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Metformin as targeted treatment in fragile X syndrome

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Abstract

Background: Individuals with fragile X syndrome (FXS) have both behavioral and medical comorbidities and the latter include obesity in approximately 30% and the Prader-Willi Phenotype (PWP) characterized by severe hyperphagia and morbid obesity in less than 10%. Metformin is a drug used in individuals with type 2 diabetes, obesity or impaired glucose tolerance and it has a strong safety profile in children and adults. Recently published studies in the Drosophila model and the knock out mouse model of FXS treated with metformin demonstrate the rescue of multiple phenotypes of FXS.

Materials and Methods: We present 7 cases of individuals with FXS who have been treated with metformin clinically. One case with type 2 diabetes, 3 cases with the PWP, 2 adults with obesity and/or behavioral problems and, a young child with FXS. These individuals were clinically treated with metformin and monitored for behavioral changes with the Aberrant Behavior Checklist and metabolic changes with a fasting glucose and HgbA1c.

Results: We found consistent improvements in irritability, social responsiveness, hyperactivity, and social avoidance, in addition to comments from the family regarding improvements in language and conversational skills. No significant side-effects were noted and most patients with obesity lost weight.

Conclusion: We recommend a controlled trial of metformin in those with FXS. Metformin appears to be an effective treatment of obesity including those with the PWP in FXS. Our study

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Conflict of interest

The other authors declare no conflicts of interest.

suggests that metformin may also be a targeted treatment for improving behavior and language in children and adults with FXS.

Keywords

fragile X syndrome; metformin; obesity; Prader-Willi-phenotype; targeted treatments

1 | INTRODUCTION

Fragile X syndrome (FXS) remains the most common inherited cause of intellectual disability (ID) and autism spectrum disorder (ASD). It is the result of CGG expansion mutation of greater than 200 repeats on the Fragile X Mental Retardation 1 gene (*FMR1*) at Xq27.3. This expansion leads to hypermethylation and transcriptional silencing of the gene and consequently the reduction in the gene's product, *FMR1* protein (FMRP). FMRP is important for neurologic function and cognitive development; hence, its absence results in varying levels of ID.[1,2]

Comorbid conditions common in FXS include behavioral problems such as ADHD, anxiety, ASD, self-injurious behaviors and aggression.[3,4] Medical comorbidities include recurrent otitis media, gastrointestinal reflux, seizures, strabismus, sleep problems, obesity and growth disorders.[1,5] Growth findings suggest that patients with FXS have a higher risk for being overweight and diminished height in adulthood.[1,6]

Obesity is a common problem seen in FXS. Male children less than 20 years old had a higher prevalence rate of obesity (31%) when compared to matched control children (18%).[6] The behavioral phenotype of FXS can include overfilling the mouth and overeating leading to an excess caloric intake compared to energy expenditure.[7]

The Prader-Willi phenotype (PWP) of FXS[8] describes a subgroup of patients that develop severe hyperphagia, obesity, hypogonadism or delayed puberty. Unlike Prader-Willi syndrome (PWS), this phenotype does not have a deletion of 15q11-q13 or maternal uniparental disomy.[2,6] Studies have shown that FMRP binds to cytoplasmic interacting *FMR1* protein (*CYFIP1*), a protein that affects synaptic remodeling. *CYFIP1* is localized to 15q11–13, a critical region in PWS. CYFIP1 expression levels are lower in those with the PWP compared to FXS without the PWP.[8] Although the PWP is seen in less than 10% of those with FXS, obesity and overeating can be part of the FXS behavioral phenotype. In addition, the frequent use of atypical antipsychotics such as risperidone or aripiprazole can also exacerbate weight gain in FXS.[9]

