Treatment of Aggression in Children and Adults with Fragile X Syndrome

by Randi Hagerman, M.D.

Aggression is a relatively common problem in children and adults with fragile X syndrome (FXS). It is related to problems with impulsivity, overreactivity to stimuli and mood instability, which are part of the behavioral phenotype in FXS [Hagerman 1999]. In childhood, impulsive hitting when the child becomes angry, upset, or overwhelmed occurs in approximately 40 percent. Usually behavioral interventions, including a negative verbal response with subsequent timing out and then positive reinforcement for not hitting, will extinguish such behavior [Braden 1997]. If problems persist, then work with a behavioral psychologist on a weekly basis is warranted.

More significant aggression occurs in approximately 20 percent to 30 percent of children or adolescents with FXS [Hagerman 1996b]. In puberty, hormonal changes can sometimes exacerbate aggressive outbursts, particularly in males. The increased size and strength of the adolescent compared to the child may also cause difficulty in handling an aggressive outburst. Typically an adolescent can become agitated or fearful with a change in activity or a new situation. A rapid change in mood can lead to hitting, throwing or destructive behavior. It is important to prepare an individual for changes with both verbal and visual input such as using a series of pictures to visualize a transition [Scharfenaker *et al.* 1996; Braden 1997]. Physical calming techniques such as brushing, joint compression or a deep pressure massage also can be helpful in diverting a physical outburst. An occupational therapist trained in sensory integration [Scharfenaker *et al.* 1996] can teach these techniques to families.

Sexual frustration is not uncommon in this age group, and it can be exacerbated by obsessional thinking. Interaction with a female with whom an adult male is infatuated may precipitate aggression. Psychological counseling is useful in many ways. It can help the adolescent or adult with FXS recognize an escalation in mood and can help the individual institute self-calming techniques [Braden 1997]. A discussion of the individual's needs, sex education and guidance regarding appropriate responses and useful alternatives is beneficial [Fegan *et al.* 1993; Craft 1994; Braden 1997].

If the above interventions do not alleviate aggression, medication can be a helpful component to treatment. A synergistic effect can be seen with the concomitant use of behavior modification through counseling, and psychotropic medication. The choice of medication for treatment of aggression depends on what the underlying symptoms are. For instance, if the child or adolescent has attention deficit hyperactivity disorder (ADHD) and the aggression stems from impulsive behavior, then the use of stimulants such as methylphenidate (Ritalin) or Adderall (a mixture of four different levo and dextro amphetamine salts) is usually helpful [Hagerman 1999]. If the behavior is marked by hyperarousal to stimuli and the aggression usually occurs in this context treatment with alpha$_2$ agonists such as clonidine or guanfacine (Tenex), which decrease norepinephrine levels, lower blood pressure and have an overall calming effect, can be helpful. Clonidine comes in a patch form (Catapres TTS1, two or three patches) that usually is changed every three to five days for a continuous blood level. Sedation occurs at first in the majority of children treated with an alpha$_2$ agonist. An EKG should be done in follow-up treatment since these medications may prolong cardiac conduction.

If anxiety is the main problem and aggression occurs in situations which escalate anxiety, treatment with a selective serotonin re-uptake inhibitor (SSRI) such as fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), or cetalopram (Celexa) should be considered. One study demonstrated that approximately 70 percent of adults with FXS had improvement of aggression on fluoxetine although approximately 25 percent may become more hyperactive or hypomanic with worsening of aggression [Hagerman *et al.* 1994]. Usually a SSRI will decrease anxiety, aggression, obsessive/compulsive behavior and smooth out irritability or minor mood fluctuations [Hagerman 1999].

If more severe mood instability occurs in association with aggression, then a mood stabilizer usually is helpful. Anticonvulsant agents such as carbamazepine (Tegretol) or valproate (Depakene, Depakote) are very effective mood stabilizers, but require careful follow-up of blood levels, electrolytes, blood count and liver function studies [Freeman and Stoll 1998]. Lithium also is an effective mood stabilizer, but similar follow-up is necessary. The new atypical antipsychotic agents such as risperidone (Risperdal), olanzepine (Zyprexa), and quetiapine (Seroquel) can be helpful for mood stabilization besides being effective antipsychotic agents [Hagerman 1999]. They have a much lower risk of chronic motor problems, called tardive dyskinesias, when used in low dose compared to typical antipsychotics. There has been significant experience with the use of risperidone in childhood, but controlled trials of the use of risperidone in fragile X has not yet been published. In our experience, it usually has been helpful for the treatment of aggression, but a problematic side effect is an increased appetite and weight gain for risperidone and olanzepine.

Early reports on newer anticonvulsants, such as gabapentin (Neurontin) or topiramate (Topamax), suggest a significant mood stabilization benefit but further trials are needed in patients with FXS. If aggression is a problem for your child, adolescent or adult with FXS, it is important to consult your doctor to discuss treatment options. Sometimes a combination of interventions is best. You can read more regarding medication in the booklet by Dr. Tranfaglia (1996-available from NFXF or FRAXA) or Dr. Hagerman [Hagerman 1996a; Hagerman 1999]. For more about counseling and behavioral interventions I suggest Brown *et al.* 1991; Scharfenaker *et al.* 1996; Sobesky 1996; Braden 1997]

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