ARTICLE

Behavioral Features in Young Adults With FG Syndrome (Opitz–Kaveggia Syndrome)

JOHN M. GRAHAM JR,* ROBIN D. CLARK, JOHN B. MOESCHLER, AND R. CURTIS ROGERS

Opitz and Kaveggia [Opitz and Kaveggia (1974); Z Kinderheilkd 117:1–18] reported on a family of five affected males with distinctive facial appearance, mental retardation, macrocephaly, imperforate anus, and hypotonia. Risheg et al. [Risheg et al. (2007); Nature Genetics 39:451–453] identified an identical mutation (p.R961W) in *MED12* in six families with Opitz–Kaveggia syndrome, including a surviving affected man from the original family reported in 1974. The previously described behavior phenotype of hyperactivity, affability, and excessive talkativeness is very frequent in young boys with FG syndrome, along with socially oriented, attention-seeking behaviors. We present case studies of five adult males who were previously published with the clinical diagnosis of FG syndrome and then subsequently proven by Risheg et al. [Risheg et al. (2007); Nature Genetics 39:451–453] to have the recurrent p.R961W mutation. These individuals had episodic and longstanding behavior patterns, sometimes aggressive or self-abusing, that occurred more frequently in puberty and early adulthood. We try to describe the triggers for these behaviors, indicate how these behaviors change with advancing age, and suggest specific recommendations and interventional strategies based on the clinical histories of affected adolescent males with FG syndrome [Graham et al., 2008; Clark et al., 2009]. Young men who exhibit these behaviors may benefit from a careful examination to detect medical problems, use of mood stabilizers if needed, and/or behavioral intervention. The transition to a community living situation can be challenging without careful planning and timely behavioral intervention. They remain impulsive and can have aggressive outbursts when making the transition to adult life, but these challenges can be managed, as demonstrated by these clinical histories.

KEY WORDS: FG syndrome; Opitz–Kaveggia syndrome; X-linked mental retardation; behavioral phenotype

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INTRODUCTION

Distinctive behavior is a very useful delineating feature of many clinical syndromes. FG syndrome (Opitz–Kaveggia syndrome, OMIM 305450) was delineated by Opitz and Kaveggia [1974] based on the clinical findings in three brothers and two of their male first cousins. In this first family, FG syndrome was defined as a multiple congenital anomaly syndrome characterized by relatively large head, broad and flat thumbs, imperforate anus, hypotonia, and moderately severe mental retardation [Opitz and Kaveggia, 1974]. Surviving males had congenital hypotonia with constipation, and during early childhood they were friendly, inquisitive, and hyperactive with a very short attention span. One older male was noted to have temper tantrums with attacks of screaming and aggressive or self-abusive behaviors requiring medication with tranquilizers [Opitz and Kaveggia, 1974]. Risheg et al. [2007] identified a recurrent p.Arg961Trp mutation in the *MED12* gene in 10 individuals from 6 families with FG syndrome including a surviving affected male and his obligate carrier mother from the original report of FG syndrome (individual V-10 in Pedigree from Fig. 1

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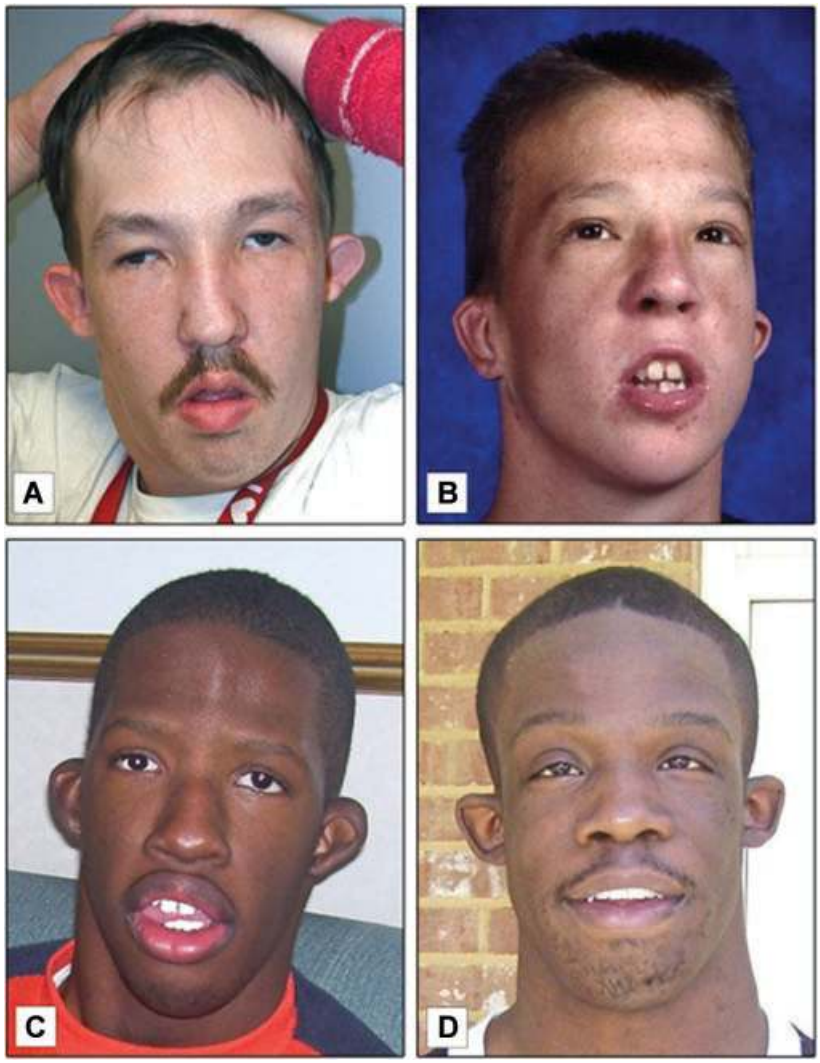