The Food and Drug Administration (FDA) approved metformin for its effects in lowering blood glucose levels in patients with non-insulin dependent, type 2 diabetes. Some studies report minimal to moderate decrease in weight in groups of patients with insulin resistance.[10] It has been shown to be effective and safe in the treatment of 10 to 16 year old children with type 2 diabetes with doses up to 1000 mg bid.[11] It has also been utilized for the treatment of obesity in children and adults, without type 2 diabetes, with a short-term reduction in BMI by 1.42 kg/m^2.[10,12] Recently metformin has been shown efficacious in the treatment of escalating BMIs in children with ASD between the ages of 6 to 17 years

compared to placebo.[13] It likewise has been effective in glycemic control in patients who are non-obese.[14] There is low risk of hypoglycemic episodes with metformin because its mechanism of action does not directly stimulate insulin.[15,16] Metformin is also currently studied for its effects on modulation of receptors for cytokines, insulin, IGF-1 and adiponectin pathways associated with aging, and when modulated by metformin there is improvement in longevity.[17] A recent study demonstrated that metformin even enhanced longevity to a greater degree in those with type 2 diabetes compared to those who were aged matched without diabetes.[18]

Metformin is also considered a targeted treatment for FXS after animal studies have demonstrated efficacy in improving the phenotype of FXS.[19,20] The fly, *Drosophila*, has a homologue of *FMR1* called the *dfmr1*. The *Drosophila* FXS model has shown that drosophila insulin-like peptide 2 (Dilp2) in insulin-producing cells results in elevated insulin signaling via the PI3K/Akt/mTOR pathway. The dysregulated insulin signaling in this fly model of FXS leads to defects in circadian rhythm and short and long-term memory deficits. Use of metformin in this study had been able to rescue and restore memory deficits.[2,19] Further studies performed in the Sonenberg lab[21] showed that adult treatment in FXS Knock out (KO) mouse rescued multiple phenotypes, including social novelty, grooming, and dendritic spine morphology in the hippocampus.[21] The mechanism for this effect is by normalizing ERK signaling, EIF4E phosphorylation and lowering expression of MMP9 to normal.[21]

Metformin decreases protein synthesis and insulin signaling (IS) via the AMPK/Akt/mTOR pathway, it also inhibits the lipid and sterol biosynthetic pathways.[22] Looking at the potential signaling pathways, metformin in FXS may decrease insulin signaling and restore the circadian output pathway and in turn have positive effects on memory and sleep.[2]

2 | MATERIALS AND METHODS

Here we report several cases of patients with FXS that have been treated clinically with metformin. All patients have signed an informed consent for developmental and molecular testing approved by the institutional IRB and all families have consented to have their clinical response to metformin published.

Cases were seen as part of the Fragile X Treatment and Research Center at the MIND Institute UCDMC for management of FXS. Each case is described with their corresponding medical and behavioral comorbidities in addition to laboratory studies pre and post treatment. Patients have been treated for at least 6 months. These cases represent the first cases treated with metformin in whom a behavioral questionnaire and laboratory studies were obtained. All but case 7 were prescribed metformin for obesity or type 2 diabetes management and were additionally observed for behavior and metabolic improvements.

3 | RESULTS

3.1 | Case 1—Overweight with impaired glucose tolerance

A 19-year-old male diagnosed with FXS and ASD at age 5 has an ongoing history of hyperphagia and lack of satiety after meals. He has not been known to hoard food nor was it necessary to lock cupboards. He is easily redirected and follows behavioral plans for meal times. He also exhibits behavioral issues of aggression with adolescence, severe skin picking and scratching, hand biting, poor eye contact, tactile defensiveness, hyperactivity, perseveration and ADHD. He has been prescribed several medications to treat these symptoms in the past including methylphenidate, amphetamine, lamotrigine, risperidone, divalproex sodium, sertraline, atomoxetine, ziprasidone, quetiapine, fluvoxamine and minocycline. At present, he is on minocycline 200 mg qd, divalproex sodium 1000 mg tid, guanfacine 2 mg bid, and fluvoxamine ER 100 mg qd. As he has gotten older, aggression of adolescence has decreased, although over the last few weeks he had become more agitated and aggressive. He continues to have hyperphagia and lacks satiation after meals.

