GUIDELINES OF CARE IN FRAGILE X SYNDROME

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Fragile X syndrome (FXS) is the most common inherited cause of mental retardation that is known. It causes a spectrum of developmental and behavioral problems, which range from mild anxiety or social interactional difficulties in individuals with normal intellectual functioning, to more severe behavioral problems and cognitive deficits, including all levels of mental retardation. Connective tissue problems are also associated with FXS and lead to some of the medical complications. The guidelines for care involve the work of multiple professionals; the following is a guide for the evaluation and treatment for males and females affected by FXS.

One can utilize the international classification of impairments, disabilities and handicaps (ICIDH) (World Health Organization, 1980) to develop a broader understanding of the nature and consequences of fragile X syndrome (Bailey & Nelson, 1995). This framework includes three components. 1) Impairment - the overall physical, biochemical, and mental deficits associated with fragile X syndrome; 2) Disability - the consequences of the impairment which leads to a restriction or a lack of an ability to perform an activity in a normal manner; 3) Handicap or disadvantage - which covers limitations on an individuals typical role or activities as a result of his or her disability or impairment.

In fragile X syndrome there is a mutation within the Fragile X Mental Retardation 1 (FMR1) gene which involves an expansion of a trinucleotide repeat (CGG). Individuals in the normal population have approximately 5 to 40 CGG repeats within FMR1 and individuals who are carriers for fragile X have approximately 60 to 200 CGG repeats (premutation). The premutation causes instability within FMR1 such that when the gene is passed on to the next generation by a female, there is a high risk for expansion to the full mutation which is greater than 200 CGG repeats. The full mutation is usually associated with methylation of FMR1, which prevents transcription and subsequent translation of the FMR1 gene into the FMR1 protein (FMRP). It is the lack of FMRP which causes fragile X syndrome. Individuals who have a significant deficit in FMRP production, however, may also be affected with a mild version of fragile X syndrome leading to learning disabilities and/or emotional problems. The impairment, therefore, in fragile X syndrome is the lack of FMRP causing significant intellectual deficits in addition to emotional problems and a connective tissue dysplasia.

Typical physical features include a long face, prominent ears, large testicles (macroorchidism), loose joints, flat feet, and mitral valve prolapse (MVP). The following guidelines discuss when and how to diagnosis and treat physical impairments associated with fragile X syndrome in addition to cognitive, emotional and behavioral deficits. The disability associated with fragile X syndrome may involve difficulties with interpersonal relationships, such as shyness and social anxiety, in addition to communication problems, behavior difficulties, motor coordination problems and academic difficulties. The multidisciplinary evaluation outlined in Table 1 provides a model framework for how disabilities in a number of areas can be assessed. Such an evaluation leads to an overall treatment program. The disabilities associated with FXS lead to handicaps or specific disadvantages which vary from patient to patient. Both males and females affected by FXS often score higher on scales which are designed to measure one's adaptive abilities than one would predict from overall intellectual assessments. An assessment scale such as the Vineland Adaptive Behavior Scale does an excellent job in assessing adaptations in communication, personal chores of daily living, communication skills and motor skills (Dykens, 1995). Although fragile X ultimately decreases the life successes of individuals who are significantly affected, there are a number of strengths particularly in daily living skills which persist throughout development.

Prenatal

Individuals who have a family history of mental retardation, or who are known carriers of the FMR1 gene mutation, can obtain prenatal diagnosis including chorionic villus sampling (CVS) and/or amniocentesis studies. The analysis of the FMR1 gene mutation should take place with appropriate molecular techniques, which demonstrate the CGG amplification within the FMR1 gene (Rousseau et al., 1994; Brown 1996). Preimplantation diagnostic services and in vitro fertilization are also available and have been reviewed by Black (1994). General guidelines regarding the prognostic differences between those that carry the premutation verses the full mutation can be provided to the family. More detailed prognostic information, for instance related to the degree of methylation, is unreliable in prenatal studies. Genetic counseling is essential for interpreting the complex DNA information for the family and providing support during and after the decision making process (Cronister 1996; McConkie-Rosell et al., 1995).

Infancy

1. The child who is diagnosed in infancy with FXS requires a careful look for possible connective tissue abnormalities including cleft palate, clubfoot, congenital hip dislocations, and gastroesophageal reflux (GER). There have also been reports of an increase in sudden infant death (SIDS), in addition to apnea (Fryns et al. 1988; Tirosh & Borochowitz, 1992) in FXS. Although most babies with FXS do well, some infants are described as excessively irritable, stiff, or unable to cuddle. Oral motor coordination problems may interfere with feeding; vomiting secondary to GER is common. The history should include questions regarding all of these problems.