Figure 1. **A**: Patient 2 at age 25 years, (**B**) Patient 3 at 19 years, (**C**) Patient 4 at 17 years, and (**D**) Patient 5 at 22 years.

in Opitz and Kaveggia [1974]). We describe this surviving male's clinical history in more detail in this report (Patient 1), as well as reporting long-term clinical histories in a male reported by McCardle and Wilson [1993] (Patient 2), and one male from Family 1 (Patient 3) and two males (Patients 4 and 5) from Family 3, which were previously reported by Graham et al. [1998]. Recently, Graham et al. [2008] reported two more adult males, and Clark et al. [2009] delineated the natural history of FG syndrome in additional affected males from nine other families who all shared the p.Arg961Trp *MED12* mutation.

A wide range of malformations is seen in FG syndrome, with the most characteristic anomalies being agenesis or hypoplasia of the corpus callosum, anal fistula, stenosis and atresia, and congenital cardiac anomalies [Clark et al., 2009]. Absolute macrocephaly (head circumference greater than the 98th centile) is seen in fewer than half of patients with FG syndrome, and eye anomalies have been reported in 10 out of 23 patients with FG syndrome [strabismus/exotropia in three patients, optic nerve hypoplasia in two patients, coloboma in two patients, phthisis bulbi, nystagmus, retinal detachment, and cataract in one patient each, Clark et al., 2009]. Such eye anomalies may affect their behavior and justify a formal ophthalmologic assessment when the

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diagnosis of FG syndrome is established. Other less common anomalies include: megacolon, pyloric stenosis, renal cysts and stones, cryptorchidism, skeletal anomalies including joint contractures, limited supination, hip dysplasia, pectus deformities, vertebral and rib anomalies, and syndactyly or oligodactyly of the fingers.

Graham et al. [2008] delineated the behavioral phenotype in males with FG syndrome and the recurrent mutation, p.Arg961Trp, in the *MED12* gene. They confirmed the previously documented friendly, loquacious, eager-to-please personality with concurrent anxiety and need for sameness. Some individuals were aggressive, impulsive, and/or obsessive–compulsive. The degree of intellectual disability varied from borderline to severe. All of these individuals had cognitive disability, with most patients IQ scores below 70. None of the patients had a level of intellectual functioning comparable to their unaffected siblings and parents. Based on these current case studies, specific recommendations are provided for anticipatory guidance and treatment strategies.

CLINICAL REPORTS

Patient 1

Patient 1 is a 43-year-old man with FG syndrome who was born in 1966. He is the only affected survivor of the original

family reported by Opitz and Kaveggia [1974]. As an infant he had a colostomy at age 4 hr for presumed anal atresia. His anus was dilated surgically and his colostomy was taken down at 3 months of age. He had a cardiac murmur that resolved by age 4–5 years.

He now resides with his parents in their home and attends an adult day program for 8 hr a day, where he is friendly and gets along well with peers and staff. He has no current behavior problems and is described as "easy-going" most of the time. He takes no medications for behavior or psychiatric problems, and his current medications are lactulose, polyethylene glycol, and rabeprazole sodium for chronic constipation and gastritis/duodenitis, as well as propranolol for cardiac arrhythmia.

He had previous episodes during his 20s when he would cry inconsolably and drop to the floor as if in pain, which have continued to the present, though less frequently. They are brought on by pain, anxiety or stress, and they are not panic attacks or seizures. These episodes were often associated with painful medical problems, such as ear infections, headaches, gastritis, duodenitis, bowel obstruction, hemorrhoids, or constipation. His ear canals are so narrow that ear infections were often not diagnosed until purulent matter was present after perforation of his ear drum. He was usually unable to communicate the site of his pain or discomfort, especially when the pain was of gastrointestinal or rectal origin. He had genu valgum and pronated feet, which resulted in knee pain in his 20s, and this pain resolved with orthotics. He also had similar episodes when he had any social difficulties with others, or when he was afraid. Over the years, his mother, an RN, became adept at figuring out what was triggering his "meltdowns." Sometimes she would take him to the local Emergency Room daily for such unexplained pain, where a physician gave him haloperidol to sedate him, and eventually this became routine whenever he had such an episode. Later a neurologist prescribed haloperidol at bedtime, although he had no difficulty sleeping, and he became sleepy if haloperidol were given during the day to help keep him calm and/or prevent an episode.

