

Aripiprazole treatment of Asperger's syndrome in the acute psychiatric setting: case report

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Abstract: Asperger's syndrome (AS) is under-recognized and may be misdiagnosed as schizophrenia in adults because of symptom overlap. Pharmacological treatment usually targets associated behavioral and mental symptoms rather than the actual core features of AS. We report a middle-aged male patient who, after many years of previous contact with mental health services, and on account of his psychotic symptoms and diagnosis of schizophrenia, was admitted to an inner-city acute psychiatric unit, where a primary diagnosis of AS was established for the first time in his life. His impairing clinical features of AS improved markedly following treatment using aripiprazole, a novel atypical antipsychotic that acts as a partial agonist at dopamine D₂ receptors. As well as sharing clinical features, there is an overlap in underlying neurobiology of AS and schizophrenia, including dopamine dysfunction, that provides a rationale for using antipsychotics of this class in the clinical management not only of associated psychotic symptoms but also of the core features of AS itself.

Keywords: Asperger's syndrome, autism spectrum disorders, schizophrenia, dopamine, aripiprazole, atypical antipsychotics

Introduction

Asperger's syndrome (AS), a pervasive neurodevelopmental disorder falling into the autism spectrum disorders, is relatively rare, but many sufferers may not receive appropriate care because AS core features could pass undetected or be misdiagnosed. The core features of AS are impaired non-verbal communication, restricted interests, and repetitive behavior (APA 2000). In contrast with autism, there is no clinically significant delay in language acquisition. Intelligence is in the normal or superior range. Under-recognition, psychiatric co-morbidity, lack of treatment, and complicating social and behavioral factors can all contribute to critical clinical events requiring acute psychiatric admissions.

We report a middle-aged male patient admitted to our acute psychiatric unit on account of his psychotic symptoms and impulsive behavior, whose original diagnosis of schizophrenia was reviewed and changed for a diagnosis of AS. His behavioral and mental symptoms, including impairing features of AS, responded to treatment using aripiprazole, a novel atypical antipsychotic that acts as a partial agonist at the dopamine D₂ and serotonin 5HT_{1A} receptors and as an antagonist at the serotonin 5HT_{2A} receptors (Bowels et al 2003).

Case description

The patient, a 41-year-old male, was compulsorily admitted to our unit after having major anger outbursts at his hostel and threatening staff with a knife. He had previously received a diagnosis of schizophrenia on the basis of his history of unusual behaviors and symptoms such as social withdrawal, concrete thinking and paranoid

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ideation. More recently he had been accusing the staff of “talking about him and calling him a paedophile”, probably an indication of auditory hallucinations, and been reported to repeatedly misinterpret routine conversations as abusive, triggering aggressive responses. He also had been using cannabis daily for many years.

His developmental history revealed no delayed milestones. His parents divorced when he was 3 years old and his mother cared for him. At school he had excelled academically in languages but was clumsy at sport and formed no peer relationships, spending most of his time in the library reading about esoteric subjects. He felt marginalized, said to have been bullied, and was expelled from school at the age of 18 after assaulting a pupil. There was no formal family history of mental illness but his father, a high achieving professional, was described as having a bad temper and being emotionally cold. Throughout his adult life he had tended to mistrust people. He had always found it difficult to establish relationships and sustain employment. In recent years he had developed an intense interest in computer hardware and adopted a repetitive daily routine around this, reacting angrily if this was disrupted.

He was referred to mental health services for the first time aged 28 after he was dismissed from his job because of aggressive behavior. He was thought to be depressed and initially received psychotherapy, followed by a trial of fluoxetine, which was discontinued due to side-effects. He was then referred to community mental health services and had been under their care ever since, refusing psychotropic medication whenever this was offered.

On admission he presented as a disheveled man who showed high levels of arousal and irritability and who was unwilling to co-operate with the interview, in the course of which he paced around the clinical room. He encroached on the interviewer’s personal space appearing intimidating. His speech was loud, sarcastic, and at times somewhat incoherent. He described his mood as angry but denied any sleep disturbance or changes in his energy levels. He was suspicious about the hospital staff and the motives behind his admission. He claimed that residents and staff at this hostel had been calling him a “paedophile” and making comments on child abuse with the specific aim of offending him. He spontaneously described being abused at school by a schoolteacher, but this had never been substantiated.

