

Fragile X Syndrome and it's Association with Autism

약체X염색체 증후군과 자폐증과의 연관

Moon Bong Yang, M.A.*

양 문 봉

요약 : 약체X염색체 증후군은 최근에 발견된 X염색체와 관련된 정신박약의 일종으로서 현재 뇌의 발달과의 연관성에 대해 집중적으로 활발히 연구되고 있는 증후군이다. 인간의 세포내에는 보통 46 개의 염색체가 있으며 그 중에서 성을 구별짓는 염색체는 X와 Y이다. 남성은 X, Y를 소유하고 있으며 여성은 두개의 X를 소유하고 있다. 그러나 많은 연구 결과에 의하면 약체 X염색체증 환자의 경우에 X염색체의 가장자리 부분이 수축되어서 쉽게 갈라지거나 손상되기 쉬워서 그 증상을 약체염색체증이라 명명하였다. 특히 남성에게 두드러지게 나타나는데 그 이유는 성을 구별짓는 염색체가 X, Y 이므로 하나의 X염색체가 손상되었을 경우에 이를 보충할 수 없지만 여성의 경우에는 또다른 X염색체가 보충할 수 있는 가능성이 높으므로 남성이 여성보다 더 많은 분포를 나타낸다.

역사적으로 고찰할 때 어느 한나라에서 집중적으로 연구된 것이 아니고 세계 각국(특히 유럽 지역과 호주)의 공동의 노력으로 이와같은 최신 정보와 연구 결과를 탄생시킬 수 있었다.

임상적 신체적 특징으로는 비대 고환과 비대 귓바퀴가 두드러지게 관찰되고 있으며 언어적 특성으로는 표현 언어 능력부족, 인지 능력지체, 제한된 단어 사용, 그리고 의미없는 반향어를 사용한다.

또한 수 많은 부적응 행동을 보이기 때문에 자폐증과의 관련 여부에 대한 연구가 활발히 이루어지고 있을 뿐만 아니라 밀접한 연관성을 뒷받침하는 연구 결과들이 계속적으로 속출하고 있다.

치료 방법으로는 실험실 연구 결과에 의해 엽산의 투여가 효과적임이 주목되고 있으며 또한 생화학적 연구가 활발해 짐에 따라 더 많은 치료 방안이 소개될 것이 기대되어 진다.

약체염색체증은 정신박약 중에서 다운씨병 다음으로 많이 분포 되어 있기 때문에 모든 정신 장애아에게 약체X 염색체 검사를 실시하는 것을 이 저널은 크게 추천하고 있다.

중심 단어 : 약체 X 염색체 증후군 · 자폐증.

Overview

The fragile X syndrome is a recently discovered form of X-linked mental retardation and its discovery has been bringing forth great interest among researchers in terms of brain development. Its frequency is close to that of Down's syndrome, making

it the second most common chromosomal cause of mental retardation(Miller 1980).

Chromosome is a microscopic rod-shaped particle which can be found in the nucleus of the human cell and contains genes, which convey hereditary characteristics. Each nucleus normally contains 46 (23 pairs) chromosomes. Of the 46 chromosomes

Director, New England Institutes for Autistic Behavior Research.

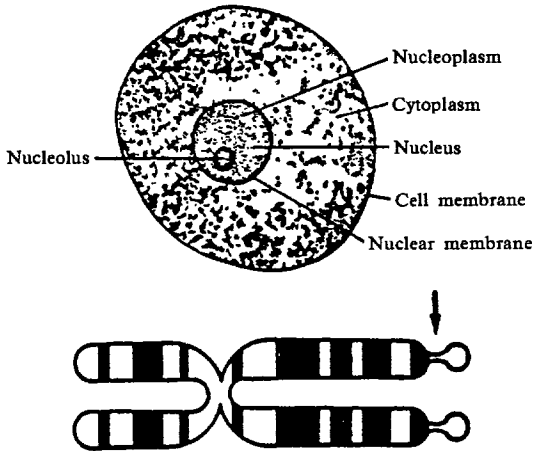


Fig. 1. Structure of the cell as seen with the light microscope.
 2. schematic drawing of the fragile X chromosome arrow points to fragile site.

in the each human cell, females have two X-shaped chromosomes and males have one X and Y chromosome.

The marker X or fragile X (Fra(X)) chromosomal abnormality is characterized in vitro by a site of constriction near each tip of the long arm of the X chromosome (figure 1). The constriction site appears prone to breakage, causing chromosomal lesion, hence the name "fragile X".