He developed headaches brought on by anxiety and worry, which were treated with hydrocodone and prevented by Midrin. He has had periods of insomnia, going up to 72 hr without sleep, which would also trigger headaches. His mother eventually realized that the insomnia was related to the temperature of his bedroom becoming too hot. As other medical problems, such as sleep apnea and constipation, became treated effectively, he had less insomnia. His mother described self-injurious behaviors in the past, where he would bang his head when frustrated in his late teens and 20s. This behavior might have been associated with puberty, which occurred in his late teens or early 20s. Head banging has since resolved.

His mother believes that as she became better at finding and treating the cause of his episodes, he needed less medication. Eventually he was admitted to the UCLA Neuropsychiatric Institute in 1994 for haloperidol detoxification. Now his mother gives him low doses of haloperidol infrequently, only once or twice a year as sedation for medical procedures, or to induce sleep after prolonged insomnia.

He lived in a group home from 1994 to 1996 because his mother felt that it would give him more social experience. She found a suitable home near their home, and he did well in the group home, without any behavior problems, often coming home on weekends. After 18 months, his mother removed him from the group home for a temporary illness, and he remained at home until this placement became permanent.

He is never aggressive, nor does he hurt or threaten others. He is generally friendly to those he knows, but shy with strangers. He has generalized anxiety that manifests as fear of barking dogs, fear of abandonment, and fear of slipping or losing his balance in the shower. He does not have a rigid need for sameness, and he has no fixed routines. He wants to know what to expect ahead of time and needs reassurance when there is a change in his routine. He tends to perseverate, asking the same questions over and over about a single topic, or about an upcoming event. This may be exacerbated by the fact that he does not like to wear his hearing aides for his sensorineural hearing loss while at home, though he does wear them at his day program.

Patient 2

Patient 2 (Fig. 1A), born in 1981, was diagnosed with FG syndrome at approximately 5 years of age [McCardle and Wilson, 1993]. By age 12 months he had delays in all developmental milestones and was reported to sit at age 15 months, walk at 26 months, and use phrases by 3 years. At age 42 months, he scored "in the mild range of mental retardation" on standardized developmental assessments. He was noted to be "awkward" in gross motor skills and "visual–motor/visual–perceptual tasks." Developmental assessments at age 4 years, 5 months indicated he was "generally functioning in the educable mentally retarded (sic) range" with some strengths in the verbal areas. His scaled scores placed him more than two standard deviations below the mean for his age in all areas except verbal functioning. At age 5 years 4 months, his mental age was assessed to be 2 years 5 months. His visual–motor skills were significantly weaker than all other domains measured. The diagnosis of FG syndrome was established at age 5 years based on characteristic physical findings, agenesis of the corpus callosum on CT scan, and positive family history (younger brother, maternal uncle) with similar clinical presentations [McCardle and Wilson, 1993; Clark et al., 2009]. At this time he was described as "very friendly, inquisitive."

He had several speech and language evaluations as a young child. His language delays were noted by age 2 years. By 3 years 6 months, his receptive skills had advanced, while his expressive speech had plateaued and both were delayed for age. His receptive skills maintained at about 60–65% of age expectation from ages 3 to 5 years. At age 5 years, he was noted to produce "syntactically telegraphic" 2–4 word

phrases. He was "hyperverbal and uses elaborate gestures and frequent circumlocutions, both indicative of word-finding difficulties" [McCardle and Wilson, 1993].

At age 13, his school plan included a specific plan to address behaviors described as "verbal/physical aggression, uncooperative relationships with staff, and the use of inappropriate language." At that time he was described as initiating and sustaining conversation easily and "very frequently" leaving the impression that he was a teen who "talks non-stop." At this age, tests of intellectual functioning demonstrated verbal IQ scores of 59, Performance IQ was 46 with Full-Scale IQ score of 49. His verbal reasoning was better than his non-verbal reasoning abilities. His affect at this time was that of "happiness" with a close relationship to his parents while having few peer friendships. His responses during the testing situation were described as "impulsive." He was noted to engage school staff and fellow students into verbal arguments about what were observed to be trivial or unimportant points. This was thought to be the result of "impulsivity, distorted understanding or perception of the motives of others, and limited social skill development." He was reported to have "difficulty developing and maintaining relationships with others."

