

Is Valacyclovir a Mood Stabilizer?

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Abstract

Growing evidence indicates the role of viral agents in neuropsychiatric conditions, such as chronic fatigue syndrome (CFS), Alzheimer's disease, and possibly autism. This case report describes a patient who was afflicted with treatment-resistant childhood bipolar disorder, who also had features associated with attention deficit hyperactivity disorder and autism spectrum disorder. After failing multiple regimens for mood stabilization (anticonvulsants, lithium, neuroleptics), a trial of valacyclovir was initiated. The decision to use an antiviral agent was based on the patient's laboratory data and the marked treatment response of the patient's sibling, who manifested symptoms of depression and CFS. The patient in this report showed a dramatic improvement in his volatile mood, irritability, concentration, social reciprocity, and overall personality. He was maintained on valacyclovir at 1000 mg BID, while the doses of the mood stabilizing agents and stimulants were reduced by as much as 50%. After 37 months of ongoing valacyclovir treatment, the patient continues to make improvements and is being mainstreamed in school. The case illustrates a potential role of viruses in neuropsychiatric and psychiatric disorders and the potential benefit of antiviral therapy in treatment-refractory cases.

Keywords: Valacyclovir; Autism; Bipolar disorder; Mood stabilizer

Abbreviations: ADHD-Attention-Deficit Hyperactivity Disorder; CFS-Chronic Fatigue Syndrome; CMV-Cytomegalovirus; EBV-Epstein-Barr virus; HHV-6-Human Herpes virus 6; HHV-7-Human Herpes virus 7; HSV-1-Herpes simplex 1

Introduction

A growing body of evidence indicates that viruses may have a role in neuropsychiatric disorders, including autism [1-3], Alzheimer's disease [4-6], and chronic fatigue syndrome (CFS) [7-9]. Research has shown a number of chronic viral infections can be found in patients with CFS. Viruses such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), and several herpes viruses (Herpes simplex 1 {HSV-1}, Human Herpes virus 6 and 7, {HHV-6, HHV-7}) may be causal or contributory to the symptoms in a large proportion of patients with CFS. These infections are described as intracellular reactivations of an old infection, rather than an acute infection; hence, an elevation of IgM antibodies is typically not seen with re-activated infections of EBV, CMV, or HHV-6 [7,10]. Indeed Nicolson et al. [11] found that 30.5% of CFS patients had active HHV-6 infection versus only 9% of controls.

Studies by Lerner et al. found that treating patients with CFS for 6 months with the antiviral medication, valacyclovir, resulted in a significant improvement in symptoms [12,13]. Similarly, Kogelnik et al. treated CFS patients with a potent antiviral, valganciclovir, for 6 months [14], if they had elevated IgG tests for HHV-6 and EBV and had at least 4 of the following symptoms: impaired cognitive functioning slowed processing speed, sleep disturbance, short-term memory deficit, fatigue and symptoms consistent with depression. Seventy-five percent had a robust response, including improved mood and cognitive functioning [14].

In a recent case series of adolescents initially diagnosed with treatment-resistant depression, the addition of the antiviral agent, valacyclovir, led to resolution of fatigue, as well as depression symptoms [15]. All of the responders had improved academic performance. Self-report measures showed improved mood, improved vigor, and improved mental function. Of note, patients indicated marked improvement on queries such as: "I have trouble paying attention" and "I am confused". The group was characterized by a high incidence of elevated IgG for EBV or HHV6 and low CD56 natural killer cell counts.

As yet, it is not clear if CFS is related to a virus, nor what virus or viruses contribute to the pathogenesis of CFS. Based on the results of antiviral therapy, member(s) of the herpes family is/are viable candidates, including HSV-1, HHV-6, HHV-7, EBV, or others [15-18]. An intriguing question is that since these prior studies indicate a virus can disrupt the neuropsychological function of vigor, concentration, motivation, and wakefulness, could virus(es) disrupt other neuropsychological functions, such as mood regulation or induce the behavioral manifestations of autism? The case presented herein would suggest that they could.

Case Presentation

The patient was first evaluated by the author at age 4 years due to violent aggression with peers and teachers at preschool and with family at home. The prenatal history was unremarkable and early development had progressed with typical milestones—walking by 13 months, first words at 12 months, and no regression in language function. Family history was positive for mother with depression, maternal uncle with Bipolar disorder (mania), paternal grandmother with Bipolar Disorder and several paternal distant relatives with Bipolar Disorder and Schizophrenia. Starting at age 3 years, the patient developed primary insomnia, often up to 2200-2400, and frequent middle insomnia. He had been evaluated previously by his pediatrician, diagnosed with ADHD, and treated with methylphenidate (Ritalin) with no obvious benefit.