On physical examination, he weighed 133.63 kg, much higher than 95th percentile for his age; BMI is 40.6 kg/m^2. He has typical features of FXS including macroorchidism. He was started on metformin 500 mg bid, after he was diagnosed with type 2 diabetes with fasting glucose of 175mg/dL with significant improvements in his hyperphagia, irritability, aggression and in the first month he lost 8 lbs; follow-up labs after 3 months of treatment with metformin reported fasting glucose 132 mg/dL his dose was adjusted by his endocrinologist to 1000 mg in the morning and 500 mg in the evening and latter increased to 1000 mg bid. With this increase he manifested mild abdominal pain for a few days without any additional side effects. He has experienced significant improvement in his communication and behavior. He is no longer focused on food like he was for many years; he now enjoys outdoor activities and has lost approximately 13.6 kg (30 lbs) over the last 5 months since starting metformin. His self-esteem has also improved considerably. Baseline and follow-up labs after 6 months are in Table 1.

3.2 | Case 2—FXS/PWP

Case 2 is a 13-year-old boy with FXS who was first seen at age 5 after his diagnosis of FXS demonstrating a full mutation. His mother had a normal pregnancy and vaginal delivery and his birth weight was 10 pounds, 2 ounces. He was breast fed for 14 months, but his development was delayed. He sat at 6 months, crawled at 8 months, he walked at 17 months, said a few words at 2 years old and phrases at 5 years old. At 10 years his Leiter IQ was 44 and his ADOS testing demonstrated a total score of 25 which was well into the ASD range. He received early intervention since age 2.5 years and subsequent ABA therapy, but behavior problems continued through his childhood. His behavior demonstrated significant aggression with kicking and hitting both at school and at home, particularly with his mother. He was severely hyperactive and impulsive with over-reactivity to stimuli. He was treated with a low dose of aripiprazole because of his severe aggression, 1 mg at bedtime. Subsequently additional medications were added including guanfacine, long-acting methylphenidate, minocycline, lovastatin and eventually lithium in an effort to curve his aggression with variable results.

After age 6 he developed hyperphagia and a lack of satiation after meals and his weight increased remarkably with a BMI peak at 34.4 kg/m^2 at 10 years. The family tried many behavioral interventions to control his aggression but to no avail and mother became more depressed as he became more aggressive toward her. If he was not given food when he wanted it he became more aggressive and finally at age 10 he was placed into a residential group home with a therapeutic environment to control his eating and aggression. His weight decreased in this placement and BMI decreased to 28.8 kg/m^2. His behavior improved but intermittent aggression persisted and at age 12 he was started on metformin beginning at 500 mg at dinnertime and subsequently increased to bid. His examination at age 12 demonstrated a small penis buried in his fat and testicles at 10 mL bilaterally. His face was round and obese with striae across his abdomen and prominent cupped ears. He met criteria for the PWP of FXS.

Metformin has been very helpful for him over the last year according to his mother and his care center. Although he initially had loose stools they subsequently normalized after a month and he had tolerated the 500 mg bid without side effects. He is calmer and patient, more responsive to rewards and able to work longer with less agitation and less aggression. He follows directions far better. He has more understanding when things are explained to him and he negotiates more with teachers. In the past before the metformin he was constantly asking for food and now he does not.

3.3 | Case 3—FXS/PWP

A 19-year-old boy diagnosed with FXS, ADHD, specific phobias and ASD. He was diagnosed with FXS at 3 years. He has episodes of behavioral outbursts that are described as impulsive and not aggressive. He has a history of persistent hyperphagia exhibited by constantly asking for food and preferring high caloric food items, and avoiding exercise. He had delayed puberty which did not begin until he was 17 years old and morbid obesity seen with a BMI of 44 kg/m^2. In addition, he has also developed hypertension and low vitamin D level.

