Title: Speak no evil, or anything else: Aggression and selective mutism in adolescent male with 16p11.2p12.2 duplication syndrome and URI symptoms

Taiwo T. Ajumobi, DO, MS
Saint Francis Children's Hospital
Tulsa, OK

History of Present Illness

A 15 yr old male was admitted to inpatient pediatrics January 2021 due to aggressive behavior and regressed communication of unknown etiology. Social history revealed that Fall 2020 patient's older sister (a nurse whom he was very close with) moved out of the house to prevent potentially exposing family members to COVID19 virus. In addition, patient's parents had divorced 2019 and patient's mom recently started dating. Lastly patient was no longer attending in-person school due to the nationwide quarantine and had to do school online. Regarding developmental history, mother states that patient did not have a prior history of aggression or behavioral problems, nor did he use any medication for treatment of symptoms linked to autism (only did speech and occupational therapy when he was younger). Patient had age appropriate receptive and expressive communication.

Before January 2021 admission, patient's PCP noted that he had unusual motor movements (sporadic flailing of arms and legs, motor tics, kicking) and was being uncooperative. Patient was tested for COVID-19 at multiple times in the past few months and all tests were negative. Patient also tested for drugs of abuse (as well as TCA, salicylate, acetaminophen), TSH, CBC, and CMP and all those labs were non-concerning. Patient was then direct admitted to inpatient hospital for Head MRI to rule out neuroanatomic abnormality being the cause of patient's symptoms.

Once admitted to inpatient floor, patient became aggressive with hospital staff and given IM 2mg Ativan and IM 5mg Zyprexa for sedation. Patient was aggressive multiple times during his 5 day inpatient stay and was given a total of 10mg IM Zyprexa, 4mg of IM Ativan, and one dose of 41mg IM Benadryl for sedation.

When patient wasn't sedated, he would repeatedly grunting and growling at residents and repeatedly say the word "cough" without using any non-verbal communication to further elaborate. Patient would also say " yes, no, and drink" Mom explained to the team that patient had ongoing cough, nasal congestion, and rhinorrhea for two months. Patient prior to admission had tried numerous medications including Benadryl, prednisone, Allegra, Prilosec, Augmentin and Vistaril to relieve symptoms. However, all of the medications were discontinued days prior to admission by PCP due to concern of the medications causing the patient's aggression and expressive communication regression. Patient's physical examination was significant for poor dentation, sandpaper-like rash on back. Orapharynx not evaluated due to patient refusal.

On day two of admission, patient's head MRI with and without contrast done. The MRI results were negative for neuroanatomical abnormality but did reveal mild left maxillary and right sphenoid sinusitis. Pediatric psychiatry was consulted and they recommended patient start Zyprexa 5 mg prn (maximum 30 mg per day) for agitation. In their evaluation the psych team raised concerns for metabolic vs encephalopathic cause of patient's acute onset of aggression and communication regression. There was also concern about patient's symptoms being due to delirium caused by the anticholinergic effect that the medications could be having on the patient. Psych team recommended avoidance of benzodiazepines, antihistamine/anticholinergics for the rest of hospitalization. Patient was given melatonin 5mg to help

with sleep which was effective. Before being discharged, patient was given 10 day course of doxycycline for the sinusitis and also recommended outpatient follow up with child adolescent psychiatry starting February 2021 and was started on multiple antipsychotic medications risperidone February 2021 and then switched to guanfacine March 2021. and given, a melatonin mix with magnesium and L-Theanine. Patient started on vitamin D and iron due to incidental finding of osteopenia and low normal iron level.

Patient's mother was concerned patient could be having seizures due to an isolated incident in January when the patient moving around on the bed and floor with no apparent purpose and his eyes were "fluttering really fast" for a few seconds. On March 2021 an EEG was done. Patient's EEG results revealed no abnormal neurological activity or spells. A long term EEG done in May 2021 also revealed no abnormal neurological activity.

In April 2021, pediatric geneticist was consulted for genetic assessment. Patient's genetic analysis revealed that he had 16p11.2p12.2 duplication syndrome. This syndrome is linked developmental delay, autistic and/or repetitive behavior, dysmorphic features, microcephaly, short stature and tapering fingers, seizures and kidney malformations. Patient's ultrasound revealed no kidney or gallbladder abnormalities. However, none of the symptoms linked to the genetic disorder explained patient's regressed communication**.**

June 2021, patient had neuropsychological evaluation done which revealed autism spectrum disorder, adjustment disorder with mixed anxiety and depressive mood, and behavioral mood disorder.

As of patient's August 2021 psychiatric visit; all ant-psychotic medications were discontinued due to multiple unpleasant side effects the patient experienced while on medications: abnormal gait (quick pace with swinging arm movements), floppy movements, and head bobbing. Patient's neuropsychological evaluation was reviewed and due to diagnosis of depressive mood led to starting him on 25mg of sertraline early August and at his follow up appointment weeks later, mom had noted that the patient seemed somewhat improved and was speaking more.