Based upon the initial evaluation, he was treated with guanfacine (Tenex) augmentation of the methylphenidate with reduction of aggression, reduction of primary insomnia/middle insomnia, although

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his sleep duration was no more than 5-6 hours per night. Notably, preschool staff and parents described the patient as often “in his own world”, socially withdrawn, and struggling with transitions or changes in routine/schedule. In the office, he was reluctant to make eye contact, disconnected, and engaged in play with toys which mostly consisted of crashing the cars together during play therapy. The Social Reciprocity Scale Version 1 (SRS) was administered and a score of 112 was obtained (in range for verbal autism, but overlap with clinical range) [19].

After 12 months on this regimen, the patient became accelerated, getting up in the night and cleaning his room, aggressive and demanding at home; grandiose at school; aggressive at school-attacked and choked a peer; awake for 22 hours on more than one occasion. A Young Mania Rating Scale-Parent Version (YMRS-P) was administered [20]. The score was 23. The patient was diagnosed with Mood Disorder Not Otherwise Specified, ADHD, and rule out Pervasive Developmental Disorder. Oxcarbazepine (Trileptal) was started as a mood stabilizer. Patient calmed, was less accelerated, less aggressive, and his sleep improved. After six months, patient was given a trial of atomoxetine (Strattera). There was marked increase in aggression, agitation, violent tantrums. The patient made suicidal statements, and his sleep duration decreased dramatically. Atomoxetine was discontinued and symptoms subsided [21]. At age 7 years, the patient again became oppositional and aggressive, with violent tantrums, outbursts at school, hitting peers, belligerence with adults, extreme reactivity, and decreased sleep duration. The patient wrote a note to his mother “*I don't (k)now wh I am dis bad all the tim. Do you (k)now wh I am dis bad mommy*”.

Risperidone (Risperdal) 1 mg was added to the patient's regimen. The patient had fewer outbursts, seemed more connected, made better transitions, was feeling “happier”, and slept better; however, after 2 months, the patient was again irritable, demanding, grandiose, rude to adults, throwing tantrums, hitting peers at school, climbing on furniture, and sleep duration decreased to an average of 4 hours per night. The patient became very rigid and controlling at home, wanting objects arranged a certain way, oblivious to others' feelings. The patient became increasingly social isolating, avoiding family activities that require interaction with anyone besides his mother. Oxcarbazepine was discontinued and valproate (Depakote) was started. The dose was titrated to serum VPA level of 97.6 mcg/ml. The patient's symptoms improved and sleep improved. After 3 months, patient again was violent with peers, grandiose, defiant, having daily tantrums, taunting teacher with scissors, and had decreased sleep duration. Increase of risperidone had no benefit. At this time a Washington University version of the Kiddie Schedule for Affective Disorders and Schizophrenia (WU-KSADS) was administered [22,23]. The results were positive for Bipolar Disorder and ADHD. The diagnosis was revised to Bipolar Disorder I (current episode manic), ADHD, and rule out Pervasive Developmental Disorder. The risperidone was discontinued and a trial of aripiprazole (Abilify) was initiated. The patient continued to be accelerated, angry, violent, threatened to kill himself on one occasion, and he choked peers on two occasions. The patient was moved into a self-contained classroom. Patient also had episodes of silly, infantile behavior. The intensive school-based program team noted the patient was socially isolated, reluctant to give eye contact, misinterpreted social cues and responded socially with anger or withdrawal.

In an attempt to regulate the patient's mood, valproate was discontinued and lithium plus aripiprazole was utilized. The patient continued to decompensate. The patient was hospitalized at the local children's psychiatric hospital due to violent aggression, visual hallucinations, paranoia, and grandiosity. Patient was described as

giddy, impulsive, explosive anger, spitting, hitting, and aggressive. The patient was evaluated by the hospital psychiatrist and diagnosed with Bipolar Disorder I. The lithium dose was adjusted and quetiapine (Seroquel) was started. Symptoms improved and psychosis abated. Unfortunately, after 3 months, the patient was again violent with peers, tantruming, defiant, and sleep duration was decreased. The patient was re-hospitalized due to violent outburst in which he threatened to kill himself with a butcher knife and assaulted his grandmother. The Young Mania Rating Scale (YMRS) was administered on three separate days and the patient scored in the manic range consistently. The treating hospital psychiatrist diagnosed Bipolar Disorder I; however, then started patient on sertraline (Zoloft). Patient discharged to Day Treatment. The treating psychiatrist in Day Treatment also diagnosed patient with Bipolar Disorder I. The patient quickly accelerated and became increasingly violent and manic. He was re-hospitalized from Day Treatment due to violent aggressive behavior in program. A repeat YMRS score was 26 consistent with mania. A fifth psychiatrist diagnosed the patient with Bipolar Disorder I. Carbamazepine (Tegretol) was added to lithium and sertraline was stopped.