On physical examination, his blood pressure was 142/87, Tanner stage IV. Behavioral concerns include enuresis, binge eating causing him to vomit almost every day, and skin picking. His medications include minocycline 100 mg qd, sertraline 50 mg qd and aripiprazole 2.5 mg qd. Because of his morbid obesity this boy was started on metformin 500 mg bid. He has been advised to have nutrition counsel regarding meals. He experienced diarrhea in the mornings after his AM dose so the family lowered his dose to 500 mg at dinner which was well tolerated. After 6 months of treatment his weight did not change from baseline of 299 lbs. His appetite was slightly lowered but he experienced significant improvements in behavior including cessation of his head-banging and other self-injurious behavior, decrease in tantrums and improvement in his communication ability. His dose was increased to 750 mg at dinner and if tolerated will increase to 1000 mg after 2 weeks. See Tables 1 and 2 for improvements in ABC and laboratory measures.

3.4 | Case 4—Overweight

A 60-year-old female adult diagnosed with FXS and mild ID, who has been seen regularly since he was 51 years. She is currently in a group home and undergoes a daily living skills development program. She has a history of morbid obesity and had undergone gastric bypass when she was 45 years old with minimal improvement in her obesity. There are concerns for her overeating, favoring and enjoying snacks and peanut butter. She has not been known to hoard food, and is mostly compliant when placed on diet restrictions. At moments that she does overeat, she presents with a bulimic-like picture and would induce vomiting. She also shows repetitive behavior and her caregivers have concerns for her memory deficits, agitation and anxiety. Other medical concerns include hypertension and gastric esophageal reflux. At present, she is on amlodipine 10 mg qd, escitalopram 15 mg qd, triamterene 12.5 mg qd, Vitamin D and calcium supplements, Vitamin B12 injections monthly, lovastatin 20 mg qd, minocycline 200 mg qd, loratadine 10 mg qd and memantine (Namenda XR) 29 mg qd. On physical examination, her weight is 97.66 kg (215 lbs) and height is 1.641 m. Her BMI is 36.27 kg/m^2.

She was started on metformin 500 mg at dinner and then increased to bid after a week. She has not had side effects and her eating habits have changed such that she is not over-eating and she is not snacking between meals. After 8 months of treatment with metformin she has lost 19 kg (41.3 lbs) and has improved her irritability and social responsiveness (see Tables 1 and 2).

3.5 | Case 5—Overweight

Case 5 is a 31-year-old man with FXS who has been followed at the MIND since age 16 when he was also diagnosed with ASD and his full scale IQ was 54 on the WISC III. He has had problems with anxiety and tantrums and he was treated with citalopram 20 mg, which was helpful for his anxiety and subsequently aripiprazole which was helpful for his aggressive behavior and intermittent tics. However, he gradually gained weight so the aripiprazole was tapered and discontinued at age 29. His father passed away at age 28 and he experienced significant grief but he had difficulty in verbalizing his sadness.

He was seen at age 30 and he was obese with a weight of 110.5 kg (243 lbs) and BMI of 30.7 kg/m^2. His glucose was 104 and his HgbA1c was 5.1. His examination was consistent with FXS including macroorchidism. Metformin was initiated to treat his obesity and behavior at 500 mg qd, increasing to 500 mg bid after 1 week.

He had an excellent response to metformin over the subsequent 6 months. His appetite decreased and he lost 14 pounds over 6 months and he was very proud of this weight loss. He has better self-initiative and he will carry out chores such as cleaning his room or cleaning the house without excessive urging or reminders. He helps his mom with gardening and is able to coordinate the rake better. Regarding his language he talks much more on metformin. He has a lot of trivia knowledge such as why the titanic sank and now he is asking more inquisitive questions such as “where is Halifax?” Mother is able to have a discussion with him even about emotional issues. He is able to talk about his grief and to relate his father’s demise to his excessive smoking and drinking problems. He seems to be

putting together concepts better and having back-and-forth conversations. His speech and language therapist has noted more language. He has not had any diarrhea nor loose stools with metformin. He continues to have a nose rubbing tic which was problematic after the aripiprazole was discontinued (see Tables 1 and 2).

