ASPERGER'S SYNDROME AND BIPOLAR DISORDER, COMORBID DISORDERS OR SEPARATE ENTITIES?

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ABSTRACT
Asperger's syndrome (AS) is a pervasive neurodevelopmental disorder, included in Autism Spectrum Disorder (ASD). Sometimes AS is difficult to diagnose because the symptomatology can be overlooked and, in such manner, AS can be misdiagnosed or even undiagnosed. It may be linked with other psychiatric diseases, especially Bipolar Disorder (BD) and this can be proven by the common genes between them. BD exacerbates AS symptomatology and is an important risk factor, thus, early diagnosis and prompt treatment are the key steps in proper management of these pacients. Treating BD in patinets with Asperger's Syndrome is also difficult because sometimes people with ASD may not respond to classic medication.

Keywords: Asperger Syndrome, Bipolar Disorder, comorbidities.

INTRODUCTION

Asperger's syndrome (AS) represents a behavioral and neurodevelopmental disorder that is integrated in Autism Spectrum Disorder (ASD). This is characterized by social dysfunction and repetitive behaviors, but the patients with Asperger's syndrome do not suffer from a linguistic or a cognitive dysfunctionality, as other subgroups of ASD [1]. It is difficult to diagnose Asperger's Syndrome in children and sometimes they are late diagnosed with a personality disorder, as Schizoid Personality Disorder, being unrecognized sometimes in the adult psychiatry.

Bipolar disorder represents a mood disorder, defined by episodes of depression and episodes of mania or hypomania (milder form of mania) that alternate, and between them there are periods of euthymia (normal mood) [2]. In some cases it is hard to diagnose bipolar disorder in children, because the symptomatology can be different than in adults.

Studies suggest that bipolar disorder is one of the major comorbidities that can occur in adolescents or young adults that suffer from Asperger's syndrome or high functioning ASD. The association between AS and BD can be explained by two possible models: a former model, when one disorder causes the other, which is unlikely in this case, or the latter model that presents how these two disorders share the same etiological factors, both being highly inherited [3].

DIAGNOSIS

In 1976 a study made by Herzberg showed that in families with autistic subjects it is more likely to find other psychiatric disorders as schizophrenia, bipolar disorder and many attempted suicides than other families.

In 1984, three scientists, Komoto, Hiratu and Usui presented three different case studies of children with autism that also have mood or affective disorders and they suspected history of depression or bipolar

disorder in their families. A case of Asperger's syndrome with cyclothymic disorder, presented by Gillberd in 1985, underlines that subjects with autistic disorder, in particular Asperger's syndrome, have a higher risk to develop mood or affective disorders, as bipolar disorder or depression [4].

Due to the fact that ASD is characterized by emotional and behavioral particularities that vary with age, it is difficult to accurately identify comorbid disorders in ASD population, although comorbidities are frequent.

Children with PDD have a two-to-six-times greater risk of experiencing comorbid psychiatric conditions than their normal peers [5]. The most often diagnosed comorbidities in/with ASD are: Oppositional defiant disorder, Depressive disorders, Attention deficit hyperactivity disorder (ADHD) and Bipolar disorder [6]. The data regarding the prevalence of BD in ASD population is scarce and varies broadly.

Rosenberg R.E. [7] notes a diagnosis of BD in 5.2% of over 4000 youth with ASD attending community mental health centers. In a small study of 44 outpatients, T Munesue [3] found out that the prevalence of BD in ASD is 27.3%, although the study had some limitations regarding the small sample size and sample bias. Recently, studies showed a link between these two illnesses and this idea can be sustained by the fact that bipolar disorder's (BD) prevalence in adults with Asperger's syndrome (AS) is up to 21.4% and the families of those who are diagnosed with both of these disorders have a double risk in developing BD, with a prevalence near 10%.

In some cases, when comorbid with Asperger's syndrome, bipolar disorder can manifest abnormal symptomatology that can lead to misdiagnosis, especially when the patients present psychotic symptoms [8]. The criteria that are needed to diagnose bipolar disorder is outlined in Table 1. [2].