Discussion

Medications side effects and autism

Our patient was psychotropic drug naïve before onset of his symptoms of increased aggression and reduced expressive language. At the onset of URI symptoms, this patient was given anti-histamine medications (Benadryl and Vistaril) both of which have anti-cholinergic properties. There are some case reports of patients with autism having side effects of irritability, aggressive behavior, and poor sleep after being given anti-cholinergic medication[1,2]. After this patient was given the IM Ativan and IM Zyprexa his expressive language further declined, and his irritability increased. Outpatient follow up notes, reveal that patient continued to be aggressive but showed signs of improvement by March 2021. Although, he did not regain significant expressive communication skills, by March 2021 he started to adapt by communication with his family using text messaging.

In the case of this patient, the team believes that the patient most likely suffered from 1) side effects from introduction to the IM benadryl and/or the IM zyprexa second generation antipsychotic medication and/or 2) side effects from withdrawal from those medications since some of the medications he discontinued days prior to inpatient admission did have anticholinergic properties. Dr. Magda Campbell's 1996 article noted that although irritability can be the reason behind the decision to use the medication (such as it was with our patient), use of the medication can actually result in the side effect of irritability—the same symptom we were trying to treat[3].

Autism spectrum disorder, COVID 19, and Mental Health

Autism spectrum disorder is a neurodevelopmental disorder that affects patient's communication and behavior. Autism's etiology has always been due to both environmental and genetic factors[4]. In this study, the patient's DNA was analyzed to help determine if the diagnosis involved genetic abnormality, and if the genetic abnormality could account for patient's change in behavior. The analysis revealed that he had 16p11.2p12.2 duplication syndrome. The 16p11.2p12.2 duplication syndrome has been linked to developmental delay, autistic and/or repetitive behavior, dysmorphic features, microcephaly, short stature and tapering fingers, seizures and kidney malformations.[5]Same researchers found that people with this genetic disorder have an increased risk of schizophrenia, anxiety, and depression.

There has been little research that studies children with autism spectrum disorder and how adverse childhood events or adverse effects in general affect their mental health and well-being [5-6]. In Fuld et al's paper, 20% of people with autism spectrum disorders are diagnosed with anxiety, and 11% suffer from depressive disorders.[7-9]

This case study brings to light two clinically relevant topics. First, that children diagnosed with autism or other neurodevelopmental disorders can have different reactions to medications than their neurotypical counter parts and should be taken into -consideration when administering medications, especially ones with known involvement of the neurologic system. Second, this case study serves as a reminder that autistic children may display symptoms of depression that are different from their neurotypical counterparts and that a multidisciplinary approach to addressing depression with these patients is recommended.

References:

1. Madden K, Hussain K, Tasker RC. Anticholinergic medication burden in Pediatric PROLONGED critical illness. *Pediatric Critical Care Medicine*. 2018;19(10):917-924. doi:10.1097/pcc.0000000000001658

2. Reid SM, Westbury C, Guzys AT, Reddihough DS. Anticholinergic medications for Reducing drooling in children with developmental disability. *Developmental Medicine & Child Neurology*. 2019;62(3):346-353. doi:10.1111/dmcn.14350

3. CAMPBELL MAGDA, ARMENTEROS JORGEL, MALONE RICHARDP, ADAMS PHILLIPB, EISENBERG ZENAW, OVERALL JOHNE. Neuroleptic-Related dyskinesias in AUTISTIC Children: A Prospective, longitudinal study. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1997;36(6):835-843. doi:10.1097/00004583-199706000-00022

4. Masi A, DeMayo MM, Glozier N, Guastella AJ. An overview of autism spectrum disorder, heterogeneity and treatment options. *Neuroscience Bulletin*. 2017;33(2):183-193. doi:10.1007/s12264-017-0100-y

5. 16P11.2 duplication: MedlinePlus Genetics. MedlinePlus. https://medlineplus.gov/genetics/condition/16p112-duplication/. Published August 8, 2020. Accessed August 31, 2021.

6. Fuld S. Autism spectrum disorder: The impact of stressful and traumatic life events and implications for clinical practice. *Clinical Social Work Journal*. 2018;46(3):210-219. doi:10.1007/s10615-018-0649-6

7. Patel JA, Badiani AA, Nielsen FBH, et al. COVID-19 and autism: UNCERTAINTY, distress and feeling forgotten. *Public Health in Practice*. 2020;1:100034. doi:10.1016/j.puhip.2020.100034

8. Clarke KA. A review of language regression in autism spectrum disorder and the role of language theories: Towards explanation. *Autism & Developmental Language Impairments*. 2019;4:239694151988922. doi:10.1177/2396941519889227

9. Steffenburg H, Steffenburg S, Gillberg C, Billstedt E. Children with autism spectrum disorders and selective mutism. *Neuropsychiatric Disease and Treatment*. 2018;Volume 14:1163-1169. doi:10.2147/ndt.s154966