

EFFECTIVENESS OF SWITCHING FROM ORAL ZIPRASIDONE TO RISPERIDONE IN A PATIENT WITH COMORBID AUTISTIC DISORDER, PROFOUND INTELLECTUAL DISABILITY, GILBERT SYNDROME, AND EXACERBATION OF PSYCHOSIS

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INTRODUCTION

Autism and intellectual disability may hinder any other coexisting psychiatric diagnosis. Diagnoses are often based on behavioral observations, directly obtained or reported by family members or operators in frequent contact with the patient, and non-verbal communications, as well as on the psychological and physical symptoms manifested by the patient.

Intellectual disability is sometimes comorbid with schizophrenia. Kraepelin (1919) held that "idiocy" or "imbecility" and other manifest intellectual deficits could underlie many dementia praecox cases. He had called this condition "Pfpopschizophrenie", i.e., schizophrenia stemming from intellectual disability. In addition, intellectual disability has been advocated to be a risk factor for developing a psychotic disease (Negueruela López et al. 2009). It is frequently associated with other psychiatric disorders, mainly including behavioral, impulse control, and psychotic disorders (Bobińska et al. 2008). Autism spectrum disorders also manifest different psychotic symptoms (Sinzig & Lehmkuhl 2011). Intellectual disability and psychosis share different biological substrates, including prominent chromosomal abnormalities (Blackwood et al. 2008, O'Donovan et al. 2009). Gilbert syndrome, which is a benign idiopathic unconjugated hyperbilirubinemia caused by an inherited deficiency in the bilirubin-conjugating enzyme uridine-diphosphoglucuronosyl transferase 1A1 (UGT1A1) (Bosma et al. 1995), has been found in patients with schizophrenia (Müller et al. 1991, Miyaoka et al. 2005a).

Atypical antipsychotics proved to be safe and effective in the treatment of certain disruptive behaviors and psychiatric symptoms in adults and children with intellectual disability, with a better side effect profile than conventional antipsychotics (neuroleptics) (Aman

et al. 2004, Cheng-Shannon et al. 2004). Atypical antipsychotics showed effectiveness for the treatment of behavioral symptoms in patients with autism (Doyle & McDougle 2012), particularly risperidone and aripiprazole (Maher & Theodore 2012). Each agent of this class has specific pharmacodynamic and pharmacokinetic mechanisms, interactions with other drugs (Patteet et al. 2012), and side effect profiles (Cha & McIntyre 2012).

CASE HISTORY

We describe the case of a 28-year-old Italian man, hospitalized in one of our long-term care wards for comorbid profound intellectual disability (IQ<25), autistic and psychotic disorders, and Gilbert syndrome, who manifested a severe exacerbation of psychosis, for which ziprasidone was prescribed. This condition paradoxically further deteriorated after the introduction of this drug. A subsequent switch to risperidone greatly and rapidly improved both psychosis-related and symptoms emerging after the introduction of ziprasidone.

Symptomatology and Diagnosis

On October 2012, the patient manifested a severe exacerbation of psychosis, with confusion, disorientation, psychomotor agitation, self-harm behavior, aggressiveness, coprophagy, encopresis, signs of visual hallucinations, obsessive-compulsive rituals, verbal and motor stereotypies, and echolalia. We could not exclude auditory or cenesthetic hallucinations. The patient also manifested dysarthria and moderate akathisia, with a total score of 20/42 on the Abnormal Involuntary Movement Scale (AIMS) (Guy 1976). His serum total bilirubin raised to 1.59 mg/dl. He was previously stable, being sufficiently able to perform daily activities at

ward and occupational and recreational therapies, receiving olanzapine 5 mg/day, haloperidol 6 mg/day, biperiden 4 mg/day, long-acting divalproex sodium 1000 mg/day, clonazepam 8 mg/day, and lorazepam 7.5 mg/day. Serum total bilirubin was about 1.15 mg/dl. At the end of October 2012, due to unexplained psychotic exacerbation, he was hospitalized for one week in a psychiatric unit in a public hospital, where he switched from olanzapine 5 mg/day to ziprasidone 120 mg/day. The remaining treatment remained unchanged.

The patient returned to our clinic, with little improvement in his state of consciousness, but with remission of coprophagy and encopresis. However, he soon manifested a paradoxical worsening of symptoms, with agitation, stereotypies, multiple unrelenting unspecific complaints, self-harm behavior, increased rituality, severe insomnia, and very severe akathisia (AIMS total score, 35/42). The patient was unable to sit during meals and to perform any more his habitual daily; he frequently needed the simultaneous help of two mental health workers, as he was unable to perform group activities. For nocturnal agitation and insomnia he often needed adjunctive intramuscular therapy with promazine 25 mg/ml and delorazepam 5 mg/ml, which was only seldom effective. His condition increased the burden of staff and mental health workers.