BP is a disorder that can be frequently misdiagnosed due to its wide time span. Early onset BP can appear with the clinical features of unipolar depression, acute psychosis or comorbid disorders such as ADHD, OCD, or eating disorders. The manic symptoms can appear later [9]. Clinicians must also consider that BD symptomatology in children may be different than the clinical features observed in adults.

Long sustained impulse control, conduct problems, rapid cycling and mixed mania are some of the main characteristics in children or adolescents diagnosed with BD [10,11]. If the clinical features of BD, regarding the elation stage, are irritability, increased energy, psychomotor activation, excessive mood reactivity or diminished need for sleep, the process of accurate identification is far more difficult [8]. The overall intensity of the symptoms can vary and be evaluated in a subjective manner, and also the behavioral changes must be noticeable enough for the patient to be hospitalized or evaluated by a specialist.

Table 1. Bipolar disorder diagnostic symptoms

Depression symptoms (at least two weeks)	Mania symptoms (at least one week)
Decreased pleasure or interest in any area	Elevated mood (euphoria) or irritable mood
Tiredness or low energy	Grandiosity or increased self-esteem
Decreased self-esteem	Sleep deprivation, because there is no need for sleep or rest
Guilt	Talkativeness
Thoughts of death and/or suicide	Spontaneous hyperprosexia
Hypoprosexia	Flight of ideas
Insomnia/hypersomnia	Psychomotor agitation
Decreased/Increased appetite	Risk-taking behaviors (drug abuse or inappropriate sexual behavior)

Bipolar disorder can co-occur in subjects with ASDs, along with anxiety and depression and it is probably the most common and also the most severe disease. Both BD and AS may present symptoms of irritability or aggression, but these are not the most important symptoms. There are some common genes that had been identified in genetic studies, for ASD, bipolar disorder, schizophrenia and others [12].

Individuals with ASD, especially those with low intellectual abilities (IQ <70), have limited verbal communication skills and inadequate facial expressions, so it remains uncertain whether they verbalize inner experiences, such as sadness or self-esteem.

In the context in which researchers consider a sad face, loss of interest in activities, frequent crying crises, insomnia and loss of appetite as depressive symptoms, and a happy face, hyperactivity, accelerated speech rhythm and increased appetite as (hypo)maniacal symptoms, establishing a diagnosis of bipolar disorder in patients with ASD and low intellectual level may be difficult for clinicians who can support such a diagnosis based on observation of facial expressions and behaviors. Thus, it would be more appropriate to study individuals with ASD who have an IQ within normal limits (IQ≥70). Such subjects might verbalize inner experiences more appropriately than individuals with reduced functioning [3].

COMPLICATIONS

There are some complications that can occur in those with Asperger's syndrome comorbid with bipolar disorder. Having both AS and BD increases morbidity and the suicide risk. The suicidal risk is increased in the depression phase of the bipolar disorder and in this case is combined with the self-injurious behaviors and suicidal ideation in adolescents or young adults with ASD. Psychosis or Catatonia may occur sometimes as complications of this association. Symptoms of psychosis (when the perception and the thought of the subject can be abnormal) may appear in the classic form of BD (in both phases of this illness) and they may be pronounced in patients with Asperger's syndrome. Some autistic patients that are diagnosed with bipolar disorder slowly develop symptoms of catatonia, a severe condition that sometimes is life-threatening [12].

MORBIDITY

In some cases, ASD patients can develop high adaptability and high functionality, and in other cases the symptomatology is more severe affecting the functionality to certain degrees. The association of BD further increases this impairment, affecting cognition and global psychological functionality, thus aggravating externalizing problems such as aggression, oppositional defiant disorder and internalizing problems, such as depression and anxiety.

The executive functions are most affected in the area of selective attention and inhibitory control [13]. Frazier suggests that BP enhances the typical ASD symptoms such as motor clumsiness, repetitive, circumscribed behaviors, and may also diminish the psycho-social functionality. In a longitudinal study that followed 368 youth, over a period of 9 years, Borue X analyzed the evolution of BD patients versus BD + ASD patients. The study shows a higher prevalence in BP + ASD individuals of depressed mood, social dysfunction and poor mood reactivity [14].