At age 20, he was hospitalized for aggression and to initiate treatment with psychotropic medications because of his aggressive behaviors. At age 25 years, he was living in a rented apartment near his family, which was maintained by the regional agency for persons with developmental disabilities. He worked 2 days each week at a pet groomers, and he was learning to shop and cook independently. He was polite, conversant, and socially appropriate. He did have abnormal movements that were described as "torsion dystonia," such that he would bend forward at the waist involuntarily. He could stand erect but his head would turn upward and to his right with his torso following. He would hold his head with his right hand in order to maintain eye contact during conversation. This made his gait unsteady at that time. He was taking Guanfacine and Risperidone to treat his aggressive behavior. Also, he was unable to walk distances efficiently due to his movement disorder. Neurology and Psychiatry specialties were involved in his care. He also was taking Docusate Sodium (Colace) for his chronic constipation, Lamotrigine (Lamictal) for seizures, Levothyroxine for hypothyroidism, and Oxybutyinin (Ditropan) for urinary incontinence.

Patient 3

This 21-year-old male (Fig. 1B) was born at term in 1989 with low Apgar scores due to poor respiratory effort and congenital hypotonia. Birth weight was 3,540 g (50th to 75th centile), length 53.5 cm (90th centile), and head circumference (OFC) 35.5 cm (50th to 75th centile). He had turricephaly; small, apparently low-set, cupped, posteriorly angulated ears; hypertelorism with down-slanted palpebral fissures; microstomia with high-arched palate; inguinal testes; lack of right middle digital ray with 4–5 syndactyly; left single transverse palmar crease; broad thumbs; and duplication of the right great toe. Imaging studies demonstrated hypoplasia of the corpus callosum.

He had a maternal uncle with severe mental retardation and absent corpus callosum. Another uncle died at 4 days with a congenital heart defect. The patient was treated for apnea and feeding difficulties, which resolved, and he was given a partial exchange transfusion for polycythemia with hematocrit of 69%. He was discharged on an apnea monitor at 8 days with persistent hypotonia, decreased brainstem auditory evoked responses, pulmonary hypertension with right ventricular hypertrophy by echocardiogram (attributed to upper airway obstruction), normal pneumogram, normal renal ultrasound findings, normal chromosome, and normal electroencephalogram. Cranial magnetic resonance imaging at 2 years demonstrated hypoplasia of the posterior corpus callosum with mild ventricular dilatation and mild frontal atrophy.

At 2 years, his length, weight, and OFC were all at the 50th centile, and his pulmonary hypertension had resolved by echocardiogram; he had only mildly decreased muscle tone. He developed seizures at 2–3 years, which were treated with phenobarbital and carbamazepine. He had become hyperactive with aggressive outbursts, so the phenobarbital was discontinued, and diphenylhydantoin therapy was initiated. An EEG at 2 years 10 months was abnormal due to recurrent right central spike and sharp waves with a few left temporal sharp waves. Seizures remained poorly controlled, so he was treated instead with valproic acid. At age 5 years he had a developmental quotient of 50 and required special education classes. He had a friendly disposition, hyperactive behavior, and a history of constipation. He was taking valproic acid, carbamazepine, and methylphenidate. His height was at the 10th centile, with weight at the 50th, and OFC at the 25th centile.

At age 12 years, his seizures were well controlled on carbamezepine twice daily, with only one grand-mal seizure in the last 2 years. His ADD was being treated with generic (Adderal tm) twice daily, with improvement in his ability to focus. He was in special education classes with a one-on-one assistant, and therapeutic horseback riding twice a week was improving his balance and posture. An eye evaluation noted optic nerve pallor bilaterally. At around this age, he started getting "rude and bossy," which progressed through age 18 years. He became impatient with being told to wait and began to make aggressive threats. Over his adolescent years he became more angry and threatened care providers more often. He became upset and jealous when he saw his older brother driving, going on dates, using a cell phone, and holding a job that allowed him to become independent. He became aggressive toward his brother over his lack of independence and began hitting, kicking, and trying to choke his siblings and parents. This was extremely difficult for his family, who refused to send him into a group home or foster home under a crisis situation. At this time he was taking generic Adderal and Risperidone (Risperdal tm). His psychiatrist increased his Risperdal after

he went through a growth spurt between age 16 and 20. And he improved for a few months but his problem with anger continued, so help was sought from a behavioral therapist. At age 18 years, he graduated from High School and began attending a transition school, where he learned independent living and job skills. These experiences gave him more independence, but he was still difficult to deal with at home.

One day he became especially angry with his father because he was not allowed to do something, and the situation escalated until all parties had to separate and regain composure. His mother called the counselor and her son's behavioral therapist to determine appropriate management. He was placed in a foster group home for young adults with disabilities. The patient visited the home and became excited to think it could be his house, that he could have roommates, and he could call his parents on his phone and have them over for dinner. The patient moved out 2 days later and readily adapted to the group home, where he could come and go to his parents' house on his schedule. His family has adjusted to his new independence with great relief.