Due to the patient's social skills deficits demonstrated during prior hospital stays and in the Day Treatment program, the hospital psychiatric staff evaluated patient with the Autism Diagnostic Observation Schedule (ADOS) [24]. Patient did not meet criteria for Autism but had a marginally high score. Hospital psychiatrist diagnosed Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) and recommended evaluation and programs for a mild Autism Spectrum Disorder. The patient was discharged back to his self-contained structured school program. Intensive family and parenting therapy was implemented.

Over the subsequent three years, the patient alternated between periods of mania and hypomania with a partial response to combination therapy of lithium, carbamazepine, quetiapine, and mixed dextroamphetamine salts (Adderall) and eventually haloperidol (Haldol). Patient remained perseverative and showed poor social reciprocity, poor social skills, and social avoidance. The patient was very cognitively rigid, demanding his mother to say things a certain way, spinning objects, arranging objects in an obsessive manner, and demanding others to follow his rigid routine. The patient obsessively taped objects in home with cellophane tape-using 2-3 rolls of tape per day. He refused social activities with family, had no friends, and was antagonistic or aloof with peers at school. The patient was placed in Day Treatment again at age 10 years. He was diagnosed with Bipolar Disorder I by a sixth psychiatrist. Carbamazepine was discontinued. Fluoxetine (Prozac) was started which sparked a manic episode. He was taken to the emergency room several times for violent episodes, but was not admitted. At age 11 years, lamotrigine (Lamictal) was started. The patient continued to be paranoid, carrying a golf club and sleeping of floor of parent's room. The lamotrigine was slowly titrated and lithium was tapered off. Side effects improved as lamotrigine dose raised and other meds lowered. Patient's mood symptoms stabilized on lamotrigine increased to 75 mg qAM, 100 mg qnoon, 175 mg qHS; quetiapine 100 mg qAM, 200 mg qnoon, 300 mg qHS; Adderall XR 30 mg qAM; bupropion SR 100 mg qAM.

Despite the improvement in mood and aggression, the patient remained socially awkward, aloof, and avoidant. He made poor eye contact. He was only willing to speak to family. He rarely spoke to or answered this psychiatrist, teachers, or staff. In the office, the patient would grunt and hide his head under his hoodie. Patient was in a specialized school for behavioral problem children and those on the autism spectrum.

In summary, the index patient had been treated since the age of 4 years for childhood Bipolar Disorder, ADHD and a rule out on PDD-NOS. He had shown only partial response to both monotherapy and combination therapy with multiple mood stabilizers. Augmentation with atypical antipsychotics and stimulants had been only partially effective. He had been hospitalized in a psychiatric facility on three occasions and placed in a day treatment program on two occasions with little improvement in his condition. While he had not been formally diagnosed with an Autism Spectrum Disorder, the diagnosis of PDD-NOS was considered by six psychiatrists, his SRS score was positive, and his ADOS score was border line. His diagnoses of Bipolar I and ADHD were made independently by six psychiatrists, repeated YMRS testing, and a WU-KSADS.

During the course of his treatment, the patient's older sister had developed CFS, characterized by fatigue, excessive sleep, mental "fogging", low motivation, muscle aches, and low mood. An 8 week trial of escitalopram at 20 mg/day made no significant change in her symptoms. Laboratory studies showed elevated viral immunoglobulin titers and low natural killer cell count. Within 6 weeks of starting valacyclovir (Valtrex, GlaxoSmithKline, Philadelphia) therapy (500 mg BID for 2 weeks, then 1000 mg BID), her symptoms began to abate. She was able to return to full-time school and part-time work in three months. Since the purported viral agent responsible for CFS, as well as its mechanism of transmission, is unknown, the possibility of horizontal transmission within the family was considered.

