Reduced Maladaptive Behavior and Improved Social Function in a Child with PDD-NOS Treated with Progesterone

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This case report presents the use of progesterone for the regulation of an atypical menstrual cycle in a girl, aged 11 years, who is also diagnosed with Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS). The progesterone injections alleviated the prolonged, heavy monthly blood flow, but also caused significant improvements in the patient's mood, behavior, and cognition within four weeks following the initial injections. The use of hormonal treatments, such as progesterone, to effect mood, behavior, and cognition should be further researched to determine other potential therapeutic uses.

Keywords: Behavior; Cognition; Menstrual cycle; Mood; Pervasive Developmental Disorder-Not Otherwise Specified; PDD-NOS; Progesterone

A girl was first seen in the Department of Psychiatry and Behavioral Medicine at the age of 4 years 8 months for extreme impulsivity, hyperactivity, inattention, and restlessness. These symptoms were noted both at home and at school. The evaluation revealed a girl with global developmental delays (eg, delayed speech and language, delayed toilet training, delayed fine and gross motor skills), stereotypies, perseveration, echolalia, poor eye contact, difficulties with social engagement, repetitive behavior (eg, lining toys up), distractibility, urinary incontinence, and compulsive skin-picking. The mental health histories of the biological parents were not available because the girl was adopted at the age of 23 months from Manila, Philippines. The adoptive parents were not aware of any pathogenic parenting or multiple foster home placements before the adoption. They were of the opinion that she bonded well with them. They did not observe any attachment difficulties, either in the way of being overly affectionate or detached. Medically, she was well-nourished without any evidence of physical distress. There was no evidence of cardiovascular or gastrointestinal diseases. There was no report of head trauma, loss of consciousness, lead poisoning, or seizure disorder. An electroencephalogram was obtained and was normal.

During an examination approximately 1.5 years later, when the girl was 6 years old, she appeared aloof, avoidant, and disengaged. Her play theme was often repetitive, and she had difficulty shifting attention. She was extremely restless, hyperactive, impulsive, and distractible. A neuropsychological evaluation was done, and on the Wechsler Intelligence Scale for Children-4th Edition (WISC-IV) she achieved a Verbal Comprehension Index composite score of 63 and a Perceptual Reasoning composite score of 59, both in the 1st percentile. Her Academic Readiness was in the 4th percentile. Her Global Language from

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selected subtests of the Wechsler Preschool and Primary Scale of Intelligence-3rd Edition (WPPSI-III) yielded a composite score of 67.

She was diagnosed with Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), along with attention deficit hyperactivity disorder (ADHD) combined type-like symptoms, expressive/receptive language disorder, and mild mental retardation. She was started on a combination drug of amphetamine and dextroamphetamine 5 mg daily titrated to 10 mg twice a day, and referred for speech and language therapy, as well as occupational therapy. The mixed-salt amphetamine was eventually discontinued after four weeks due to lack of effectiveness and intolerable side effects (eg, insomnia, increased anxiety).

Blood tests and a genetic evaluation were done 6 months later while the girl was still 6 years old. She was screened for William's syndrome, 22q deletion, Fragile X syndrome, and inborn errors of metabolism; all were negative. The MECP2 genetic analysis for Rett syndrome was negative. Other genetic syndromes, including Smith-Lemli-Opitz syndrome and Noonan syndrome, were also ruled out.

Over the years, she was prescribed several psychotropic medications in an attempt to regulate her mood, improve attention span, and reduce anxiety, hyperactivity, and impulsivity. Unfortunately, at the age of 9 years, she was admitted to a psychiatric hospital for severe anxiety, disjointed thinking (eg, flight of ideas, jumping from topic to topic, train of thought could not be followed), frequent temper tantrums, and severe insomnia. Her compulsive skin picking had escalated to cutting herself. The parents had become overwhelmed and unable to care for her in the home environment. She was discharged on clonidine 0.1 mg twice a day, dexamethylphenidate hydrochloride 20 mg in the morning, dexamethylphenidate 10 mg in the afternoon, and aripiprazole 5 mg twice a day. Her impulsivity improved on this medication regimen, but she remained generally immature and disjointed. Her attention span remained poor, and she could not participate in typical social functioning, such as singing in choir concerts, or in reciprocal relationships with similar aged children.

At the age of 11 years, she attained menarche. Her menstrual flow was monthly, would last ten days, and was rather heavy. Given her medical and psychiatric history, her primary care physician consulted with a gynecologist and a decision was made to start the 11-year-old girl on progesterone 150 mg injections to regulate her menstrual cycle and possibly eliminate the monthly blood flow. Progesterone can be prescribed to help with early onset, heavy and irregular menses, accompanied with mood and behavioral issues.¹

Interestingly, there was a rather significant change in her mood, behavior, and cognition within the first four weeks following the initiation of progesterone therapy. She was able

to participate in several choir concerts without any distress. The incontinence disappeared. She was no longer picking at her skin or cutting herself. She was able to make eye contact. She was able to participate in swimming lessons. Her ability for reciprocal relationships improved, and she was able to maintain friendships. Her speech and language improved, enabling her to engage in reciprocal conversation. Her range of interests also improved to include typical pre-adolescent interests, such as sitting in the classroom with other students and engaging in reciprocal conversation. The mother started receiving more positive feedback about her from school, and she indicated there were now more good days than bad ones.