Treatment

After four weeks, during which these symptoms did not show any improvement, we decided to progressively taper-off ziprasidone, gradually increasing haloperidol to 9 mg/day, and valproate to 1200 mg/day. This change soon improved insomnia, with the patient being able to sleep for about 5 hours per night. There were no significant changes in blood chemistry, with serum total bilirubin decreased to 1.25 mg/dl and unconjugated bilirubinemia to 0.96 mg/dl after nocturnal sleep improvement. Other symptoms remained unchanged, until he received risperidone 1 mg/day, increased to 4 mg/day in one week. This was followed by consistent symptom improvement, with remission of sleep disorder and self-harm behavior. Psychomotor agitation and akathisia improved impressively, with AIMS total score dropping to 12/42. As a result, the patient returned to perform both daily ordinary activities and occupational therapies, and had a stable circadian rhythm. He also returned to sit during meals, did not need the help of more than one worker, and sometimes participated in group activities. This improvement allowed us to progressively reduce haloperidol to 3 mg/day, with a further increase of risperidone to 6 mg per day.

Improvements were maintained at a six-month follow-up, with serum total bilirubin 1.06 mg/dl and its unconjugated form 0.87 mg/dl. Currently, the patient still manifests some ritualistic behavior, verbal and motor stereotypies, and complaints, but to a lesser extent. He has a good sleep, mild akathisia (AIMS total score,

12/42), does not exhibit coprophagia nor encopresis, and manages to perform various individual and group rehabilitation activities.

DISCUSSION

Several epidemiological studies report frequent comorbidities between autism, intellectual disability, and psychosis, i.e., autism and psychosis (Sinzig & Lehmkuhl 2011), intellectual disability and psychosis (Bobińska et al. 2008), autism and intellectual disability (Nordin & Gillberg 1998), and all these diseases are accompanied by various behavioral disorders (Kraijer 2000, Benson & Brooks 2008, Levy et al. 2009), even in patients residing in institutional settings (Ballinger et al. 1991, Baumeister et al. 1993, Deb et al. 2001). Several data suggest that autism can be considered as an infantile-onset chronic psychosis related to synaptic pruning of the supplementary motor area (Saugstad 2011), with abnormal functioning of brain regions associated with mirroring and mentalizing (Marsh & Hamilton 2011).

Our patient is affected by comorbid autism, intellectual disability, psychosis, and maladaptive behaviors. He manifested a psychotic exacerbation, and a paradoxical worsening of symptoms after introduction of ziprasidone. This atypical antipsychotic drug was effective in suppressing coprophagy and encopresis, but was followed by a paradoxical state of excitement, with worsening of stereotypies, akathisia and severe insomnia. Although ziprasidone has been associated with decreased need for antiparkinson medication than risperidone (Rummel-Kluge et al. 2012), and similarly to most atypical antipsychotics showed a lower propensity for extrapyramidal side effects and hyperprolactinemia, compared to neuroleptics (Citrome 2011), in our patient was followed by severe akathisia, which improved upon introduction of risperidone. It is unclear whether severe akathisia was related to some unknown ziprasidone-haloperidol interaction, anyway this symptom greatly improved after introduction of risperidone.

Risperidone-related improvement is consistent with an existing line of evidence of its effectiveness in autism (Matson et al. 2011, Dove et al. 2012, Maher & Theodore 2012), intellectual disability (Aman et al. 2004), and related maladaptive behaviors (Hässler & Reis 2010).

Another point that should be emphasized is the correlation between the levels of bilirubin and psychopathological symptoms. Serum total bilirubin, which in our patient was stable around 1.15 mg/dl before the reported psychosis exacerbation, increased to 1.59 mg/dl in the most severe phase of disease, and dropped first to 1.25 mg/dl and then to 1.06 mg/dl with symptoms progressively improving. This evidence is consistent with some existing data that showed psychotic symptom improvement and a relative decrease in

bilirubin plasma concentration in patients affected by comorbid psychotic disorder and Gilbert syndrome (Molina Ramos et al. 2006). Significantly higher frequency of hyperbilirubinemia has been reported in patients with schizophrenia, as compared to patients with other psychiatric disorders and the general healthy population (Müller et al. 1991). Miyaoka and colleagues conducted a series of studies focusing on schizophrenia and Gilbert syndrome, reporting different brain functional alterations, and suggesting that these comorbid conditions may represent a more severe schizophrenia subtype, regarding both psychopathological aspects (Miyaoka et al. 2000), and brain structure (Miyaoka et al. 2001, 2005a) and function (Miyaoka et al. 2005b).