3.6 | Case 6—FXS/PWP

Case 6 was originally seen at age 10 years 4 months and his history included hypotonia in infancy with a poor suck after birth and oral motor coordination problems. Although he was thin in early childhood he developed a voracious appetite between 6 to 8 years of age and a lack of satiation after meals. He subsequently gained weight and was 222 lbs at age 15 although dieting helped to lower his weight somewhat. He had delayed puberty, at age 15.

On examination at age 16, his BP was 112/68, head circumference was 59.5 cm, height 176.2 cm and weight 94.7 kg. He had severe anxiety with intermittent aggression toward his father during the examination because of fear of the genital exam. He was tanner stage IV, his phallus was small (4 cm) and his testicular volume was 20 mL which is small for FXS showing no macroorchidism. The rest of his examination was consistent with FXS including soft skin and flat feet along with poor eye contact. His DNA testing demonstrated a full mutation with methylation mosaicism. His cognitive testing demonstrated a full scale IQ of 50 and the ADOS module 3 documented ASD. He was continued on citalopram 40 mg qd and minocycline 100 mg bid.

He participated in the basimglurant trial and did well with improvement in his language at age 20. He also participated in the mavoglurant trial and also did well in this trial but when discontinued from the trial his behavior worsened. He also experienced a traumatic episode when he became aggressive to family members and to the physician staff at a hospital where he was evaluated and he was tazered by the police and he required sedation and then intubation at the hospital because of his aggression. This event led to severe deterioration of his behavior and a dramatic increase in his anxiety, aversion to people, intermittent aggression and headaches. He gradually improved with the addition of other medications at different times including risperidone 1 mg bid, alprazolam 0.5 mg bid, guanfacine 2 mg bid, buspirone 10 mg tid, lithium 300 mg bid and an increase in his citalopram to 60 mg qd. The minocycline was discontinued because of the headaches but they continued until acetazolamide was added to his regimen. He began exercising regularly and he received intensive OT therapy and counseling and he continued to improve behaviorally although his weight remained high.

At age 24 he was started on metformin at 500 mg bid for his obesity and behavior difficulties. He had a dramatic improvement in his behavior on metformin and he has not had an outburst since he started treatment approximately 9 months ago. He also seems happier, more active and his family reports improvement in his language. He is able to carry out a two way conversation and he became more outgoing socially with less anxiety. He has not experienced any change in appetite nor weight loss, he currently weighs 300 pounds, similar to baseline; however, he now eats without gorging himself. The metformin dose was increased to 1000 mg bid to help him improve his weight loss after the initial 9 months of treatment.

3.7 | Case 7.—Child

This 4 year and 6-month-old boy with FXS was diagnosed at 14 months when *FMR1* DNA testing was carried out because of motor delays. He was born after a normal pregnancy and his birth weight was 7 lbs 6 oz. He had problems latching to the breast and he was generally hypotonic. He had motor delays and began sitting independently at 10.5 months, and walking independently at 22 months. His language was delayed and at a chronological age of 16 months his language age was 9 months for both expressive and receptive language on the Mullen. He had staring spells but his EEG did not show spike wave discharges. At 2 years, there was no language and his parents self-treated him with cannabinoid (CBD) tincture at approximately 40 mg qd and saw a decrease in staring spells. They felt that he began to verbalize more and his anxiety improved. They began low-dose sertraline at 2 years 3 months at 2 mg/day and subsequently 4 mg/day and his verbalizations improved with speaking in words. Minocycline was started at 25 mg/day before age 3 years and parents saw improvement and he was putting 2 words together by age 3 years 3 months. He was also receiving OT and Speech and Language therapy twice a week in addition to preschool and Early Start Denver Model in home at 9 hours a week.