2. At the time of diagnosis, families should be referred to a genetic counselor so that further family studies can be carried out and ongoing support given to the family (Cronister, 1996).

3. A developmental team evaluation including audiology, occupational therapy (OT), physical therapy (PT), psychology, speech and language, and pediatrics should take place within the first year (Table 1). Referral to a developmentally appropriate infant program should also take place.

4. Infants with FXS are at high risk for recurrent otitis media and subsequent hearing loss related to fluid in the middle ear. Treatment of recurrent otitis media should be aggressive and usually includes the placement of PE tubes by an ENT physician.

4. After the diagnosis is made at any age, a referral to a parent support group is helpful. The health care provider should also provide the family with written information on fragile X syndrome. The National Fragile X Foundation can also be contacted for further information for both parents and professionals and for a list of parent support groups around the country at (800) 688-8765 or (510) 763-6030.

5.

Toddler and Preschool Period

1. Developmental progress needs to be followed, preferably, on a yearly basis utilizing standardized tests such as the Bayley Scales of Infant Development or the Kaufman Assessment Battery for Children.

2. Language delays are most notable after 2 years of age. The initiation of more intensive speech and language (S&L) therapy on an individual basis is recommended at this time. Consideration of combined OT/S&L therapy may be helpful for the child (Scharfenaker et al.,

1996). If the child is nonverbal after 2 years, consider augmentative and alternative communication evaluation and treatment.

3. Motor problems including hypotonia, fine and gross motor in coordination, motor planning difficulties and sensory integration deficits are common. An evaluation by an occupational therapist and/or physical therapist is recommended with ongoing follow-up treatment.

4. Behavioral difficulties often become significantly problematic in the 2nd or 3rd year and they may include tantrums, hyperactivity, eating problems, and/or sleeping difficulties. Psychological evaluation and treatment of the behavioral problems is frequently indicated and both family therapy and individual therapy can be utilized. Behavioral modification or management techniques can be helpful.

5. The utilization of a preschool developmental educational program is often indicated. A multidisciplinary evaluation (Table 1) can outline an optimal education and therapy program for the child. Usually children with FXS can be mainstreamed or included in an educational setting with normal children since modeling of appropriate behavior is quite helpful for children with FXS. These educational settings usually include individual and group therapy with a speech and language therapist, and an occupational therapist and/or physical therapist.

6. Pharmacological intervention is most helpful after 3 years of age, although below 5 years side effects are common. Medication intervention issues usually focus on decreasing attention deficit hyperactivity disorder (ADHD) symptoms or tantrums. Medications which can be used include methylphenidate, dextroamphetamine, guantacine, and clonidine (Hagerman 1996b, Hagerman 1999).

7. The health care provider should be alert for possible seizures which occur in 15 to 20% of children with FXS. The seizures may be partial motor, generalized, or partial complex. If there is history of staring spells or seizure-like activity, an electroencephalogram (EEG) should be obtained in both the waking and sleeping state. Anticonvulsant medication should be utilized if seizures are present.

8. An ophthalmological evaluation is recommended by 4 years of age. This should take place earlier if obvious difficulties, such as strabismus, ptosis, nystagmus, or other ocular abnormalities, are present. Approximately 50% of children with FXS have a visual problem; treatment, such as patching for strabismus, is usually indicated at an early age (Maino et al., 1990; King et al., 1995).

9. Delays in toilet training are common in young children with FXS. The average time for successful toilet training in males is between 5 and 6 years of age and for females by 4 years of age (Fragile X Society, 1995). Behavioral approaches for toilet training can be helpful, (Luxem and Christopherson 1994) and the use of a videotape to help with positive behavior reinforcement can be beneficial. An example is a tape developed by Duke University (1-800-23POTTY) (Crepeau-Hobson & O'Connor, 1996).

School age

1. If the child is identified at this age, then subsequent genetic counseling and the use of DNA testing to confirm diagnosis is recommended (Cronister, 1996; Rousseau et al., 1994).

2. Educational intervention for children with FXS requires the expertise of special education teachers, speech and language pathologists, occupational/physical therapists, and psychologists. Positive behavior reinforcement in the classroom, inclusion settings whenever possible, and individual work in the language and motor areas are almost always helpful

(Wilson et al., 1994; Spirdiogiolissi et al., 1994; Scharfenaker et al., 1996). A thorough evaluation and an educational plan should be prepared by these professionals in conjunction with the family and reviewed on a yearly basis (Table 1). If problems develop, a review should occur more frequently.