CONCLUSIONS

In short, our case indicates that bilirubin levels in Gilbert syndrome may be related to the severity of psychopathology. This could be mediated by stress due to the psychotic exacerbation, increased red blood cell vulnerability due to psychomotor agitation, and other unknown mechanisms. Our case also emphasizes the unpredictability of responses to specific psychotropic medications in patients affected by autism, intellectual disability and psychotic disorders. The reasons for which this occurs is the subject of further research.

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Conflict of interest:

In the past two years, P.G. has received research support from Lilly and Janssen, and has participated in Advisory Boards for Lilly, Otsuka, Pfizer, and Schering and received honoraria from Lilly; R.B. has participated in Advisory Boards for Lilly, Otsuka, Pfizer, and Angelini. However, support received by any author did not interfere in any form or way in the writing of this manuscript and in the views supported. All other authors of this paper have no relevant affiliations or financial involvement with any organization or entity with a financial interest in, or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

1. Aman MG, Gharabawi GM: *Special Topic Advisory Panel on Transitioning to Risperidone Therapy in Patients With Intellectual disability and Developmental Disabilities: Treatment of behavior disorders in intellectual disability: report on transitioning to atypical antipsychotics, with an emphasis on risperidone. J Clin Psychiatry* 2004; 65:1197-210.
2. Ballinger BR, Ballinger CB, Reid AH, McQueen E: *The psychiatric symptoms, diagnoses and care needs of 100 mentally handicapped patients. Br J Psychiatry* 1991; 158:251-4.
3. Baumeister AA, Todd ME, Sevin JA: *Efficacy and specificity of pharmacological therapies for behavioral disorders in persons with ment retard. Clin Neuropharmacology* 1993; 16:271-94.
4. Benson BA, Brooks WT: *Aggressive challenging behaviour and intellectual disability. Curr Opin Psychiatry* 2008; 21:454-8.
5. Blackwood DH, Thiagarajah T, Malloy P, Pickard BS, Muir WJ: *Chromosome abnormalities, intellectual disability and the search for genes in bipolar disorder and schizophrenia. Neurotox Res* 2008; 14:113-20.
6. Bobińska K, Florkowski A, Galecki P: *Charakterystyka zaburzeń psychicznych u hospitalizowanych psychiatrycznie z upośledzeniem umysłowym - doniesienie wstępne. [Characteristics of mental disorders in psychiatric patients with intellectual disability - preliminary communication; Article in Polish]. Pol Merkur Lekarski* 2008; 25(Suppl 1):8-12.
7. Bosma PJ, Chowdhury JR, Bakker C, Gantla S, de Boer A, Oostra BA et al.: *The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. N Engl J Med* 1995; 333:1171-5.
8. Cha DS, McIntyre RS: *Treatment-emergent adverse events associated with atypical antipsychotics. Expert Opin Pharmacother* 2012; 13:1587-98.
9. Cheng-Shannon J, McGough JJ, Pataki C, McCracken JT: *Second-generation antipsychotic medications in children and adolescents. J Child Adolesc Psychopharmacol* 2004; 14:372-94.
10. Citrome L: *Drug safety evaluation of ziprasidone. Expert Opin Drug Saf* 2011; 10:437-48.
11. Deb S, Thomas M, Bright C: *Mental disorder in adults with intellectual disability. 2: the rate of behavior disorders among a community based population aged between 16 and 64 years. J Intellect Disabil Res* 2001; 45:506-14.
12. Dove D, Warren Z, McPheeters ML, Taylor JL, Sathe NA, Veenstra-VanderWeele J: *Medications for adolescents and young adults with autism spectrum disorders: a systematic review. Pediatrics* 2012; 130:717-26.
13. Doyle CA, McDougale CJ: *Pharmacotherapy to control behavioral symptoms in children with autism. Expert Opin Pharmacother* 2012; 13:1615-29.
14. Guy W: *ECDEU Assessment Manual for Psychopharmacology: Revised (DHEW publication number ADM 76-338). Rockville, MD: US Department of Health, Education and Welfare, Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976, p. 534-7.*
15. Hässler F, Reis O: *Pharmacotherapy of disruptive behavior in mentally retarded subjects: A review of the current literature. Dev Disabil Res Rev* 2010; 16:265-72.