SUICIDAL BEHAVIOR

When referring to suicidal behavior we have in mind suicidal attempts and suicidal ideation. The evolution from suicidal ideation to suicidal attempts can be exacerbated by a number of psychological factors that can be individual or attributed to different psychiatric conditions. The most severe

consequence of suicidal behavior is suicidal completion, which of course is the loss of life itself. Because depression is the main psychiatric comorbidity reported in ASD population [15], suicidal ideation or even suicide attempts are not uncommon. It is most common in adolescent or young adult population [16]. There are not enough studies regarding this topic, so the data is not sufficient to establish a certain an approximate incidence of suicide or suicidal ideation in ASD population. Cassidy [17], in a clinical cohort study on adults diagnosed with ASD found out that 66% reported suicidal ideation and 35% reported suicidal attempts.

According to prior data, the early onset of BD is a risk factor for suicidal behavior [18]. Different studies have reached different results regarding the prevalence of suicidal ideation in pediatric population diagnosed with BD. Goldstein T.R. noted that one-third of the BP patients included in the study, exhibited suicidal behavior, and that the most relevant risk factors regarding suicide attempts were: substance abuse, psychosis, self-injurious behavior, and panic disorder [19]. Bhangoo, in a clinical sample of 87 bipolar patients, reported a 27.6% rate of suicide attempts [20]. Strober, in a study of 54 adolescents diagnosed with BP, reported a 20% rate of suicide attempts [21]. Rucklidge, noted that BP patients displayed impaired coping skills in problem solving and maintaining a positive attitude, anger management issues, low self-esteem and external locus of control. These factors further increase the risk of suicidal behavior [22].

In a comparative study, Lewinsohn, reported a 44% rate of suicide attempts in adolescents diagnosed with spectrum disorder and BP, compared to 22% rate of unipolar depressed teens [23]. There were no studies found regarding suicidal behavior in ASD and BD patients, but we can assume based on the aforementioned studies that the rates of suicidal attempts are notable, especially considering the fact the clinical features of BD and ASD can overlap or enhance each other.

TREATMENT

An important issue that still needs to be addressed is whether specific treatments for psychiatric disorders that have been shown to be effective in children without ASD could eventually have the same efficacy when the same disorders are present in comorbidity with ASD.

The implications of treatment are also complicated by the fact that patients with ASD are systematically excluded from clinical trials of drugs used to treat mania, depression, anxiety and ADHD, which limits the scientific evidence needed to establish treatment. When drug studies focused specifically on children with ASD, the response to treatment appeared to be less robust, with higher rates of side effects than in children without ASD [24].

Lainhart [25] found that classic antipsychotics such as haloperidol, chlorpromazine, thioridazine, and mood stabilizers, such as lithium and carbamazepine are less effective in treating mania in children with autism. In other more recent studies [26, 27], risperidone has been shown to be well tolerated and effective in managing irritability, destructive, self and heteroaggressive behavior in young people with autism.

Studies in adult patients with bipolar disorder and other pervasive comorbid developmental disorders (PDD) have shown that valproate administration has had good results, with positive effects on the symptoms corresponding to comorbid disorders [28]. A positive response to the administration of mood stabilizers in combination with second-generation antipsychotics has also been reported by Raja and Azzoni [9] in the case of two adult patients diagnosed with bipolar disorder and Asperger's syndrome.

Irritability and mood disorders, although not a basic feature of ASD, are common and have been the subject of research that has attempted to control these problematic behaviors with risperidone. Pharmacological treatments with lithium carbonate or lithium and combined neuroleptics have been reported to be helpful in treating selected patients diagnosed with childhood autism and bipolar symptoms, as shown by studies published by Kerbeshian [29] or Steingard and Biederman [30].

In a study published by Frazier [31], is reported the case of a patient who had received numerous diagnoses over time and had followed several treatment regimens without any improvement. He is eventually diagnosed with bipolar disorder and Asperger's syndrome and begins treatment with lithium in combination with risperidone and clonazepam, with a significant improvement in behavior.