The girl is currently on a combination of dexamethylphenidate hydrochloride 20 mg in the early morning and at 11 AM, dexamethylphenidate 10 mg in the morning, aripiprazole 5 mg twice a day, and clonidine 0.1 mg in the morning and at 7 PM. The progesterone, supplied as medroxyprogesterone hormone injection (Depo-Provera) (150 mg), is administered every ten weeks. Interestingly, of all the medications tried, the progesterone seems to have made the most remarkable difference in her behavior. The girl, a pleasant 12-year-old, continues to benefit from the progesterone 150 mg injection every ten weeks, along with the ADHD medications and mood stabilizers taken in the doses mentioned above.

Discussion

This patient had a rather unusual response to the progesterone therapy, thus a Medline and PubMed search of the English language literature from 1950 to the present using the terms progesterone, autism, and social ability, was performed to see if there are other cases described. No previous documentation was found of such dramatic improvement in functioning in a child with autism treated with progesterone.

There are a number of possible explanations for the improvement shown. First, the improvement in some of the symptoms might be due to the change in the girl's menstrual flow following the progesterone injections. Second, changes to the timing of doses for a couple of the drugs within the combination may have lead to the improvement in some of this girl's symptoms. Since the psychiatric hospital discharge, an 11 AM dose of dexamethylphenidate hydrochloride 20 mg was added in addition to the morning dose, and the dexamethylphenidate 10 mg was changed to a morning dose from the afternoon.

A third explanation may be the possible role of neurochemical contributions to the pathophysiology of autism. Several studies have researched the role of glutamate dysfunction, while other researchers have proposed that gamma-aminobutyric acid may have an important role. Glutamate, the primary excitatory amino acid neurotransmitter, is found in high concentrations throughout the brain and is thought to be crucial in neuronal plasticity and higher cognitive functioning.² Gamma-aminobutyric acid (GABA), another amino acid neurotransmitter, is the primary inhibitory neurotransmitter in

the brain and is synthesized from glutamate by glutamic acid decarboxylase (GAD).² Studies analyzing peripheral levels of these neurotransmitters, along with those examining the genes and proteins involved in glutamate and GABA functioning, in autistic individuals have varied widely, so interpretation as to their role has been difficult.²

Neuroactive steroids, synthesized in nervous tissue or endocrine glands or produced synthetically, cause many effects on brain functions. In addition to their effect on postsynaptic receptors, most neuroactive steroids, including progesterone, effect the release of neurotransmitters like glutamate and GABA and also effect mechanisms involving presynaptic receptors like the GABA(A) receptor.^{3,4} Many of these effects occur in brain regions involved in learning, memory, emotion, motivation, motor skills, and cognition.^{3,4}

Studies on the effect of GABA(A) receptor modulators such as progesterone have shown opposing results. Some have revealed beneficial properties such as mood balancing, sedation, anticonvulsant effects, and anxiolytic effects, while others have indicated adverse effects such as anxiety, irritability, mood swings, and aggression, which are linked to the negative mood symptoms some women experience during their menstrual cycle or from the use of hormonal contraceptives or hormone therapy that utilizes progesterone.⁵ These results may be due to the fact that several GABA(A) receptor modulators have biphasic effects, with low concentrations having an adverse effect while higher concentrations show beneficial properties.⁵

The beneficial effects of progesterone on the GABA(A) receptor may be one of the explanations for the improvement in the symptoms seen in this girl. This may be further explained by looking at oxytocin, the neuropeptide which consists of nine amino acids and is produced by the paraventricular and supraoptic nuclei of the hypothalamus. It is released into the circulation to provide peripheral effects and also delivered to several structures of the brain.⁶

Oxytocin is known to promote maternal-infant bonding, play a role in sexual behavior, and affect social situation behaviors. It has widespread beneficial effects such as inducing a general sense of well-being (including calmness), improved social interactions, increased trust, and reduced fear; however, an oxytocin dysfunction may be associated with neuropsychiatric conditions such as autism, especially in regards to social behaviors.^{7,8} It has been shown that children with autism have lower levels of plasma oxytocin and increased levels of oxytocin precursors, suggesting a defect in the way oxytocin is processed.⁶

Many studies have been done to support the role of oxytocin in the treatment of several aspects of autism, such as social deficits, repetitive behavior, fear and trust, and improvements in all of these areas has been shown. Although none of the studies that looked at oxytocin and its effects (both beneficial

and adverse) also looked at progesterone, their effects are quite similar.

It is unclear if any of the above discussed explanations played a role in this particular case, or if there are other unknown factors that could explain the outcome. This is the first published account of progesterone therapy playing a major role in the significant improvement of several symptoms in a girl diagnosed with PDD-NOS; however, this effect is only reported in one patient, and she was also taking other medications concomitantly.

Further research in the area of hormonal treatments and their effect on mood, behavior and cognition, followed by placebo-controlled clinical trials are necessary. Clinicians should be encouraged to report additional cases similar this one.

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