The delay in recognition of this chromosomal abnormality in the retarded population was the result of the need for specialized tissue culture media for its detection. In fact because the fragility of the X chromosome is not demonstrated in a regular chromosomal analysis, the fragile X syndrome is currently underdiagnosed (Hageman, McBogg 1983 a)

The unfolding fragile X story may have broad implications. For example, persons afflicted with fragile X retardation appear to be otherwise normal. That is, they don't suffer the facial deformities, uncoordinated movements and other physical problems seen in certain types of retardation, which suggests that the defective genes in fragile X chromosome affect nothing other than brain development

(Bishop 1982). Based on this suggestion recently quite a few studies on the association among fragile X chromosome and brain development delay have started focusing on the association of fragile X syndrome with autism.

The clinical picture of the fragile X syndrome includes unusual physical features, including large or prominent ears and macroorchidism, behavioral and emotional dysfunction, and characteristic speech delay, the great deal of which can be widely observed in the autistic population.

Another outstanding feature of fragile X syndrome is that there is an excess of incidence in males in relation to the females. If a male inherits a defective X chromosome, he will suffer the consequences. On the contrary, females are even far less subject to the fragile X because they have inherited an X chromosome from each parent: if one of the two X's is defective and the other is normal, the latter can serve as a "backup". Although a woman won't overtly suffer a disease borne by a defective X chromosome, there is a 50/50 chance that she will pass the disease on to her male child.

The purpose of this paper is to review the historical aspects, clinical features of this common form of X-linked mental retardation, its association of with autism, and the treatment.

Historical Aspects

The discovery of fragile X chromosome represents a major advance in this field and its history is a exciting saga of international contributions.

X-linked inheritance was not fully understood until the 1920's. However, the present era of active interest in the diagnosis and the treatment of the mentally retarded had its origin in the mid 19th century, at which period the incidence of the mental retardation may have been high at birth, but the number of the mentally retarded individuals who survived throughout the childhood was low. The one major group that would be expected to survive

is X-linked mental retardation because of their lack of significant anomalies (Hageman, McBogg 1983b). The eugenic movement, which was stemming from Charles Darwin's "the survival of the fittest" and Sir Francis Galton's "the unchecked fertility of the unfit", had a profound influence on the care of the mentally retarded. From then to the 1950's, there were very few new gains in the area of mental retardation. The first report, however, of sex-linked inheritance in association with severe mental retardation in males was reported by Martin and Bell in 1943. They described severe dementia in 11 males over two generations without apparent unusual physical features and described two mildly involved females in the same kindred, one who appeared to be mildly retarded and the other learning-disabled. They also reported that unusual psychotic-like behaviors were observed in two of the severely dysfunctional males and that significant language delays associated with extremely limited vocabulary and an inability to speak in complete sentences was noted in all the dysfunctional males. The authors emphasized the lack of unusual physical features which can be observed in many cases of mental retardation.

This first description of these mental diseases provided the ground of high degree of its association with autism.

Subsequent reports associating mental retardation with a sex-linked inheritance and a lack of distinctive physical features include those of Dunn et al and Renpenning et al. Henry Dunn, a pediatric neurologist in 1963, reported a very detailed description of an X-linked kindred with 20 affected males spanning three generation who were living in Western Canada. In the previous year of 1962, Renpenning, who was the co-author of this study, published another study of a family with X-linked mental retardation, but unlike a kindred involving a Canadian family with 20 retarded males which was reported with Henry Dunn in 1963, the family of his study has been shown not to have the fragile site. Most of Renpenning's cases were severely retarded

with microcephaly, which is not seen in the fragile X syndrome.

A new wave of medical interest in mental retardation began in 1956, when the human chromosomes were first clearly seen and counted by microscopy. Two years later in 1958 the extra chromosomes were discovered in Down Syndrome. In early 1960's amino acid analysis of blood and urine allowed recognition of metabolic errors associated with intellectual handicaps, which introduced the biochemical studies over behavioral and mental disorders.

In 1966, Prader published the normal range of testicular size according to chronological age.

This led to the development of the orchidometer which later helped to identify the enlargement of the testes as one of physical features observed in the fragile X patients.

In 1969, a geneticist named Herbert A. Lubs¹⁰ reported the first documenting the existence of the marker X chromosome in a kindred involving four retarded males over three generation. However at the contemporary time scientists carefully have avoided saying that the defective X chromosome "caused the mental retardation, for they presumed that the possibility exists that the chromosome defect is a byproduct of another cause of the retardation and that the defect may be present in some males who aren't retarded. Several years later Lubs' findings were confirmed in other countries such as Australia and France.