Patient 4

This 17-year-old young man (Fig. 1C) was born in 1992. He is the younger nephew of Case 5. He was born small for gestational age with respiratory distress, small ventricular septal defect (VSD), and membranous imperforate anus. His birth weight was 1,335 g (10th to 25th centile). He had a prominent forehead with partial absence of the corpus callosum, upswept frontal hair pattern, down slanted palpebral fissures, small cup-shaped ears, mildly broad thumbs and halluces, and bilateral inguinal hernias that required surgical correction. He did not have hypotonia. At 2 months, when discharged from his initial hospitalization, he weighed 3,300 g (<3rd centile), measured 50 cm in length (<3rd centile), and had an OFC of 35.2 cm (<3rd centile). He was hospitalized for pneumonia at 8 months, and by 11 months he was found to have severe myopia with moderate developmental delay. He developed seizures at age 32 months and was treated with clonazepam. CT scan documented partial agenesis of the corpus callosum. At $5\frac{1}{2}$ years he had an OFC of 52 cm (60th centile), broad thumbs, and facial anomalies similar to those of his uncle.

There have been no noticeable changes in his behavior. He is now 17 years 8 months of age. He is 173 cm tall and weighs 61 kg. He is still non-verbal and is completely dependent upon others for personal care. He is not potty trained. He must have toys that play music or make some type of sound with him most of the time. The family goes though hundreds of batteries each year. He is not very outgoing and does not bond with strangers very well. His patience is short. He communicates by pulling your hand, gently nudging with his elbow, or scratching violently or softly, depending upon his mood and the person he's attempting to communicate with. He gets very frustrated when not understood and will lash out on occasion. His closest bond is with his mother but he also directs his most violent outrages towards her.

He developed an extreme case of sleep apnea because of his narrow palate, causing his airway to be blocked by his tongue, but he will not wear CPAP. Treatment with benztropine does not appear to help much. The family is looking at surgical options to address this problem.

Changes in the patient's life over the past 5 years include a new brother (age 4 years 11 months) and a new sister (age 4 months). He pays little attention to them and initiates no interaction with them. He still demands his attention when desired and generally stays in his room or private space until he wants to eat or drink, or his grandparents visit. He is closely bonded to his father as well as to all his grandparents.

He is followed by a neurologist for seizures that are under control with Keppra, 900 mg in the morning, 1,000 in the evening and Lamictal, 50 mg in the morning and 50 mg in the evening. He has recurrent ear and sinus infections and drools profusely, and he has a very high tolerance for pain.

He attends school daily in a TMD environment. He occasionally becomes frustrated and has been known to scratch his teachers and shadows, but otherwise appears to tolerate his school environment well. His parents are extremely patient with him and provide a comfortable loving environment. His mother is with him at all times when he is at home.

Patient 5

This 22-year-old man was born in 1988. He was the product of a term vertex vaginal delivery, born to a 36-year-old G4P3Ab1 woman with a negative family history for other males with mental retardation. His birth weight was 3,665 g (75th centile) length 53.5 cm (90th centile), and OFC 34 cm (25th centile). At birth he had congenital hypotonia, membranous imperforate anus, and small, posteriorly angulated cup-shaped ears. An echocardiogram was normal, and he developed tracheomalacia with a pectus excavatum. At 6 months he was seen by a neurologist who noted developmental delay, generalized hypotonia, alternating exotropia that increased with downward gaze, and abnormally placed thumbs. He did not have seizures, and his OFC was at the 50th centile. At 11 months an ophthalmologist noted mild optic atrophy with subnormal visual acuity, and he has had two surgical procedures for exotropia. Cranial imaging at 40 months demonstrated partial agenesis of the corpus callosum. During adenoidectomy surgery, a vocal cord cyst was found and removed.

Developmental assessment at 15 months demonstrated a developmental quotient of 50 on the Bayley Scales of Infant Development. On the Vineland Scales his communicative skills were at 10 months, daily living skills at 11 months, socialization skills at 12 months, and motor skills at 8 months. His performance at this age suggested mild to moderate cognitive disability. At age 18 months during his initial genetic evaluation, he was found to have mildly broad thumbs and halluces, prominent

forehead, mild ocular hypertelorism with bilateral epicanthal folds, and persistent hypotonia, suggesting the diagnosis of FG syndrome. The patient returned for follow-up at age 4 years. Facial anomalies were unchanged, his sagittal suture was ridged, and he had a narrow palate. He had developed a friendly, loquacious personality, with occasional temper tantrums and persistent developmental delay.

He is now 22 years 2 months of age. He is 170 cm tall and weighs 63.5 kg. His physical characteristics have changed very little. He has had difficulty with stuttering for the past 10 years, and there is a positive family history for early-onset stuttering in his maternal aunt and uncle. He has become verbally aggressive towards those people he knows well, but acts shy around people he does not know. It does not take long for him to warm up to new people and begin smiling and talking profusely with them. He is overly sensitive and is very easily offended. He was recently placed in temporary respite group home because his behavior at home had become more aggressive, both verbally and physically. He would loudly scream profanities when upset at home, and he would actually begin to fight when attempts were made to restrain this behavior. He would become extremely upset over seemingly nothing, and this would begin by growling and moaning, and his behavior at this point appeared to resemble demonic possession. He is always very apologetic and remorseful after regaining composure from violent episodes. At times he confabulates.

