Common Behavioral Features of Autism, Fragile X Syndrome, and 22q11.2 Deletion Syndrome

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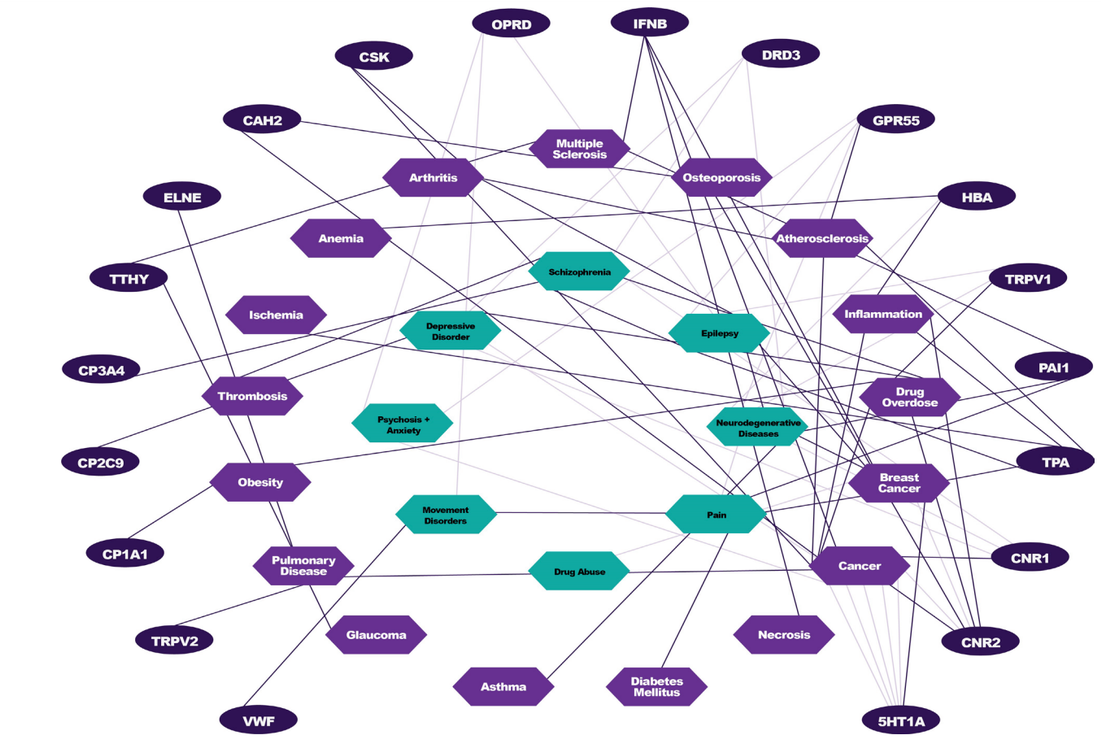
INTRODUCTION

- Autism Spectrum Disorder (ASD), Fragile X Syndrome (FXS), and 22q11.2 deletion syndrome (22qDS) are complex neurodevelopmental conditions with considerable overlap in neuropsychological and behavioral symptomatology[1]
  - ASD is characterized by problems in social communication and social interaction, as well as restricted and repetitive patterns of behavior, interests, or activities[2]
  - FXS is a rare genetic condition caused by CGG repeat expansion in the FMR1 (fragile X mental retardation 1) gene located on the X chromosome; behavioral symptoms may include social withdrawal, anxiety, avoidance of eye contact, sensory hypersensitivity, echolalia, and hand flapping[3]
  - 22qDS is one of the most common microdeletion syndromes; [4] and often involves behavioral symptoms of social limitations and difficulty in maintaining relationships with peers
- The socio-behavioral deficits seen in ASD and FXS have been attributed to dysregulation of the endocannabinoid system,[5] which is comprised of[6-9]:
  - Two G-protein-coupled receptors
    - Cannabinoid receptor type 1 (CB_1) – located primarily in the CNS
    - Cannabinoid receptor type 2 (CB_2) – located in multiple systems throughout the body
  - Endogenous cannabis-like ligands (endocannabinoids) that bind to CB1 receptors and modulate synaptic transmission throughout the CNS; the two best described are:
    - Anandamide (AEA)
    - 2-arachidonoylglycerol (2-AG)
- Cannabidiol (CBD) is a non-euphoric cannabinoid
- CBD has low affinity for CB_1 and CB_2 receptors, yet the vast chemogenomic targets suggest a broad polypharmacology for CBD producing a wide spectrum of physiological responses (Figure 1), including antagonism of GPR55 (a G-protein coupled receptor located in the caudate nucleus and putamen); partial agonism of 5-HT_{1A} receptors; promotion of intracellular calcium release and peroxisome proliferator-activated receptor-gamma agonism; and allosteric modulation of mu- and delta-opioid receptors[10,11]