Reports of the fragile X site associated with mental retardation continued to appear in the literature, particularly in Australia. In 1977, Grant R. Sutherland, a young laboratory geneticist in Australia was the first to recognize the tissue culture dependency of the appearance of the fragile X site. He recultured a case with known chromosomal fragility, and the fragility disappeared in the enriched media which was a kind of nutrient broth with folic acid and high level of thymidine (Sutherland 1979). In 1978, Gillian Turner and his colleagues documented the

association of the fragile X chromosome and macroorchidism in certain males with sex-linked mental retardation.

A significant portion of cases of mental retardation with X-linked inheritance are not only reported to be associated with the fragile X chromosome, but characteristic physical features are documented by Herbst in 1980, Turner in 1989, Howard-Peebles in 1979, Fishburn in 1983 and others.

In the 1980's, many researchers have started getting more interested in the studies on the association of the fragile X syndrome with autism. In 1982, for the first time Brown and his colleagues of New York State Institute for Basic Research undertook to determine whether there is an association between autism and the marker X chromosome and also reported that autism was demonstrated in 4 males out of 16 fragile X positive males.

In the same year of 1982, David L. Meryash and his colleagues in Harvard medical school discussed the possibility of a syndrome of autism occurring in children with the fragile X syndrome in their study involving a 6-year-old mentally retarded child.

Subsequent reports over the associations of fragile X with autism include those of Levitas et al in 1983, Randi J, Hagerman et al in 1986, August et al in 1984 and others. Currently many researches in this area are being performed fervently and more positive results are expected.

Incidence

In 1980, Turner et al reported only 7 of 23 families with the fragile X chromosome, but others have found a higher incidence. For example, in 1979 Howard-Peeble and Stoddard reported three of three families, and in 1980 Jacobs et al reported six of seven families. If these studies are averaged, it appears that approximately 50% of families of X-linked mental retardation carry the fragile X (Miller 1980). Herbst and Miller (Miller 1980) calculated the frequency of X-linked mental retardation in Bri-

tish Columbia using the health surveillance registry over a 20-year period. They found a frequency of 1.83 per 1000 males and using the 50% figure they estimated the fragile X chromosome at 0.92 per 1000 male births. If this estimation is correct, the fragile X syndrome is second only to Down's syndrome as an identifiable chromosomal cause of mental retardation.

The fragile X chromosome has been also found in a variety of ethnic and racial groups. In a survey of moderately mentally retarded brothers of Australia in 1983, Fishburn et al reported the incidence of the fragile X was 1.9 per 10,000 normal males. In 1982, Blomquist et al reported a 6% incidence of fragile X in severely mentally retarded males in a northern Swedish county.

Clinical Features

A. physical features

Macroorchidism The major physical finding of the fragile X syndrome is macroorchidism or large testicles. This finding is most consistent after puberty and is seen in approximately 80% of patients (Turner 1980). Testicular enlargement has been variously reported from two to four times the normal adult volume (upper limit of normal is 25ml) unilaterally or bilaterally, to only mild increase in size (Prader 1966). An orchidometer can be used to measure the volume by comparison to similar ellipsoid shapes. Alternatively the volume can be calculated using the formula $V = 3.14/6(\text{length})(\text{width})(\text{Canty } 1976)$.

Facial features Other physical features, occurring with variable incidence in the fragile X syndrome, include: large or prominent ears, a large head circumference, a high or prominent forehead, elongated face with heavy features, mild hypoplasia of the middle third of the face, high arched palate, and a prominent chin (Turner et al 1980) (Jacobs et al 1980). Most of these features occur in less than 50% of patients. But the large or prominent

ears are the most common and obvious facial feature in the fragile X syndrome and are seen in the majority of patients : over 80% in most studies¹⁾ This feature is considered to be more frequent than macroorchidism. In fragile X adults, the pinnae length is often 7cm or longer. The ears are rarely low set or rotated but often protrude more than 30 degrees from the side of the head(McEritt 1947).

Growth Parameters On the contrary to these physical features, the growth percentiles demonstrate usually normal height and birth weight is also normal but it is often larger than in nonfragile X siblings(Yurner et al 1980).

B. Speech and language dysfunction

The fragile X patient exhibits language dysfunction ranging from nonverbal to verbal speech with moderate to severe expressive language delays. These characteristics include echolalia, perseveration, dysfluency, unusual speech melody, poor grammar closure, and the inability to maintain conversation and share information. The speech pattern has been described as jocular, narrative, staccato and repetitive(Turner et al 1980)(McEritt 1947).