He recently spent 7 days in an emergency room setting for aggressive behavior and at other times, his family sought assistance from the Sheriff's Department. He has an extremely high tolerance for pain and using force causes injuries to him that could go unnoticed. He regains composure more easily when others are involved because he does not want them to dislike him. He is not afraid of anyone, including policemen. The deputies were able to escort him out of the home by play-acting wrestling scenes where the champion wrestler is escorted to the ring for his protection.

His neurologist prescribed clonidine to address his ticks and calm him down when he became enraged, but it did not appear to help. He fell asleep after he has acted out his frustrations over a period of hours. The reasons for his aggressive behaviors at home remained elusive. His mother died in 2004, he left high school in 2008, and he became a new uncle in 2005 and again in 2010. None of these occurrences appeared to negatively affect his character or behavior. He only cried once when his mother died, and he seldom talks about her. He loves being an uncle and is very protective of his nephews (17 and 5) and niece (4 months). He plays video games and watches TV while at home. He loves wrestling action figures and has a compulsive behavior of needing to have a toy in his hands most of the time, and he still sleeps with them.

He required frequent medication changes while adapting to his new group home, and his current medications include valproic acid, haloperidol, and lorazepam. During longer home visits he reverts to verbally abusive behavior until being returned to the group home, where he regains his composure. Parents are attempting behavioral therapy to teach him the results of negative behavior, as well as other interventions that will assist in controlling his aggressive tendencies.

DISCUSSION

There is a consistent behavior phenotype in males with FG syndrome and the p.Arg961Trp in *MED12*. It is important to consider FG syndrome in males who present with developmental delay and/or a behavioral phenotype of hyperactivity, affability, and excessive talkativeness along with the clinical features of FG syndrome [Graham et al., 1999; Risheg et al., 2007; Clark et al., 2009; Lyons et al., 2009]. Males with this recurrent p.Arg961Trp mutation in *MED12* have strengths in socialization and daily living skills, despite their communicative deficits [Graham et al., 2008]. Their strengths in socialization skills may mask their communicative deficits. Although parents may report

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that boys with FG syndrome are social and talk excessively, they may have problems in articulation, pragmatic language use, syntax, and intonation, which may be further complicated by their low facial muscle tone and oral–motor discoordination. These language deficits may lead to secondary behavioral problems and difficulties in performing routine daily living skills, such as toilet training, feeding, or dressing. Males with FG syndrome commonly have increased frustration and attention problems, which may also be related to their poor expressive language skills. Thus, early and ongoing language interventional therapy is essential in all males with FG syndrome. Language therapy should

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also include oral–motor exercises to improve tone, strength, and coordination. Total communication strategies combining non-verbal (e.g., sign language and augmented communication devices) and verbal skills should be considered. Males with FG syndrome also have significant externalizing behaviors, especially in the aggression domain and are at increased risk for aggressive behavior because they have major deficits in communication skills [Visootsak et al., 2007; Graham et al., 2008]. Deficits in communication skills, specifically within the expressive communication domain, often lead to frustration, tantrums, and isolation.

Patient 1 illustrates that pain can be a trigger for maladaptive behavioral outbursts. Males with FG syndrome should be carefully examined by their physicians when unexplained behaviors occur. A maladaptive emotionally charged episode, especially one that includes aggression or self-abuse, may be so disruptive that an underlying medical problem might go unrecognized by a treating physician. Diagnosis of medical problems in males with FG syndrome can be challenging in any setting due to their inability to communicate, but this is especially so in an emergency room where there may be an assumption of a primarily psychiatric rather than a medical disorder. When possible, individuals with FG syndrome, who have acute episodes of maladaptive behavior, should be examined by their personal physicians who may be better able to recognize changes in their baseline medical and emotional condition.

FG syndrome is a disorder of multiple congenital anomalies and many organ systems can be impaired even in adulthood. The behaviors and psychiatric problems of seven young adults with FG syndrome [the five patients reported here plus two from Graham et al., 2008] are summarized in Table I and their characteristic facial features are demonstrated in Figure 1. As most males with FG syndrome have poor GI motility and constipation throughout their lifetimes, gastrointestinal sources should be sought for unexplained pain including gastroesophageal reflux, constipation, and hemorrhoids. Hypotonia and joint laxity, which are common in FG syndrome, can cause joint misalignment and pain. Headaches, insomnia, and sleep apnea are also common and may exacerbate maladaptive behaviors. Stressors in the social, school, and family life should be explored. Finally, medications for seizures and other medical problems can cause side effects and drug–drug interactions. Any of these factors, or more than one factor, may contribute to pain, stress, frustration, disordered sleep and fatigue, emotional lability, and physical changes that individuals with FG syndrome may not be able to articulate. Identifying and treating the medical causes of pain or other triggers can reduce the number and severity of their behavioral outbursts.