On laboratory testing, the index patient indeed showed results suggestive of CFS, including low CD56 natural killer cell (NK) count [25,26], as his sister had. A trial of valacyclovir was therefore considered. After explaining the risks and side effects of valacyclovir, as well as the speculative nature of the treatment, the patient assented and the parents consented to a trial of valacyclovir starting at 500 mg BID. Within 6 weeks, noticeable improvement was seen in the patient's mood and behavior. When the valacyclovir dose was increased to 1000 mg BID, the patient experienced a dramatic improvement in his symptoms. His mood and behavior dramatically improved. He became much more social, seeking the company of his family, joking, and conversing. As the parents describe, "It was like an awakening...now he is quick to apologize when he's been disrespectful, rude, or demanding...he developed a constant hunger for knowledge and a desire to understand everything and everyone around him". He became kind, helpful with household activities, and courteous. The patient, for the first time, greeted his psychiatrist warmly, rather than with surly growls or hiding under the hood of his jacket.

Three months after starting on valacyclovir, reductions in his doses of medications were attempted. The patient's medication doses were greatly reduced to lamotrigine 250 mg/day, bupropion ER 100 mg/day, quetiapine 150 mg/day, and mixed amphetamine salts 30 mg/day. These changes were tolerated well, unlike previous attempts to reduce his doses. The patient showed marked improvement in concentration and school performance, despite a lower dose of stimulant medication. He reported, "Now that I am awake, I understand everything they are saying...I'm 14 years old and I need to start learning...You need to let me help you more...I never noticed the burners on the stove were different sizes...I need to start learning how to cook". The patient made friendly connections to peers and teachers at school. He expresses a sense of humor, as well as a thoughtful sensitivity to the needs and feelings of his family members.

After 37 months on valacyclovir, the patient continues to do well. He is being mainstreamed into a regular school. Brief episodes in which

valacyclovir doses were missed (e.g., vacation trip) were associated with an increase in irritability and difficulty concentrating.

Discussion

This case study illustrates an important concept, not strictly limited to pediatric psychiatry. This case raises the possibility that viral pathogens may complicate and worsen mood disorders, including Bipolar Disorder. Moreover, in this case, the patient's symptoms of poor social skills, low social reciprocity, and cognitive rigidity resolved with valacyclovir treatment. These symptoms are often found in patients on the Autism Spectrum. A number of previous studies have made an association between Herpes family viruses and Autism Spectrum disorders [2,3,27,28].

The role of Herpes family viruses in the etiology of neurological disorders, such as CFS and multiple sclerosis, has been the subject of considerable research. Conflicting data from viral epidemiological studies [16,18,29] does exist. Nonetheless, a distinguishing feature of the herpes family viruses is the capacity to integrate into neurons on a long-term, if not lifelong, basis. In particular, HHV-6 has strong neurotropic and gliotropic properties [30,31] and is epidemiological associated with CFS [32] and autism [1-3]. Moreover, HHV-6 has shown the capacity to integrate in the host chromosome [33,34]. A recent case series demonstrated that patients presenting with depression, particularly treatment-resistant depression, with low energy or mental "dullness" or "foginess" as a prominent symptom, may instead have virally mediated CFS.

An intriguing alternative hypothesis is the clinical response to valacyclovir was not due to its antiviral properties; rather, it is acting as a novel mood stabilizer. Cases in which mania has been induced with acyclovir [35] or valacyclovir [36] in patients with Bipolar Disorder have been reported. This is the first reported case of mood stabilization following the introduction of valacyclovir.

Certain limitations need to be noted. This is a single case and may represent an epiphenomenon. The absence of a placebo control is inherent to single case studies. Lastly, a viral encephalopathy or even a viral infection was not definitively demonstrated in this case, although it bears close resemblance to a case series in which viral infection was definitively demonstrated.

The present case illustrates a dramatic improvement in symptoms normally associated with Bipolar Disorder, ADHD, and possibly Autism Spectrum Disorders with antiviral therapy. Taken together with previous work on the association between Herpes family viruses and depressive symptoms, further study of the proposed association between these viruses and neuropsychiatric symptoms is encouraged. The potential benefit of antiviral therapy, particularly, in treatment-refractory cases, is striking. In no way should this report be interpreted as a call to avoid vaccinations; indeed, this case and many others seen in the author's clinical practice, along with the recently demonstrated association between HSV-1 and Alzheimer's disease [6] and the association between herpes family viruses, autism [2,3,27,28] and CFS, would argue that low-grade chronic viral encephalopathy may be more common than previously suspected. Expedited efforts to develop a vaccine for HSV-1 seem warranted.

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Dr. Henderson is the President of The Synaptic Space, a neuroimaging consulting firm and co-founder of Neuro-Luminance Corporation. Theodore A. Henderson is responsible for all aspects of

the study conceptualization, design, data collection, and manuscript preparation.

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