The language presentation of fragile X patients is helpful in suggesting the diagnosis. The original report by Martin and Bell in 1949 of fragile X patients emphasized their verbal disability⁶⁾. Lehrke also emphasized the verbal disability found in sex-linked mental retardation in general and postulated the presence of major genes related to language and intelligence on the X chromosome(Lehrke 1972).

The fragile X patients also demonstrate speech characteristically associated with autistic children in terms of perseveration on a word, phrase or thought, immediate echolalia, and palilalia(Kethy et al 1983) Many researchers and theorists believe that the production of immediate echolalia, which has been defined as the meaningless repetition of a word or word group just spoken by another person, may be explained as a coping strategy or as a primitive attempt to maintain social interaction (Prizant 1983).

Palilalia, reiteration of his/her own words and phrases in a perseverative manner, has been described in detail in the literature by Ferguson and Boller as "compulsive repetition of words and phrases... reiterated with increasing rapidity and with a decrescendo of voice volume(Ferguson and Boller 1977)." Most of the palilalia of the fragile X patients occurs at the end of a phase or sentence without accompanying behaviors such as eye blinking or tension around the mouth.

When listening to the speech of the fragile X patients, noticeable and unusual prosody and intonation patterns could be observed. Prosody is the melody of speech including changes in pitch, quality, strength, duration and rhythm. These patients had a characteristic rhythmic intonation to their speech which turner et al 1980 described as "litany" speech¹⁴⁾.

Auditory memory ability, which is the ability to recall a series of test digits, syllables, words or sentences, was reported not to increase as mental age increased(Kethy et al 1983) whereas these skills are considered to increase normally with age and intelligence. When responding to 'wh' questions or describing pictures, the patients usually provide appropriate answers. However, there are frequent instances when they provide a related but out-of-context response instead of an appropriate answer owing to disturbed processing of auditory information.

C. Behavior dysfunction

Significant behavioral dysfunctions are frequently observed in patients with the fragile X syndrome. The spectrum of behavioral dysfunction is wide, ranging from severely selfabusive behavior to pleasant social interaction marred only by subtle lack of eye contact(Lévitass et al 1983). Although early reports emphasized sociable behavior in the fragile X, occasional dysfunctions such as hyperactivity, self-injury, schizophrenia and autism were also reported(Martin and Bell 1943)(Turner et al 1980).

The association with autism

individuals are being carefully studied, the association of the fragile X syndrome and autism has become more pronounced. Brown et al 1982 were the first to identify an association between autism and the fragile X syndrome¹⁶⁾. This association was also confirmed by Levitas et al(1983)¹⁷⁾ who performed behavioral evaluations on 10 fragile X patients diagnosed at the child development unit of the children's hospital, denver, colorado and reported that 60% of the fragile X patients met sufficient DSM-III criteria for the diagnosis of infantile autism or infantile autism residual state.

The extended studies of the same research team, on all 23 fragile X patients diagnosed at the same child development unit demonstrated a 69% incidence of autism(Levitas et al 1983). There was a clearly a spectrum of autism ranging from mild to severe among those patients.

The overall cognitive, language and perceptual dysfunctions which can be easily observed in the fragile X syndrome influence the behavioral dysfunction which may involve a spectrum of autistic features(Levitas et al 1983).

In 1986 the same research team(Hagerman, Jackson, Levitas, Rimland, and Braden) performed another extended study on an analysis of autism in 50 males with the fragile X syndrome identified by a chromosomal analysis. These 50 males were evaluated for autism using the following three criteria : 1) The DSM-III diagnostic criteria for autism (APA 1980), 2) The autism behavioral checklist (ABC) of the autism screening instrument of educational planning (ASIEP)(Kurç et al), and 3) The diagnostic checklist for behavior disturbed children, form E2 by Rimland(1984)³³⁾.

Sixteen percent of patients fulfilled all of DSM-III criteria for infantile autism and an additional 30% fulfilled criteria for infantile autism residual state. Thirty-one percent of patients had autism

using the ABC checklist but none of the patients fit the classical kanner syndrome as described by the E2 questionnaire. Some autistic traits were seen in almost all of the 50 fragile X patients, including eye avoidance in 90%, hand stereotypies in 88%, and echolalia speech in 96%. A pervasive lack of responsiveness was seen in 18% at their present age and in 44% in earlier childhood only. On the basis of their study findings that autistic symptoms are common in the fragile X syndrome, they recommended any patient with developmental delays and autism or autistic manifestations should have a chromosomal analysis, including the fragile X examination.