At age 4 years 6 months his BP was 108/76, height was 97 cm (9%ile) and weight was 14.8 kg (47%ile). His physical features were typical for FXS including a broad forehead, prominent ears and an intermittent right exotropia, high palate, hyperextensible finger joints and flat feet.

After hearing about the KO mouse research at the National Fragile X Foundation (NFXF) conference the mother was interested in trying metformin for her son. After 6 months of a dose of 50 mg, the family felt he has fewer outbursts or tantrums, better attention, less hyperactivity and improvements in his language. Developmental testing after 4 months of treatment at 4.5 years showed expressive language at the 31 month age equivalent. There have been no noted side effects, and labs after 9 months of treatment are in Table 1. His scores on the Aberrant Behavior Checklist (ABC) are seen in Table 2.

4 | DISCUSSION

Metformin has not been previously used specifically for treatment of FXS.[9] However, the recent reports of improvement in the phenotype of FXS in animal models[19,21] have generated new attention to metformin and the conditions that it treats including obesity and type 2 diabetes. Diabetes is very rare in FXS presumably because of upregulation of the insulin receptor as documented in the *Drosophila* model of FXS.[19] Here we describe a rare case of type 2 diabetes in Case 1 who improved significantly in his metabolic parameters including lowering of his elevated HgbA1c in addition to improvement in his fasting glucose with metformin treatment. Most importantly, however, he has improvement in his behavior and language suggesting a cognitive benefit from metformin. Other cases described here include those with obesity with and without the PWP and metformin is indicated clinically in such cases. The PWP of FXS is not uncommon and these patients can benefit from metformin because of their significant obesity and eating behavior which can improve on metformin as is seen in Cases 2 and 3. Those with significant obesity even without the PWP can also benefit from metformin even at an older age as demonstrated in Case 4.

An important element in all of these cases is a general improvement in behavior as documented in the ABC seen in Table 2. There are consistent improvements (lower scores) in irritability, social unresponsiveness, hyperactivity, and social avoidance on the ABC in addition to comments from the family regarding improvements in language and conversational skills. This very preliminary data suggests that metformin may also be a targeted treatment for improving behavior, language and cognition in FXS. In case 7 there was no indication of obesity or the PWP and the child was under 5 years. The mother has seen significant benefits in behavior and language suggesting that further study of this treatment as a targeted treatment to enhance cognition is indicated even in young patients with FXS. However, these cases are not a controlled trial of metformin and a placebo effect is very likely since the families continually seek treatments of behavioral difficulties associated with FXS. Only a randomized, double-blind-controlled trial will assess the efficacy of metformin for behavior and cognition. Controlled trials have been carried out to document the efficacy in treating obesity[12] and in treating children with ASD who have increasing BMIs on atypical antipsychotics[13] so we recommend metformin for treatment of obesity including those with the PWP in FXS as seen in the cases reported here.

Metformin demonstrated improvement in behavior and cognition in both the Drosophila and mouse model of FXS.[19,21] The neurochemical changes that occur with metformin include improvement in the insulin receptor and down regulation of the mTOR/MEK/ERK pathway which is significantly up-regulated in FXS. It is likely that treatment in early childhood would be more likely to have an effect on cognition and behavior than treatment in adulthood. Such a benefit has been seen in the use of low-dose sertraline in young children aged 2 to 6 with FXS.[23] Only 1 case described here included the use of metformin in a child under 5 and further studies of children with FXS are needed before metformin can be recommended in those who are not obese.

Although lifestyle change is the most effective means of weight loss in obese adults, this has not been very effective in those with FXS because of cognitive and behavioral difficulties. Although a meta-analysis of behavioral interventions in obese adolescents reported a significant effect size at 6 months this did not include individuals with FXS or other neurodevelopmental problems.[12] It is particularly difficult to institute this behavioral change and dietary modification in patients with neuropsychiatric disorders.[10] Sometimes with holding of food can lead to an increase in aggression particularly in patients who are obsessed with food as in many with FXS. Therefore metformin may be a helpful treatment because it could target both obesity and behavior in FXS.