The combination of lithium and risperidone was also effective in another adolescent patient whose psychiatric history is described in the paper published by Zinoviy [32]. In this case, the risk-benefit balance tilted in favor of treatment, considering that side effects, such as significant weight gain and changes in glucose metabolism, can be controlled with diet, exercise and Metformin. Although pediatric patients are more vulnerable to the side effects of treatment with atypical antipsychotics, they appear to respond better than adults to Metformin administration [33].

The case study presented by Nermin Gündüz [34], shows that specific treatment may be possible when problematic behaviors in a patient with ASD are seen as a manifestation of a comorbid psychiatric pathology. In this case, a combination of valproate and risperidone was chosen to treat the manic episode with psychotic elements in a patient diagnosed with high functioning autism.

In patients with Asperger's syndrome and comorbid bipolar disorder, other difficulties in establishing treatment may occur when obsessive-compulsive symptoms are present. Selective serotonin reuptake inhibitors (SSRIs) are frequently used in the treatment of obsessive-compulsive disorder, but in their administration to people with Asperger's syndrome, increases in aggressive behaviors have been reported, as well as manic states [35]. SSRI administration in those with bipolar disorder also showed an increase in symptoms severity.

At the same time, other published studies [36, 37] have shown the efficacy of paroxetine in the treatment of obsessive-compulsive symptoms in patients with Asperger's syndrome. Therefore, choosing an optimal treatment is not an easy decision, and so far, the first treatment options remain mood stabilizers or second-generation antipsychotics [38].

There is very little information on pharmacological treatments in ASD associated with bipolar disorder, found mainly in observational studies and case studies. However, most published papers show that mood stabilizers should be considered the first line of treatment. Antipsychotics with 5-HT2a antagonism have proven useful in controlling psychotic and behavioral symptoms, and SSRIs are effective in treating anxiety, depression, and obsessive-compulsive symptoms, provided that close monitoring of the latter is necessary as hypomanic or manic changes have been reported in nearly a half of treated subjects [39].

DISCUSSION

In conclusion to diagnose a patient with Asperger's syndrome it may be difficult in children and can be misdiagnosed in adults, also it is a higher risk for patients with autistic disorder, especially those with AS, to develop other psychiatric diseases as Bipolar Disorder. When comorbid with Asperger's syndrome, bipolar disorder may lead to some

serious complications like higher risk of suicide, psychosis and others. There is a genetic link between these two illnesses explained by the genes that are common in AS and BD and the fact that in families with autistic subjects the prevalence of bipolar disorder is higher.

Early assessment of risk factors and prompt management through therapy and suitable medication could successfully decrease and prevent suicidal attempts. Managing the BD symptomatology is a key factor to alleviate the ASD functional impairment. Clinicians must have in mind the complex presentation of BD in pediatric population, especially when ASD is also diagnosed. The overlapping symptoms might cause a misdiagnose and the outcome could be inadequate.

The treatment used in children with bipolar disorder does not have the same results when administered to patients with autism spectrum disorder and comorbid bipolar disorder. Studies investigating different treatment options for mood disorders do not usually include people with ASD, which limits access to information needed to determine a specific treatment. In order to establish an effective treatment, a good differentiation is necessary between the symptoms of autism spectrum disorder and those corresponding to the associated psychiatric pathology. The first line of treatment for ASD associated with bipolar disorder remains mood stabilizers along with second generation antipsychotics. SSRIs administration, when necessary, should be closely monitored to prevent hypomanic or manic symptoms.