Current tendency is that two issues are to be analyzed : 1) the incidence of autism among patients with the fragile X syndrome who are ascertained completely and in an unbiased manner ; 2) the incidence of the fragile X syndrome among autistic patients. Most of reports has focused on the first issue : the incidenc of the autism among patients with the fragile X syndrome. The second question has been also studied in a limited number of autistic patients. Goldfine et al(1985) found no fragile X positive individuals in 30 autistic males studied and venter et al(1984) found the same in 40 autistic patients. Both of these recent reports have questioned the association of autism and the fragile X syndrome after cytogenetically studying a small number of autistic children who did not demonstrate the fragile site. However, McGillivray et al (1984) demonstrated the fragile X chromosome in 3 of 40(7.5%) autistic institutionalized males. Watson et al(1984) screened 76 autistic males and found a 5.3% incidence of the fragile X site. A larger multicenter swedish study(Blomquist et al, 1984) demonstrated the fragile X site in 13(16%) of 83 males with autism. Fisch et al(1985) reported cytogenic studies of 134 autistic patients demonstrated 19(14%) with the fragile X site. The trend of the studies about the association between the fragile X and autism menifests that larger screening endea-

vors are identifying a greater association (Hagerman et al 1986).

Treatment

Treatment for the fragile X patients consists of intervention from numerous disciplines. Adequate intervention requires a team involving parents, educators, speech pathologists, occupational and physical therapists, behavior and mental health specialists and physicians. A comprehensive program could be successful if team members communicate frequently and plan for common goals. In this writing I will focus mostly on the medical management.

The influence of folic acid on the fragile X chromosome in vitro suggested the possibility of a positive effect in vivo. The history of clinical use of folate therapy began with anecdotal reports. The treatment of the fragile X patients with high doses of folic acid was first reported by Lejeune (1981) in France. The next year of 1982, Lejeune found significant improvements were noted in seven of eight psychotic-like patients. At that time the patients were treated with intramuscular (I.M.) 5-formyltetrahydrofolate at doses around 0.5 mg/kg/day. Three out of eight patients were described as "almost fully recovered" from their psychotic symptoms. Lejeune also reported the use of oral folic acid in a dose of 1mg/kg/day in the treatment of an 18-month-old fragile X patient. The patient's motor coordination and developmental progress were said to have improved remarkably.

In 1982, another anecdotal report by Harpey in France described three fragile X patients who improved in "comportment" and in learning ability as well as behavior after treatment with oral intramuscular doses of folic acid.

Brown et al (1982) also documented improvement in attention span and activity level in two fragile X males, ages 10 and 18 years, who were treated with folic acid on the basis of the finding that the improvement in the activity level and atten-

tion span disappeared when the folic acid was discontinued.

The exciting potential of treatment of common cause of mental retardation as well as a number of cases of autistic traits has stimulated researchers to organize carefully controlled studies of treatment with high dose of folic acid.

The folic acid is a relatively benign drug even in large doses. However folic acid can be toxic to epileptic patients because some types of seizure activity can worsen on high level (Reynolds 1967).

In 1982, further supportive evidence (Lejeune et al 1982) for the role of folate in the development of the fragile X patients is found in the report by Lejeune of a fragile X child who deteriorated in psychomotor development after taking trimethoprim/sulfamethoxazole called Bactrim or Septra. This is an antibiotic which interferes with two steps in folate metabolism. This unusual response in the fragile X child is most probably related to the effect of the medication on folate metabolism. Therefore it is recommended that any medication which interferes with folate metabolism including INH, nitrofurantoin, Phenyton, Trimethoprim, and sulfamethoxazole, should be avoided in the fragile X patient.

In 1987, Rimland suggested in a fragile X foundation newsletter that in the case of the patients who did not improve under folic acid treatment, they probably should need extra amounts not only of folic acid, but of vitamin C, B1, B2, B6, etc, perhaps the minerals zinc, magnesium, manganese, etc. For in such cases folic acid alone could be expected to produce only limited effects.