Figure 1. CBD Target-Disease Network



Dark purple oval nodes represent the targets for CBD identified through target mapping. Lighter purple hexagonal and green hexagonal nodes represent different diseases. Green nodes are neurological-related diseases and are placed in the center for emphasis. Targets are connected with diseases with edges in the corresponding color. Legend for abbreviated protein targets: VMF-von Willebrand factor; TRPV2-Transient receptor potential cation channel subfamily V member 2; CP1A1-Cytochrome P450 1A1; CP2C9-Cytochrome P450 2C9; CP3A4-Cytochrome P450 3A4; TTHY-Transthyretin; ELNE-Leukocyte elastase; CAH2-Carbonic anhydrase 2; CSK-Tyrosine-protein kinase CSK; OPRD-Delta-type opioid receptor; IFNB-Interferon beta; DRD3-Dopamine receptor 3; GPR55-G-protein coupled receptor 55; HBA-Hemoglobin subunit alpha beta; TRPV1-Transient receptor potential cation channel subfamily V member 1; PAI1-Plasminogen activator inhibitor 1; TPA-Tissue-type plasminogen activator; CNR1-Cannabinoid receptor 1; CNR2-Cannabinoid receptor 2; 5HT1A-5-Hydroxytryptamine receptor 1A[11] (Figure adapted by permission from SpringerNature)

OBJECTIVE

- The objective of this study was to conduct a retrospective literature review on patients with ASD, FXS, and 22qDS to determine the nature and extent of symptomatic overlap in these conditions and to suggest a possible role for CBD in the management of these shared symptoms based on insights from our open-label, 12-week study evaluating the safety, tolerability and initial efficacy of transdermal CBD for the treatment of behavioral and emotional symptoms associated with child/adolescent FXS[12]

METHODS

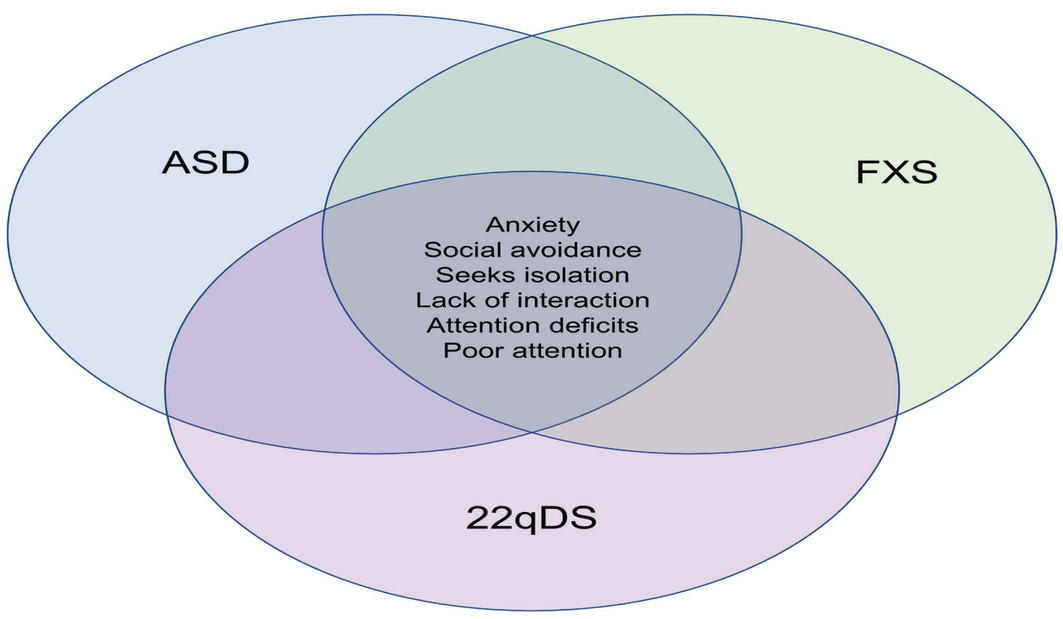
- A search of the PubMed database was conducted using the terms 'behavior," "behavioral symptoms," "autism spectrum disorder," "ASD," "Fragile X Syndrome," "FXS," "22q11.2 deletion syndrome," "parents," "caregivers," and "CBD and treatment of anxiety" with no restriction on date or publication type
- Records were analyzed for relevance