REFERENCES

1. Tarazi F., Sahli Z., Pleskow J. and Mousa S. Asperger's syndrome: diagnosis, comorbidity and therapy. Expert review of Neurotherapeutics, 2015, 15(3), 281-293.
2. Smith D., Whitham E.A. and Ghaemi S.N. Bipolar disorder. Handbook of Clinical Neurology, 2012, 251-263.
3. Munesue T., Ono Y., Mutoh K., Shimoda K., Nakatani H. and Kikuchi M. (High prevalence of bipolar disorder comorbidity in adolescents and young adults with high-functioning autism spectrum disorder: A preliminary study of 44 outpatients. Journal of Affective Disorders, 2008, 111(2-3), 170-175.
4. Robert DeLong G. and Dwyer J.T. Correlation of family history with specific autistic subgroups: Asperger's syndrome and bipolar affective disease. Journal of Autism and Developmental Disorders, 1998, 18(4), 593-600.
5. Frazier J.A., Biederman J., Bellordre C.A., Garfield S.B., Geller D.A., Coffey B.J., Faraone S.V. Should the diagnosis of attention deficit hyper-activity disorder be considered in children with pervasive developmental disorder. J Attention Disord, 2001, 4:203-211.
6. Bryson S.A., Corrigan S.K., McDonald T.P., Holmes C. Characteristicsof children with autism spectrum disorders who receivedservices through community mental health centers. Autism, 2008, 12:65-82.
7. Rosenberg R.E., Kaufmann W.E., Law J.K., Law P.A. Parent Report of Community Psychiatric Comorbid Diagnoses in Autism Spectrum Disorders. Autism Res Treat, 2011, 1-10.
8. Vannucchi G., Masi G., Toni C., Dell'Osso L., Erfurth A., Perugi G. Bipolar disorder in adults with Asperger's Syndrome: A systematic review. Journal of Affective Disorders 2014, 168, 151–160.
9. Raja M., Azzoni A. Comorbidity of Asperger's syndrome and Bipolar disorder. Clin Pract Epidemiol Ment Health 2008, 4, 26.
10. Geller B., Zimerman B., Williams M., Bolhofner K., Craney J., DelBello M., et al.Diagnostic characteristics of 93 cases of a prepubertal and early adolescent bipolar disorder phenotype by gender, puberty, and comorbid attention deficit hyperactivity disorder. Journal of Child and Adolescent Psychopharmacology 2000, 10(3), 157–164.
11. Wozniak J., Biederman S., Faraone S., Frazier J., Kim J., Millstein R., et al. Mania in children with pervasive developmental disorder. Journal of American Academy of Child and