Anxiety is also noted in all these males with the FG syndrome and the common *MED12* mutation, and this appears to be heightened by changes in routines and transitions. Based on these findings, it is important to provide a highly structured environment for males with FG syndrome since they prefer routines. Providing frequent explicit warnings of transitions and changes in their routines will lessen anxiety, improve coping, and reduce maladaptive behavior. Use of a calendar system may help them anticipate changes in the future. Positive behavioral attributes include an interest in helping others and in socializing with their peers; however, their socialization may be inappropriate and immature for their age. For these reasons, it is important to provide prompting to encourage interaction with peers, especially when it provides opportunities to imitate and model appropriate behavior. Exposure to typically developing peers may be especially helpful in achieving these goals.

Anxiety is also noted in all these males with the FG syndrome and the common MED12 mutation, and this appears to be heightened by changes in routines and transitions. Based on these findings, it is important to provide a highly structured environment for males with FG syndrome since they prefer routines.

Additionally, behavioral assessment and intervention should be offered for males with the FG syndrome. Because there are no empirical studies on the effectiveness of behavioral treatments in these males, behavior therapy should be individualized and designed to meet the individual's specific needs. Behavior challenges may also wax and wane with increasing age; thus, therapy should be adapted to these changes. For example, puberty can be a time of emotional instability for males with FG syndrome. Many of the patients described in this report had deterioration of their behavior in late teens, coincident with growth spurts. Hyperactivity may subside during adulthood with withdrawal and anxiety being more prominent. Parents should also be instructed on how to implement behavior therapy at home. Principles of functional behavior analysis, positive behavioral supports, and the Antecedent–Behavior–Consequence model may be useful as they are based on how maladaptive behaviors are maintained, rewarded, and how they can be replaced by positive reinforcement of appropriate behaviors.

Psychopharmacologic intervention should be combined with other interventional strategies, including speech therapy, sensory integration therapy, an individualized educational plan, and tailored behavioral treatments to enhance developmental outcome and minimize maladaptive behaviors. Presently, there is no psychopharmacologic research specific for individuals with FG syndrome. Based on the results of our data, externalizing and internalizing maladaptive behaviors are common in males with FG syndrome. For these reasons, selective serotonin reuptake

TABLE I. Behavioral Changes in Males With FG Syndrome

Previously reported patients

Patient 1: Graham et al. [2008]

Childhood: ADHD, easy frustration, prolonged temper outbursts, unusual rituals, verbal and motor tics, impulsive, diagnosed with Tourette syndrome at age 10. Methylphenidate hydrochloride improved his attention but not his tics and rituals. Poor self-esteem developed because of his behavior. Calmer and happier after methylphenidate hydrochloride was discontinued, but still impulsive and hyperactive

Adolescence: Diagnosed with obsessive compulsive disorder (OCD) with continued tics and temper outbursts. Haloperidol reduced his tics and made him calmer. Addition of fluoxetine hydrochloride made him more obsessive, and suicidal ideation required hospital admission to wean him off all medications. Consistent behavioral management trained him to self-monitor his behavioral issues. OCD was treated with pimozide. Propranolol was ineffective and caused weight gain

Adulthood: Received one-on-one support in a group home setting, and continued on pimozide for OCD, with resolution of tics and better self-control. Paroxetine hydrochloride was added to pimozide, but his tics and behavior worsened, so he was weaned off pimozide and placed on Risperidone. Tics and behaviors continued to worsen, so paroxetine hydrochloride was discontinued and Risperidone was increased with an excellent response

Patient 2: Graham et al. [2008]

Adolescence: Prolonged temper tantrums and manic behavior with aggression was treated with lithium, psychiatric hospitalizations, and numerous other psychotropic medications. He had poor self-esteem and excessive anxiety, impulsivity and depression, which were treated with citralopram, desmopressin, valproic acid, lithium, and lorazepam, resulting in marked mood improvement

Currently reported patients

Patient 1

Childhood: Demeanor was generally friendly, talkative and socially welcoming. He was anxious about changes in his environment, and perseverated on a narrow range of topics

Adolescence: Puberty marked the onset of episodes of self-abusive behavior (head banging) and spells of out-of-control behavior, described as "meltdowns," where he rolled on the floor and acted as if in pain. These were treated with haloperidol by emergency room physicians to deal with his acute crises. Gastrointestinal medical problems, such as gastroesophageal reflux, gastritis, duodenitis, hemorrhoids, and/or constipation usually precipitated these episodes. He also had anxiety headaches, insomnia, and sleep apnea. He briefly resided in a group home with good results, leaving only because of an illness

Adulthood: He maintains good relationships at home with his parents and at his adult day program. His emotional outbursts have become less frequent as has self-abusive behavior. He has never been treated by a psychiatrist and takes no psychotropic medications routinely. His maladaptive behaviors often had a medical basis, or could be attributed to psychological stress in his environment. When these triggers were identified and treated, such episodes became less frequent