RESULTS

ALL CONDITIONS

- The most common behavioral manifestations across all conditions are anxiety-related; such as social avoidance, irritability, attention deficits, stereotypy, poor communication, and social unresponsiveness (Figure 2)

Figure 2. Common Behavioral Features of ASD, FXS, and 22qDS



RESULTS *cont.*

ASD

- Anxiety-related symptoms are common in patients with ASD, with up to 84% of children experiencing some degree of debilitating anxiety[13]; rates of physician-diagnosed anxiety disorders range from 42-55%[14,15] and may include simple phobias, generalized anxiety disorder, separation anxiety disorder, obsessive-compulsive disorder, and social phobias
- Comorbid anxiety disorders can be broad-ranging and associated with behaviors such as aggression/irritability and isolation from same-age peers[16]
- Inattention and hyperactivity are often present in Attention Deficit-Hyperactivity Disorder and ASD, and they are common to their respective diagnostic criteria
- Children with ASD who have severe intellectual disability ([ID] IQ<40) showed higher levels of psychiatric symptoms (anxiety, mood, sleep, organic syndromes, and stereotypies/tics) than those with ID but no ASD[17]

FXS

- In FXS, severe cognitive and social impairments are more common in males than in females[18]
- FXS usually has profound effects on the life of patients (comorbid conditions, social impairment) as well as their caregivers and families (mental health, absence from work/school)[19]
- Anxiety and social avoidance are considered core features of FXS[20-22]
  - Social avoidance has been defined as a behavioral response to anxiety that arises from fear of social interaction; thus, anxiety can be thought of as a foundational precipitant to social avoidance
  - Social avoidance encompasses behaviors that may include seeking isolation (eg, stay in their room to avoid others), lack of interaction, social escape (eg, face-hiding, leaning away), and gaze avoidance that distance the individual from his/her social counterparts
- Variation in FMR1 protein expression has been linked to avoidant behaviors among females with the disorder[23]
- In a study that used interviews of parents/caregivers (n=97) of boys and girls with FXS to determine the prevalence of anxiety (based on DSM-IV criteria), 82.5% of participants had at least 1 anxiety disorder, irrespective of sex, age, presence of autism, or IQ, with the most common diagnoses being[20] specific phobia (59.6%); social phobia (58.3%); selective mutism (25.3%); generalized anxiety disorder (23.7%), and obsessive-compulsive disorder (23.7%)
- The presence of ID in patients with FXS impairs their ability to self-report symptoms of worry and fear, increasing reliance on caregiver observations of outward behavioral manifestations of anxiety characteristics, which may include any of the following[22,24,25]: social avoidance; nervous behavior during social situations; shyness; refusal of activities with social demands; poor understanding of social cues from inattention to faces, socioemotional processing, social skills during interpersonal interactions; fearfulness; social escape behaviors

22qDS

- The most common behavioral/psychiatric diagnoses in children with 22qDS are ADHD, ASD, and anxiety[26-28]
- A large-scale, collaborative study (>1400 participants aged 6-68 yrs) reported ADHD in 37% of 6-12 year-olds and in nearly 24% of 13-17 year-olds; ASD peaked in 13-17 year-olds (25.54%); anxiety disorders were more prevalent than mood disorders at all ages, but especially in children and adolescents with at least 33% of 6-17 year-olds reporting an anxiety disorder
- Up to one-third of patients with 22qDS will develop schizophrenia or schizo-affective disorder by late adolescent and early adulthood,[27] and over 40% of patients have been reported to a schizophrenic spectrum disorder after 25 years of age[28]
- Although these diagnoses are reported in individuals with 22qDS, the diagnosis of ASD is particularly controversial in this population and may be related to poor clinical understanding of the typical behavioral phenotype
- The emergence of social deficits during adolescence can represent a major source of disability in some individuals with 22qDS; cross-sectional studies show that children with 22qDS[26,27,29-32]:
  - Are withdrawn and shy
  - Have social impairments which may be less of a concern to the individual