Although metformin is an obvious treatment for those patients with FXS with obesity, the PWP of FXS and those with type 2 diabetes, the patients reported here suggest that there may also be benefits to language, cognition and, behavior problems such as overeating, irritability, social avoidance and aggression. Because of the dual effects on metabolism in those with obesity in addition to the cognitive and behavioral effects, we recommend a controlled trial of metformin in children and adults with FXS to better understand the safety and efficacy in both behavior and cognition.

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TABLE 1

Summary of cases

Case/Age/Sex/DNA	Diagnosis	Primary concern	Physical features	Laboratory findings	Follow-up lab	Metformin dose	Other medications
Case 1. 18-year-old male	FXS ASD ADHD Obesity Type2 diabetes	Aggression Picking/scratching Hyperactivity Perseveration Hyperphagia	Height: 181.4 cm (P76th) Weight: 133.63 kg ($P > 95$th) BMI: 40.6 kg/m^2 Obese Prominent ears Acanthosis nigricans Tanner stage V Normal phallus Macroorchidism Hyperextendible Unable to tandem walk	Normal IGF-1 ANA negative Normal CBC HgbA1c 7.7% Glucose 175 mg/d L Cholesterol 184 mg/d L Triglycerides 436 mg/dL	Normal CBC HgbA1c 6.0% Glucose 109 mg/dL Cholesterol 144 mg/dL Triglycerides 372 mg/dL	Starting dose 500 mg bid, current dose 1000 mg bid	Divalproex sodium 1000 mg bid Guanfacine 2 mg bid Fluvoxamine ER 100 mg Minocycline 200 mg
Case 2. 13-year-old male	FXS/PWP ASD	Anxiety Aggression Hyperphagia	Blood pressure: 108/62 Height: 156.7 (P53th) Weight: 70.7 kg ($P > 95^{th}$) BMI: 28.8 kg/m^2 History of obesity BMI 34.4 Prominent ears High palate Tanner stage 1 Small phallus	HgbA1c 4.7% Glucose 78 mg/dL ANA negative Alk Phos 253 Triglycerides 213 mg/dL Cholesterol 133 mg/dL	HgbA1c 4.5% Glucose 85 mg/d LANA negative Alk phos 180 Triglycerides 118 mg/dL Cholesterol 87 mg/dL	500 mg bid	Minocycline 100 mg Aripiprazole 2 mg bid
Case 3. 19-year-old male	FXS/PWP ASD ADHD Specific phobias ID Obesity Secondary hypertension	Impulsiveness Limited communication Hyperphagia Binge eating	Blood pressure: 142/87 Height: 167.1 cm (P9th) Weight: 135.8 kg ($P >$ 99th) BMI: 48.6 kg/m^2 Obese Acanthosis nigricans High and narrow palate Residual partial nipples Tanner stage IV Low testicular volume Small phallus	Normal IGF-1 HgbA1c 5.4% Glucose 108 mg/dL	Normal CBC HgbA1c 5.3% Glucose 88 mg/dL LFTs normal	500 mg qd Dose increased to 750mg qd	Minocycline 100 mg Sertraline 50 mg Aripiprazole 2.5 mg
Case 4. 60-year-old female	FXS ID Obesity	Memory Agitation Anxiety Hyperphagia Hypertension	Blood pressure: 145/81 Height: 164.1 cm Weight: 97.66 kg BMI: 36.28 kg/m^2 Obese Ears normally placed Normal intact palate Striae on abdomen Normal tone and strength	Glucose 78 mg/dL Triglycerides 162 mg/dL Normal CBC	HgbA1c 5.2% Triglycerides 118 mg/dL Normal CBC KFTs normal	500 mg qd increased to bid	Amlodipine 10 mg Escitalopram 15 mg Triamterene 12.5 mg Vitamin D/B12 Calcium Lovastatin 20 mg Minocycline 200 mg Loratadine 10 mg Memantine 29 mg
Case 5 31-year-old male	FXS ASD ID Obesity	Anxiety Tantrums Aggression Intermittent tics Difficulty verbalizing emotions	Blood pressure: 122/82 Height: 190 cm Weight: 110.5 kg BMI: 30.7 kg/m^2 Obese Long face Prominent ears Prominent jaw Hyperextendible fingers Macroorchidism	HgbA1c 5.1% Glucose 104 mg/dL Elevated cholesterol and triglycerides Normal CBC	HgbA1c 5.0% LDL123 Glucose 101 mg/dL	500 mg bid	Citalopram 20 mg
Case 6. 24-year-old male Full mutation with methylation mosaicism	FXS/PWP ASD ID Obesity	Hyperphagia Severe anxiety Aggression Aversion to people	Blood pressure: 112/68 Height: 176.2 cm Weight: 94.7 kg BMI: 30.5 kg/m^2 Obese Soft skin Flat feet Tanner stage IV Low testicular volume Small phallus	HgbA1c 5.0% Glucose 92 mg/dL	Normal CBC HgbA1c 4.8% Glucose 80 mg/dL Triglycerides 142 mg/dL Cholesterol 107 mg/dL LFTs normal KFTs normal	Starting dose 500 mg bid, recently changed to 1000 mg bid	Citalopram 60 mg Minocycline 100 mg bid (discontinued) Risperidone 1 mg bid Alprazolam 0.5 mg bid Guanfacine 2 mg bid Buspirone 10 mg bid Lithium 300 mg bid