16. Kraepelin E: *Dementia Praecox and Paraphrenia*. Translated by RM Barclay, edited by GM Robertson E & S Livingstone. Edinburgh, 1919.
17. Kraijer D: Review of adaptive behavior studies in mentally retarded persons with autism/pervasive developmental disorder. *J Autism Dev Disord* 2000; 30:39-47.
18. Levy SE, Mandell DS, Schultz RT: Autism. *Lancet* 2009; 374: 1627-38. Erratum in: *Lancet* 2011; 378: 1546.
19. Maher AR, Theodore G: Summary of the comparative effectiveness review on off-label use of atypical antipsychotics. *J Manag Care Pharm* 2012; 18:S1-20.
20. Marsh LE, Hamilton AF: Dissociation of mirroring and mentalising systems in autism. *NeuroImage* 2011; 56:1511-9.
21. Matson JL, Sipes M, Fodstad JC, Fitzgerald ME: Issues in the management of challenging behaviours of adults with autism spectrum disorder. *CNS Drugs* 2011; 25:597-606.
22. Miyaoka T, Seno H, Itoga M, Iijima M, Inagaki T, Horiguchi J: Schizophrenia-associated idiopathic unconjugated hyperbilirubinemia (Gilbert's syndrome). *J Clin Psychiatry* 2000; 61:868-71.
23. Miyaoka T, Seno H, Itoga M, Inagaki T, Horiguchi J: Structural brain changes in schizophrenia associated with idiopathic unconjugated hyperbilirubinemia (Gilbert's syndrome): a planimetric CT study. *Schizophr Res* 2001; 52:291-3.
24. Miyaoka T, Yasukawa R, Mihara T, Mizuno S, Yasuda H, Sukegawa T et al.: Fluid-attenuated inversion-recovery MR imaging in schizophrenia-associated with idiopathic unconjugated hyperbilirubinemia (Gilbert's syndrome). *Eur Psychiatry* 2005a; 20:327-31.
25. Miyaoka T, Yasukawa R, Mizuno S, Sukegawa T, Inagaki T, Horiguchi J et al.: Proton magnetic resonance spectroscopy (1H-MRS) of hippocampus, basal ganglia, and vermis of cerebellum in schizophrenia associated with idiopathic unconjugated hyperbilirubinemia (Gilbert's syndrome). *J Psychiatr Res* 2005b;39:29-34.
26. Molina Ramos R, Villanueva Curto S, Molina Ramos JM: Enfermedad de Gilbert y esquizofrenia [Gilbert's syndrome and schizophrenia; Article in Spanish]. *Actas Esp Psiquiatr* 2006; 34:206-8.
27. Müller N, Schiller P, Ackenheil M: Coincidence of schizophrenia and hyperbilirubinemia. *Pharmacopsychiatry* 1991; 24:225-8.
28. Negueruela López M, Ceverino Domínguez A, Quintero J, Pérez Rodríguez MM, Fernández del Moral A, Jiménez Arriero MA et al.: Retraso mental como factor de riesgo para el desarrollo de un trastorno psicótico [Intellectual disability as a risk factor to develop a psychotic disease; Article in Spanish and English]. *Actas Esp Psiquiatr* 2009; 37:21-6.
29. Nordin V, Gillberg C: The long-term course of autistic disorders: update on follow-up studies. *Acta Psychiatr Scand* 1998; 97:99-108.
30. O'Donovan MC, Craddock NJ, Owen MJ: Genetics of psychosis; insights from views across the genome. *Hum Genet* 2009; 126:3-12.
31. Patteet L, Morrens M, Maudens KE, Niemegeers P, Sabbe B, Neels H: Therapeutic drug monitoring of common antipsychotics. *Ther Drug Monit* 2012; 34:629-51.
32. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Kissling W et al.: Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. *Schizophr Bull* 2012; 38:167-77.
33. Saugstad LF: Infantile autism: a chronic psychosis since infancy due to synaptic pruning of the supplementary motor area. *Nutr Health* 2011; 20:171-82.
34. Sinzig J, Lehmkuhl G: Komorbiditäten bei Autismus-Spektrum-Erkrankungen. Stand der Forschung und Aufgaben für die Zukunft [Comorbidities with autism spectrum disorders - present state of research and future outlook; Article in German]. *Z Kinder Jugendpsychiatr Psychother* 2011; 39:91-8; quiz 99.

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