On the ward he was noted to be socially withdrawn but his sleep and appetite were normal. His irritability abated after a few days, during which he received no medication but

discontinued his cannabis smoking and responded to nursing care. Although no further incidents or aggressive outbursts were reported, he remained socially isolated, displaying flat affect yet often evincing irritability and suspiciousness. He was subsequently observed to have awkward, fleeting eye contact, a pedantic and almost theatrical use of language, and a remarkably unchanging facial mimicry.

In the absence of any obvious continuing psychotic symptoms, and in view of both his encouraging response to the ward environment and clinical features that seemed to be traits rather than symptoms, we decided to review his diagnosis in the light of DSM-IV criteria for AS (APA 2000), all of which he seemed to meet. We further corroborated the diagnosis of AS by applying the Autism-Spectrum Quotient (AQ) (Baron-Cohen et al 2001), a self-rating scale, in which he scored 32, well above the suggested screening threshold of 26 for an autism-spectrum disorder.

We then offered him psycho-education sessions where the diagnosis of AS was discussed, as well as reading material on this topic. He read the literature with interest and stated that the diagnosis was a useful way to understand his life-long social and behavioral difficulties. We also suggested that he could benefit from drug treatment using an antipsychotic, as this could reduce his suspiciousness and persistently heightened levels of anxiety, in addition to enhancing his motivation, whereby he could acquire more control over his temper and social interactions.

With his consent, he was prescribed aripiprazole orally at an initial dose of 10 mg daily, which he tolerated well and was increased to 15 mg daily after 3 weeks. Two weeks after his initial dose the clinical team noted a favorable change in his overall behavior and psychological state as he began to interact with the other patients and actively engage in social activities, such as playing pool and chess and joining occupational therapy groups. The patient himself reported that he felt less anxious and less suspicious and more able to control his temper, enabling him to have more social confidence and interact more with the clinical team. No adverse effects were observed. After 4 weeks a meeting was scheduled with his community mental health team and hostel staff to discuss his diagnosis and its implications, and to establish an aftercare plan that took these into account. His participation was remarkably insightful, particularly as he was able to accept that he had been misinterpreting other people’s behaviors and responding inappropriately to these. He was willing to return to the hostel and was discharged back to the care of his community team on aripiprazole

15 mg daily. Several months later he has remained well and adhering to his treatment, with no adverse effects or further incidents reported.

Discussion

The estimated 4.7/10,000 prevalence of AS in the general population probably underestimates the true rate (Lauritsen et al 2004). AS may present with symptoms similar to those seen in schizophrenia, depressive disorders and some personality disorders. It may also co-exist with Tourette's syndrome and many other clinical conditions (Gillberg and Billstadt 2000). This may partly explain why many sufferers receive a diagnosis of AS for the first time only after reaching adulthood. AS may be associated with psychotic episodes (WHO 1992) and its clinical features may overlap with symptoms of schizophrenia, especially negative symptoms (Rausch et al 2005). This, and the fact that the former is more rare than the latter, may account for many sufferers who are misdiagnosed as having schizophrenia. Among 2500 adults admitted to a psychiatric intensive care unit, 5 (0.2%) received a diagnosis of AS for the first time in their lives, which is 4 times the rate in the general population (Raja and Azzoni 2001). For this reason, Raja and Azzoni (2001) warn against overvaluing psychotic symptoms when specific features of AS are present. Additional features to substantiate a diagnosis of AS may include male gender, clumsiness, and obsessive-compulsive symptoms, as well as violent behavior and unusual restricted interests

The patient we described—an adult male of normal intelligence with a history of repetitive behavior, clumsiness, impaired social functioning, aggressive outbursts, and restricted interests in a technically demanding pursuit—met virtually all DSM IV criteria for AS (APA 2000). The ideas of reference and auditory hallucinations he had experienced before admission probably obfuscated his AS features, thus culminating in his previous diagnosis of schizophrenia. However, cannabis abuse was probably a major contributing factor to his positive psychotic symptoms, which abated after he discontinued his cannabis consumption. Moreover, his features of AS, some of which could have been misconstrued as negative symptoms, had only become evident after his cannabis-induced psychotic symptoms had ameliorated.