Case/Age/Sex/DNA	Diagnosis	Primary concern	Physical features	Laboratory findings	Follow-up lab	Metformin dose	Other medications
Case 7. 4 year and 6-month-old male	FXS ID	Language delay Anxiety	Blood pressure: 108/76 Height: 97 cm (P9th) Weight: 14.8 kg (P47th) Broad forehead Prominent ears Intermittent right exotropia High palate Hyperextensible finger joints Flat feet		Normal CBC HgbA1c 5.4% Fasting glucose 91 mg/dL LFTs and KFTs are normal	50 mg qd	Sertraline 6 mg Folic acid 5 mg Cannabinoid (CBD) 50 mg

TABLE 2

Aberrant Behavior Checklist (ABC)- Prior to metformin treatment and after 6 months to 1 year of treatment at the 2nd visit

Case	ABC subgroup	Initial	Second
1	Irritability	25	10
	Socially unresponsive	12	3
	Stereotypy	2	1
	Hyperactivity	22	9
	Inappropriate speech	7	3
	Social avoidance	6	2
2	Irritability	17	12
	Socially unresponsive	4	2
	Stereotypy	8	6
	Hyperactivity	13	9
	Inappropriate speech	7	6
	Social avoidance	0	0
3	Irritability	46	15
	Socially unresponsive	22	14
	Stereotypy	15	3
	Hyperactivity	10	5
	Inappropriate speech	3	2
	Social avoidance	10	4
4	Irritability	22	9
	Socially unresponsive	22	11
	Stereotypy	0	0
	Hyperactivity	2	1
	Inappropriate speech	1	1
	Social avoidance	12	4
5	Irritability	11	8
	Socially unresponsive	3	2
	Stereotypy	3	4
	Hyperactivity	5	3
	Inappropriate speech	5	5
	Social avoidance	4	3
6	Irritability	7	8
	Socially unresponsive	25	19
	Stereotypy	7	7
	Hyperactivity	3	3
	Inappropriate speech	8	8
	Social avoidance	11	9
7	Irritability	22	10
	Socially unresponsive	2	2

Case	ABC subgroup	Initial	Second
	Stereotypy	10	6
	Hyperactivity	20	9
	Inappropriate speech	3	2
	Social avoidance	0	0