ROLE OF CBD

- CBD has diverse pharmacologic effects
- Based on our findings from the open-label study in children/adolescents with FXS[12] and a retrospective literature review, CBD may improve multiple symptoms experienced by patients with ASD, FXS, and 22qDS, and it is generally well tolerated in children and adults[33,34]
- Results from receptor pharmacology studies investigating the possible role of CBD in the treatment of behavioral symptoms associated with ASD, FXS, and 22qDS CBD suggest:
  - A role for the endocannabinoid system in regulating behavioral symptoms
  - The pharmacology of CBD is broad, continues to be defined, and may prove to be beneficial in addressing important symptoms[11]
- Findings from the first crossover trial testing the effects of CBD on symptoms of social anxiety in adults with social phobia found significant and clinically meaningful reductions in both physiological and cognitive indicators of anxiety,[35] which may translate to therapeutic effects in patients with ASD, FXS, and 22qDS
- A recent case series provided initial evidence that CBD may lead to broad improvement in childhood FXS symptomatology, including symptoms of anxiety and social avoidance[36]
- An open-label, 12-week study evaluated the safety, tolerability and initial efficacy of transdermal CBD for the treatment of behavioral and emotional symptoms associated with child/adolescent FXS and found both positive effects on the emotional and behavioral symptoms of FXS, including for many, an increase in social confidence which may be translatable to the other defined populations[12]

Conclusions

- Patients with ASD, FXS, and 22qDS share a constellation of socio-behavioral symptoms that includes anxiety, leading to seeking isolation behavior (social avoidance), irritability, attention deficits, and poor communication
- Preliminary evidence shows that CBD improves social anxiety and associated behavioral manifestations suggesting that CBD may prove to be effective in managing the spectrum of behavioral symptoms associated with these conditions

References

1. *Front Neurosci.* 2016;10:316; 2. *Am J Hum Genet.* 2013;93(5):825-839; 3. *Front Pediatr.* 2018;6:102; 4. *Nat Rev Dis Primers.* 2015;1:15071; 5. *Mol Autism.* 2018;9:18; 6. *Neuro Endocrinol Lett.* 2009;30(2):153-179; 7. *Pharmacol Rev.* 2006;58(3):389-462; 8. *Neuron.* 2012;76(1):70-81; 9. *Curr Opin Neurobiol.* 2014;29:1-8; 10. *Crit Rev Eukaryot Gene Expr.* 2018;28(1):73-86; 11. *Acta Pharmacologica Sinica.* 2019;40(3):374-386; 12. *J Neurodev Disord.* 2019;11(1):16; 13. *Clin Psychol Rev.* 2009;29(3):216-229; 14. *J Autism Dev Disord.* 2007;37(5):877-886; 15. *J Am Acad Child Adolesc Psychiatry.* 2008;47(8):921-929; 16. *Pediatrics.* 2016;137 Suppl 2:S115-123; 17. *J Autism Dev Disord.* 2004;34(2):151-161; 18. *Clin Neuropsychol.* 2016;30(6):815-833; 19. *BMC Psychiatry.* 2016;16(1):318; 20. *J Neurodev Disord.* 2011;3(1):57-67; 21. *J Autism Dev Disord.* 2012;42(7):1377-1392; 22. *J Autism Dev Disord.* 2017;47(12):3741-3755; 23. *Pediatrics.* 2001;108(5):E88; 24. *Am J Ment Retard.* 1988;92(5):436-446; 25. *J Autism Dev Disord.* 2006;36(7):935-947; 26. *J Am Acad Child Adolesc Psychiatry.* 2006;45(5):596-603; 27. *Res Dev Disabil.* 2009;30(4):763-773; 28. *Am J Psychiatry.* 2014;171:627–39; 29. *Am J Med Genet C Semin Med Genet.* 2015;169(2):172-181; 30. *Am J Med Genet.* 1999;85(2):127-133; 31. *Dev Med Child Neurol.* 2002;44(1):44-50; 32. *J Paediatr Child Health.* 2018;54:311-315; 33. *Lancet Neurol.* 2016;15(3):270-278; 34. *Front Pharmacol.* 2016;7:422; 35. *Neuropsychopharmacology.* 2011;36(6):1219-1226; 36. *Cannabis Cannabinoid Res.* 2019;4(1):3-9.

HHH has received honoraria and research support from Zynerba Pharmaceuticals; DG and TS are employees of Zynerba Pharmaceuticals.

Presented at the 22nd SSBP International Research Symposium, September 4-6, 2019, Birmingham, UK