Currently limited information concerning the role of folic acid in the central nervous system has been introduced. In 1979 Botez and Reynolds reported that 5-methyltetrahydrofolate donates a methyl group to methionine which is eventually used in the metabolic pathways (via S-adenosyl methionine) of at least 3 neurotransmitters including norepinephrine, serotonin and dopamine. It was also reported that since a metabolic block has not been desc-

ribed in the fragile X syndrome, folic acid is not known to overcome or circumvent such a block. Instead folic acid was reported to perhaps simply effect the balance among neurotransmitters which may be beneficial in developmental progress and behavior. It has been suggested by many researchers such as Geller et al (1982), Ritvo et al (1970), Boullin et al (1970), Yuwiler et al (1971), etc., that autistic children should have higher level of serotonin than the normal group. Also it was suggested by Geller et al that imbalance of neurotransmitters may be associated with autistic symptoms in hyper-serotonemic patients. It must be left to future investigations to delineate the specific functions of folate in the central nervous system or perhaps to find a more direct metabolic treatment for the fragile X syndrome as well as to find the effectiveness of folic acid in improving the fragility at the DNA level and in improving the clinical picture at both the behavioral and cognitive level.

Discussion

The fragile X syndrome is relatively common cause of X-linked mental retardation associated with unusual physical features, such as macroorchidism, prominent ears, significant behavioral and emotional dysfunction, and language delays. Recently as considerable similarities between the fragile X syndrome and autism have been reported continuously, the focus of many studies have been on the association of the fragile X site with autism. Actually autism represents a final common pathway in behavioral dysfunction for a small number of patients with a variety of organic disorders (Hagerman et al 1986). The incidence of autism in mental retardation is approximately 2.3% (Loffer 1978) and in congenital rubella approximately 7.4% (Chess 1977). Besides, problems such as Rett syndrome (Holm, 1985), hyparrhythmia (Taft and Cohen, 1971), chromosome abnormalities (Mariner et al, 1985), congenital infections (Rutter and Lockyer,

1967), phenylketonuria (DeMeyer et al, 1981), tuberous sclerosis (Lotter 1974), and Willams syndrome (Reiss et al, 1985) have been associated with autism. These disorders cause global cerebral dysfunction but usually fewer than 10% of patients in each diagnostic category develop autism.

On the contrary, many studies have demonstrated autism mostly in more than 10% of the fragile X patients. Furthermore, autistic-like characteristics such as hand stereotypies or echolalic and perseverative speech are seen in 90% of fragile X males (Hagerman et al 1986). Since the fragile X chromosome is seen in 5.3% (Watson et al, 1984) to 16% (Blomquist et al, 1985) of large population studies of autistic male, any male with autism or autistic-like traits should have a chromosome evaluation for the fragile X site (Levitas et al 1983) (Hagerman et al 1986).

An explicit definition of autism has been needed because of the heterogeneous nature of disorders which can lead to autism. In order to facilitate comparisons between studies concerning autism, a unified definition eventually culminated in DSM-III criteria (APA, 1980). The definition has tried to clarify the boundaries of autism that have varied in the past according to differences in the emphasis of individual researchers. However, one must examine critically the purpose of a definition because a unified theme of autism is the search for the cause of the syndrome of autism. A narrow definition of autism defines a more homogeneous group of patients that can be compared from one study to another (Hagerman et al 1986).

Many similarities between autism and fragile X in terms of the clinical behavioral or linguistic characteristics suggest that they represent a subgroup of autism which perhaps is related to a common neurophysiological dysfunction associated with the specific chromosomal anomaly of the (Levites et al 1983) fragile X. So a careful evaluation of the neurobiological or neurophysiological dysfunction in the fragile X syndrome holds promise for understand-

nding autism. The possibility of an effective treatment to modify the underlying neurophysiological dysfunction in the fragile X syndrome is an exciting prospect. However, although there have been promising anecdotal reports of the effectiveness of high-dose folic acid in the fragile X syndrome, the results of carefully controlled study are not yet available. Therefore the biochemical connection between fragility at the DNA level and disturbed neurophysiological development has yet to be made.