Adolescent Psychiatry, 1997, 36(11), 1552–1559.
12. Ghaziuddin M. and Ghaziuddin N. Bipolard Disorder and Psychosis in Autism. Child and Adolescent Psychiatric Clinics in North America. 2020.
13. Adam S. Weissman, Marsha E. Bates. Increased clinical and neurocognitive impairment in children with autism spectrum disorders and comorbid bipolar disorder. Research in Autism Spectrum Disorders, 2010, Volume 4, Issue 4.
14. Borue X., Mazefsky C., Rooks B.T., Strober M., Keller M.B., Hower H., Yen S., Gill M.K., Diler R.S., Axelson D.A., Goldstein B.I., Goldstein T.R., Ryan N., Liao F., Hunt J.I., Dickstein D.P., Birmaher B. Longitudinal Course of Bipolar Disorder in Youth with High-Functioning Autism SpectrumDisorder, Journal of the American Academy of Child & Adolescent Psychiatry. 2016.
15. Ghaziuddin M., Widmer-Mikhail E., Ghaziuddin N. Comorbidity of Asperger syndrome: a preliminary report. J Intellect Disabil Res. 1998, 42: 279-283.
16. Gillberg C. A guide to Asperger's syndrome. Cambridge: Cambridge University Press. 2002.
17. Cassidy S., Bradley P., Robinson J., Allison C., McHugh M., Baron-Cohen S. Suicidal ideation and suicide plans or attempts in adults with Asperger's syndrome attending a specialist diagnostic clinic: a clinical cohort study. The Lancet Psychiatry 2014, 1(2), 142–147.
18. Jolin E.M., Weller E.B., Weller R.A. Suicide risk factors in children and adolescents with bipolar disorder. Current Psychiatry Reports 2007, 9(2), 122–128.
19. Goldstein T.R., Birmaher B., Axelson D., Ryan N.D., Strober M.A., Gill M.K., Keller M. (2005) - History of suicide attempts in pediatric bipolar disorder: factors associated with increased risk. Bipolar Disorders, 2005, 7(6), 525–535.
20. Bhangoo R.K., Dell M.L., Towbin K., et al. Clinical correlates of episodicity in juvenile mania. J Child Adolesc Psychopharmacol 2003, 13: 507– 514.
21. Strober M., Schmidt-Lackner S., Freeman R., et al. Recovery and relapse in adolescents with bipolar affective illness: a five-year naturalistic, prospective follow-up. J Am Acad Child Adolesc Psychiatry 1995, 34: 724– 731.
22. Rucklidge J.J. Psychosocial functioning of adolescents with and without paediatric bipolar disorder. J Affect Disord 2006, 91: 181– 188.
23. Lewinsohn P.M., Klein D.N., Seeley J.R. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity and course. J Am Acad Child Adolesc Psychiatry 1995, 34: 454– 463.
24. Posey D.J., Erickson C.A., Stigler K.A., McDougle C.J. The use of selective serotonin reuptake inhibitors in autism and related disorders. J Child Adolesc Psychopharmacol 2006, 16:181–186.
25. Lainhart J.E., Folstein S.E.M. Affective disorders in people with autism: a review of published cases. J. Autism Dev Disord 1994, 24:587-601.
26. Nagaraj R., Singhi P., Malhi P. Risperidone in children with autism: Randomized, placebo-controlled, double-blind study. J Child Neurol 2006, 21:450-455.
27. Shea S., Turgay A., Carroll A., Schulz M., Orlik H., Smith L., Dunbar F. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. Pediatrics 2004, 114:634-641.
28. Sovner R. The use of valproate in the treatment of mentally retarded persons with typical and atypical bipolar disorders. J Clin Psychiatry 1989, 50: 40-43.
29. Kerbeshian J., Burd L., Fisher W. Lithium carbonate in the treatment of two patients with infantile autism and atypical bipolar symptomatology. J Clin Psychopharmacol 1987, 7:401–405.
30. Steingard R., Biederman J. Lithium responsive manic-like symptoms in two individuals with autism and mental retardation. J Am Acad Child Adolesc Psychiatry 1987, 26:932–935.
31. Frazier J.A., Doyle R., Chiu S., Coyle J.T. Treating a child with Asperger's disorder and

comorbid bipolar disorder. Am. J. Psychiatry 2002, 159, 13–21.
32. Zinoviy A. Gutkovich, Gabrielle A. Carlson, Harold E. Carlson, Barbara Coffey B., Wieland N. Asperger's Disorder and Co-Morbid Bipolar Disorder: Diagnostic and Treatment Challenges. Journal of Child and Adolescent Psychopharmacology 2012, 247-256.
33. Klein D.J., Cottingham E.M., Sorter M., Barton B.A., Morrison J.A. A randomized, double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of atypical antipsychotic therapy in children and adolescents. Am J Psychiatry 2006, 163:2072–2079.
34. Gündüz N., Karakaya I., Turan H., Çelik F. Diagnosis and treatment process of comorbid bipolar disorder in a patient diagnosed with autism. Case report. Turkish J Clinical Psychiatry 2019, 22:243-247.
35. Damore J., Stine J., Brody L. Medication-induced hypomania in Asperger's disorder (letter). J Am Acad Child Adolesc Psychiatry 1998, 37: 248-249.
36. Sasayama D., Sugiyama N., Imai J., Hayashida A., Harada Y., Amano N. High-dose paroxetine treatment for an adolescent with obsessive-compulsive disorder comorbid with Asperger's disorder. Psychiatry Clin Neurosci 2009, 63 (2): 251.
37. Williams K., Wheeler D.M., Silove N., Hazell P. Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). Cochrane Database Syst Rev. 2010, 4 (8): CD004677.
38. Sasson Y., Chopra N., Harrari E., Amitai K., Zohar J. Bipolar comorbidity: from diagnostic dilemmas to therapeutic challenge. Int J Neuropsychopharmacol 2003, 6: 139-144.
39. Vannucchi G., Perugi G., Masi G. Bipolar Disorder and ASD. In: Keller R. (eds) Psychopathology in Adolescents and Adults with Autism Spectrum Disorders. Springer, Cham. 2019.