3. The assessment and treatment of attention problems and hyperactivity are important components of both the medical and educational program for school aged children with FXS. The use of behavior checklists, particularly for hyperactivity, can be helpful for monitoring treatment effects (Conners, 1973; Barkley, 1990). The health care provider should also receive information from both the parents and the teachers regarding the child's behavior and progress in school.

4. The medical evaluation includes an assessment of possible connective tissue problems, which can lead to scoliosis, flat feet, hernias, and cardiac abnormalities.

5. Mitral valve prolapse can occur in approximately 50% of males with FXS, in addition to some females, and it is more common as the patient ages. If a click or murmur is detected on physical examination, then it is recommended that the child be referred to cardiology for an evaluation, which also includes an echocardiogram (Hagerman, 1996a). If mitral valve prolapse is confirmed, it is usually recommended that the child receive prophylaxis for subacute bacterial endocarditis (SBE), particularly for dental procedures or surgery that may be contaminated by endogenous bacteria (Durack, 1995).

6. If scoliosis is detected, baseline films of the total spine should be performed and clinical follow up on a regular basis is recommended. For significant scoliosis, referral to an orthopedist is recommended.

7. Enuresis is a common problem in FXS and behavioral interventions, in addition to restricting fluids, should be tried (reviewed by Schmitt, 1995). If enuresis continues, a trial of alarm systems can be utilized and these are discussed in Hagerman (1996b). Medications can also be utilized for enuresis (Thompson & Rey, 1995; Hagerman, 1996b).

8. If behavioral problems are significant at this time, referral to a child psychologist with expertise in children with developmental disabilities, is recommended.

9. Girls with a full mutation should also be evaluated by a multidisciplinary team. Since approximately 50% have significant cognitive deficits, IQ testing is also recommended (deVries et al., 1996). Shyness and social anxiety are common problems in females (Freund et al., 1993; Sobesky et al., 1995). An emotional evaluation will clarify the need for ongoing counseling. Medication may be helpful for ADHD problems, anxiety or mood lability (Hagerman, 1996b).

Early Adolescence

1. Behavior difficulties such as ADHD persist even in adolescence, although hyperactivity tends to improve with age. Aggression may become a more significant problem in early puberty requiring a careful assessment of precipitating factors. Often a positive behavior reinforcement program and modification of over stimulating aspects of the environment can decrease aggression. Frequently psychopharmacological intervention can be helpful for behavior problems and this includes the use of selective serotonin reuptake inhibitors, anti-anxiety agents, stimulants, clonidine or other medications. Atypical antipsychotic medications can be used to treat aggression, disorganization in thinking or significant psychotic ideation (Hagerman 1999). Evaluation by a psychologist is helpful, in addition to ongoing counseling.

2. Macroorchidism emerges in late childhood and it is more obvious in early adolescence (Lachiewicz et al., 1994). It does not require intervention, however, children with FXS are at risk for hernia or hydrocele formation (Fryns, 1994; Hagerman, 1996a).

3. Decline in cognitive functioning may become noticeable in late childhood or adolescence (Lachiewicz et al., 1987; Hodapp et al., 1990). A significant IQ decline is seen in approximately 1/3 of boys and girls with FXS, but it does not represent neurological deterioration or loss of milestones (Wright-Talamante et al., 1996).

Late Adolescence and Adulthood

The transition into adulthood and independent or community supported living is difficult for all individuals with developmental delays. Vocational training is an important need in high school and on-site job training is usually indicated as the adolescent makes the transition into the working world. Behavioral or emotional difficulties, including anxiety, social avoidance, and tantrum behavior or aggression, may be a significant problem at this stage.

1. The combined intervention of counseling and medication can be helpful for these difficulties. Again a careful assessment of the environment, including staff changes, possible infatuations with staff or peers, exposure to crowds or over stimulating situations, should be assessed.

2. Sex education is essential during adolescence and a counseling setting offers an appropriate environment for utilization of sex education programs designed for use with developmentally disabled persons (Circles, 1993).

3. At least yearly physical examinations to monitor cardiovascular parameters including blood pressure, growth, weight changes and neurological findings should be carried out, particularly for individuals who are treated with medication. Some medications require blood tests on a regular basis to monitor serum levels, liver functions studies, or other parameters.

4. In some cases, speech and language therapy, occupational therapy and physical therapy may be helpful even in the adolescent and adult, particularly if significant social/language deficits are present, or if severe sensory integration problems exist.

For more updated and detailed information regarding treatment, please visit our website at www.FragileX.org/medical/medical follow-up.

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