References

- American Psychiatric Association (APA)**(1980) : Diagnostic and statistical manual of mental disorders. Third edition. Washington, DC pp87-99
- Blomquist HK, Bohman M, Edvinsson SO, Gillberg C, Gustavson KH, Holmgren G, and Wahlstrom J**(1984) : Frequency of the fragile X syndrome in infantile autism. *Clin Genet* 26 : 513-517
- Blomquist HK, Gustavson KH, Holmgren G, Nordenson I, and Sweins A**(1982) : Fragile site X chromosomes and X-linked mental retardation in severely retarded boys in a northern swedish county. A prevalence study. *Clin Genet* 21 : 209-214
- Boullin D, Coleman MO, Brien A**(1970) : Abnormalities in platelet 5-HT efflux in patients with infantile autism. *Nature* 226 : 371-372
- Brown T, Jenkins E, Friedman E, et al**(1982) : A controlled trial of folic acid therapy in fragile X individuals. Presented at the 33rd annual meeting of the American Society of Human Genetics, Detroit, MI, Sept 29-Oct 2
- Brown WT, Jenkins EC, Fridman E, Brooks J, et al**(1982) : Autism is associated with the fragile X syndrome. *J Aut Dev Dis* 12 : 303-308
- Cantu JM, et al**(1976) : Inherited congenital normofunctional testicular hyperplasia and mental deficiency. *Hum Genet* 33 : 23-33
- Chess S**(1977) : Follow-up report on autism in congenital rubella. *J Aut Child Schiz* 7 : 68-81
- David LM, Ludwik SS, Park SG**(1982) : Infantile autism associated with the fragile X syndrome. *J Aut Dev Dis* 12 : 295-301
- DeMeyer MK, Jackson RK et al**(1981) : Infantile autism reviewed. A decade of research. *Schizophrenia Bulletin* 7 : 388-451
- Dunn HG, Renpenning H, et al**(1963) : Mental retardation as a sex-linked defect. *Am J Ment Defic* 67 : 827-848
- Ferguson KJ, Boller FA**(1977) : A different form of agaphia : Syntactic writing errors in patients with motor speech disorders. *Brain Lang* 4 : 382-389
- Fichbum J, Turner G, Daniel A, Brookwell R**(1982) : The diagnosis and frequency of X-linked conditions in a cohort of moderately retarded males with affected brothers. *Am J Med Genet* 14 : 713-724
- Fisch GS, Cohen IL, Wolf EG, Brown WT, Jenkins EC, and Gross A**(1985) : Autism and the fragile X syndrome submitted to *Am J Psychiatry*.
- Geller E, Ritvo ER, Freeman BJ, Yuwiler A**(1982) : Preliminary observations on the effect of fenfluramine on blood serotonin and symptoms in three autistic boys. *N Eng J Med* 307 : 165-168
- Gerald J August and Lillian H Lockhart**(1984) : Familial autism and the fragile X chromosome. *J Aut and Dev Disorder* 14 : 197-204
- Goldfine PE, McPherson PM, Heath GA, Hardesty VA, Beauregard LJ, and Gordon B**(1985) : Association of fragile X syndrome with autism. *Am J Psychiatry* 14 : 108-110
- Hagerman RJ, Jackson III AW, Levitas A, Rimland B, and Braden M**(1986) : An analysis of autism in fifty males with the fragile X syndrome. *Am J Med Genet* 23 : 359-374
- Hagerman RJ, Jackson AW, Levitas A, Rimland B, and Braden M**(1986) : An analysis of autism in fifty males with the fragile X syndrome. *Am J Med Genet* 23 : 359-374
- Hagerman RJ, Levitas A**(1983) : Dilantin and the fragile X syndrome. *New Eng J Med* 308 : 1423
- Hagerman RJ, McBogg P, et al**(1983) : The fragile X syndrome : Diagnose, Biochemistry and intervention. Dillon, Colorado : Sectra Publishing Co., Inc., pp1-75
- Hagerman RJ, McBogg P, et al**(1983) : The fragile X syndrome : History, diagnosis, and treatment. *Dev and Behav Pediatrics* 4 : 122-130
- Harpey JP**(1982) : Treatment of fragile X. *Pediatrics* 69 : 670
- Herbst D Miller**(1980) : Nonspecific X-linked mental