Patient 2

Childhood: At age 3 years he was described as "talkative child" with limited attention to specific tasks and poor imitation skills. By age 6 years, methylphenidate was prescribed for hyperactive behavior with some improvement. His family stopped this medication when his behavior was no different from that while off medication. By age 9 years, his behavior became maladaptive and difficult, with aggression and impulsivity. By age 10 years, his family was considering residential placement because of his aggression. He also had ADHD with some mild self-injurious behaviors

Adolescence: By age 13 years, he was described as "verbally argumentative" by an examining psychologist who noted that he would "attempt to draw the examiner into discussions that were irrelevant to the evaluation process." He enjoyed attention from others, but it was difficult for him to maintain cooperative relationships with others. He appeared to be happy and was attached to his parents and dependent on them for support. He was socially immature

Adulthood: During his 20s, he underwent psychiatric hospitalizations for aggressive behavior towards others, and to refine his medication treatment. He lived in a rented apartment and worked as a pet groomer. At age 27, he was taking Guanfacine and Risperidone for his aggressive behaviors

Patient 3

Childhood: He was hyperactive with occasional aggressive outbursts. Seizures were treated with anticonvulsants. He had a friendly disposition, hyperactive behavior, and a history of constipation. He took valproic acid, carbamazepine, and methylphenidate

Adolescence: He became impatient, rude, and bossy, with escalating aggressive outbursts, which were treated with Risperidone. He remained on Adderal for his hyperactive behavior. Behavioral therapy allowed him to become more independent, control his anger, and regain his composure

Adulthood: He was placed in a foster group home for young disabled adults, where he quickly adapted and enjoyed his new independence. He was on clonazepam, Adderal, and Risperidone

Patient 4

Childhood: Described as introverted, with obsessive–compulsive behaviors. Seizures began at age 32 months and still occur infrequently—prescribed clonazepam

Adolescence: Seizures, introverted, and OCD are persistent. He is prescribed levetiracetam and Lamotrigine for seizure control

Adulthood: At age 17 he has no significant behavioral problems and remains introverted, impatient, and easily frustrated

Patient 5

Childhood: Easily frustrated, prolonged temper tantrums, motor tics, extroverted, OCD, claustrophobic. A trial of carbamazepine did not provide any noticeable improvement

Adolescence: Easily frustrated, argumentative, impatient, verbally aggressive. Negative behavior often re-directed at family; however, he remained very personable with strangers. Clonazepam was tried for management of tics, but without any noticeable improvement. Clonazepam was helpful as a sedative and a sleep aid

Adulthood: Easily frustrated, OCD, argumentative, highly impatient, verbally and physically abusive accompanied by profane outbursts. These behaviors became more intense and more frequent. It became increasingly more difficult to re-direct his negative behavior. Behavior became uncontrollable and temporary respite care in a group home was required. He required frequent medication changes while adapting to his new group home, and his current medications include valproic acid, haloperidol, and lorazepam

inhibitors (SSRIs) may be considered to treat mood disorder, anxiety, and obsessive–compulsive behaviors. Atypical antipsychotics (e.g., respiridone) have been used to treat self-injury, aggressive behaviors, and autism. Adverse side effects associated with antipsychotics include weight gain, sedation, nausea, constipation, diabetes, and tardive dyskinesia. Individuals with hyperarousal to sensory stimuli can be treated with α2-adrenergic agonists (e.g., clonidine), which are thought to dampen sensory input to the brain and have shown good efficacy in decreasing these behaviors in boys with Fragile X syndrome [Berry-Kravis and Potanos, 2004]. Stimulants are also helpful in targeting symptoms of hyperactivity, impulsivity, and distractibility. Their efficacy and side effects vary for each individual, and the response rate to stimulants may be lowered in adult males with FG syndrome because of their increased anxiety and decreased activity level.

Overall, males with FG syndrome (and the recurrent p.Arg961Trp *MED12* mutation) are lower functioning in their communication domain compared to their socialization and daily living skills, and they are at higher risk for externalizing and internalizing maladaptive behaviors.

These deficits appear to persist into adulthood based on our results. Hence, it is important to offer anticipatory guidance throughout childhood and adulthood with sufficient parental, educational, and social support. Therapeutic interventions should include physical therapy, occupational therapy, language therapy, and behavioral modification. An individualized educational plan with appropriate resources (e.g., functional behavioral assessment and plan, positive behavioral supports, and adaptive physical education) is essential in ensuring that the individual with FG syndrome continues to make progress.

Overall, males with FG syndrome (and the recurrent p.Arg961Trp MED12 mutation) are lower functioning in their communication domain compared to their socialization and daily living skills, and they are at higher risk for externalizing and internalizing maladaptive behaviors.

As they transition into adulthood, young men with FG continue to manifest their underlying behavioral phenotype. They may benefit from mood stabilizers if indicated, and their transition to a community living situation can be challenging without careful planning and timely behavioral intervention. They remain impulsive and can have aggressive outbursts, but these episodes can be managed, as demonstrated by these clinical histories.

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