detection of ASD children is suggested to be a priority in the field of national health programs.

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Conflicts of interest

There are no conflicts of interest.

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