Pharmacotherapy is not seen as the ultimate treatment of the core features of AS itself but has a definite place in the management of specific troubling symptoms (Bostic and King 2005). Treatment approaches may include antidepressants, mood stabilisers and antipsychotics. Yet, in

addition to clinical similarities, the neurobiological overlap between AS and schizophrenia may provide a tentative rationale for the therapeutic use of antipsychotics in AS. Like schizophrenia, AS has been associated with soft neurological signs (Tani et al 2006), brain maturation abnormalities (Brambilla et al 2004) and abnormal central connectivity (Welchew et al 2005). Frith (2004) claimed that core features of AS are related to reduced activation and poor connectivity of the medial prefrontal and temporal cortex network, which is the neural substrate of intuitive mentalizing. Abnormal fronto-striatal pathways, resulting in defective sensorimotor gating, may lead to difficulties inhibiting repetitive thoughts, speech and actions (McAlonan et al 2002). Also like in schizophrenia, AS has been associated with dopamine dysfunction. Compared with normal subjects, AS patients were found to have increased presynaptic dopamine function in the striatum (Nieminen-von Wendt et al 2004).

Accordingly, dopamine-antagonist antipsychotics such as haloperidol and risperidone have been shown to significantly improve repetitive behavior, aggression, and mood symptoms associated with pervasive developmental disorders (McDougle et al 1998). Risperidone has been shown to also ameliorate the negative symptoms spectrum associated with AS (Rausch et al 2005). However, the use of haloperidol is constrained by the risk of tardive dyskinesia, particularly in the long term, and the use of risperidone by the risk of weight gain and hyperprolactinaemia (British National Formulary 2005).

Some clinical features of our patient, such as his vulnerability to psychotic symptoms and lifelong suspiciousness, suggested that he could benefit from antipsychotic treatment. Aripiprazole is an atypical antipsychotic that has a low potential for inducing extrapyramidal side-effects, hyperprolactinaemia and weight gain (Bowles 2003) but, to our knowledge, no systematic study of using aripiprazole to treat AS has ever been conducted. Yet two findings of a previous study in our unit, which had shown that aripiprazole can be effectively used to treat actively psychotic patients with schizophrenia, indicated that it could also be useful in AS. First, therapeutic responses to aripiprazole included the amelioration of negative symptoms (Dratcu et al 2006). Second, we found that aripiprazole could prove helpful in the treatment of disorders other than schizophrenia alone where dopamine dysfunction is also thought to play a role, like tardive dyskinesia.

After receiving therapeutic doses of aripiprazole for two weeks, the patient experienced a range of positive clinical

changes, such as reduced levels of anxiety, arousal and suspiciousness, coupled with improved social interaction and self-control and better insight into his social and psychological difficulties. These were all recognized by the patient himself and sustained as he continued to comply with treatment, in the course of which no adverse reactions were noted. Similar findings have been previously reported in a case involving an adult male with a history of intractable AS, who responded to aripiprazole after failing to respond to multiple psychological and pharmacological interventions (Staller 2003). Like in our patient, responses to aripiprazole included improved sociability and self-awareness, reduced rigidity/anxiety/irritability, and reduced preoccupation with esoteric interests.

Thus, our findings seem to add to the clinical evidence that, as well as treating psychotic symptoms co-existing with AS, some antipsychotics like aripiprazole may potentially ameliorate core features of AS itself, a prospect that finds support in the neurobiological overlap of AS with schizophrenia. Unlike dopamine antagonists, aripiprazole may restore more functional levels of dopaminergic activity because its antagonistic action is dependent on the availability of dopamine itself. If this could explain the therapeutic effects of aripiprazole on the positive and negative symptoms of schizophrenia and in other dopamine-related syndromes, perhaps it may also explain the therapeutic effects of aripiprazole in AS, where dopamine dysfunction may likewise be implicated.

Increasing awareness among clinicians about the diagnosis of AS, so that sufferers can be offered appropriate help at earlier stages, is by far the best option to prevent that they are further impaired by the psychiatric and other complications that may ensue. Psycho-education can prove invaluable to sufferers, but there are probably many who are likely to also benefit from pharmacological approaches that can attenuate the pervasive and impairing features that they endure. In view of its mode of action and safety profile, and also of the paucity of evidence on alternatives that can be effectively and safely used for this purpose, particularly in the long term, the use of aripiprazole in the treatment of AS warrants further scrutiny. Such studies are also likely to provide further insights into the pathogenesis and clinical management of AS.

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