- retardation. II. The frequency in british columbia. *Am J Med Genet* 7 : 461-469
- Holm VA**(1985) : Rett's syndrome : A progressive developmental disability in girls. *J Dev Behav Pediatr* 6 : 32-36
- Howard-Peebles PN and Stoddard GR**(1979) : X-linked mental retardation with macroorchidism and marker X chromosomes. *Hum Genet* 50 : 247-251
- Hunter R, Barnes J, Oakeley HE, Matthew DW**(1970) : Toxicity of folic acid given in pharmacological doses to healthy volunteers. *Lancet* 1 : 61-63
- Jacobs P, Glover T, Mayer M**(1980) : X-linked mental retardation : A study of seven families. *Am J Med Genet* 7 : 471-489
- Jerry E, Bishop**(1982) : Gene defect linked to retarded males may solve mysteries : Does 'Fragile X Chromosome' account for many cases of hereditary condition ? *Wall Street Journal*, Jan 29
- Kathy Newell, et al**(1983) : Speech and language dysfunction in the fragile X syndrome. In Hagerman RJ, McBogg P(eds) : "The fragile X syndrome : Diagnosis, Biochemistry, and Intervention" Dillon, Colorado : Spectra Publishing Co., Inc., pp175-199
- Kurg BA, Arick JR, Almond PJ**() : Autism screening instrument for educational planning, revised, portland, oregon : ASIEP Educational Co.
- Lehrke RG**(1972) : A theory of X-linkage of major intellectual traits. *Am J Ment Defic* 76 : 611-619
- Lejeune H**(1982) : Is the fragile X syndrome amenable to treatment ? *Lancet* 1 : 273-274
- Lejeune J**(1981) : Metabolisme des monocarbones et syndrome de l'x fragile *Bull Acad Natl Med*(Paris) 165 : 1197-1206
- Lejeune J et al**(1982) : Fragilite du chromosome X et effets de la triméthoprimine. *Ann Genet*(Paris).25 : 149-151
- Levitas A, et al**(1983) : Behavioral dysfunction in the fragile X syndrome. In hagerman RJ, McBogg p (eds) : "The fragile X syndrome : Diagnosis. Biochemistry, and Intervention" Dillon, Colorado. : Spectra Purclishing Co., Inc.
- Levitas A, Hagerman RJ, Braden M, Rimland B, McBogg P Matus I**(1983) : Autism and the fragile X syndrome. *Dev Bev Pedia* 4 : 151-158
- Lotter V**(1978) : Childhood autism in africa. *J Child Psychol Psychiatry* 19 : 231-244
- Lubs HA**(1949) : A marker X chromosome. *Am J Hum Genet* 21 : 231-244
- Martin JP, Bell J**(1943) : A pedigree of mental defect showing sex-linkage. *J Neurol Psychiatry* 6 : 154-157
- Mariner R, Jackson AW, Levitas A, Hagerman RJ, Braden M, McBogg P, Berry R, and Smith AM**(1985) : Autism, mental retardation, and chromosomal abnormalities. *J Aut Dev Disorder*(in press)
- McEvitt W**(1947) : The problem of the protruding ear. *Plast Reconstructive. Surg* 2 : 480-496
- McGillivray BC, Dill FJ, Sandercock J, Herbst DS, and Tischler B**(1984) : Infantile autism-an occasional feature of X-linked mental retardation Abstract. *Am J Hum Genet* 36 : supplement. p35
- Prader A. Testicular size**(1966) : Assessment and clinical importance. *Triangle* 7 : 240-243
- Penpenning H, Gerrard JW, Zalesti WA, et al**(1962) : Familial sex-linked mental retardation. *Can Med Assoc J* 87 : 954-956
- Prizant B**(1983) : Language acquisition and communicative behavior in autism : Toward an understanding of the "whole" of it. *J Sp Hearing Dis* 48 : 296-307
- Reynolds EH**(1967) : Effects of folic acid on the mental state and fit frequency of drug treated epileptic patients. *Lancet* 1 : 1086-1088
- Rimland B**(1987) : The vitamin treatment of fragile X syndrom : A suggestion. In *Fragile X Foundation Newsletter*. Vol 3, Iss2, Spring
- Ritvo E, Yuwiler A, Geller E, Ormits E, and et al**(1970) : Increased blood serotonin and platelets in early infantile autism. *Archives of General Psychiatry* 23 : 566-572
- Sutherland GR**(1977) : Fragile sites on human chromosomes : Demonstration of their dependence on the type of tissue culture medium. *Science* 197 : 265-266
- Sutherland GR**(1979) : Heritable fragile sites on human chromosomes. I Effect of composition of culture media on expression. *Am J Hum Genet* 31 : 125-135
- Taft LT, Cohen HJ**(1971) : Hypsarhythmia and infantile autism : A clinical report. *J Aur Child Schiz* 1 : 327-335, 1971
- Turner G, et al**(1980) : X-linked mental retardation, Macroorchidism and Xg 27 fragile site. *J Pediatrics*

96 : 837-841

Turner G, Till R, Daniel A(1978) : Marker X chromosomes, Mental retardation and macroorchidism. N Engl J Med 299 : 1472

Venter P, Op's hof J, coetzee D, Van der walt C, and retief A(1984) : No marker X syndrome in autistic children. Hum Genet 67 : 107

Watson MS, Leckman JF, Annex B, Breg WR, Boles D,

Volkmar FR, Cohen DJ, Carter C(1984) : Fragile X in a survey of 75 autistic males(letter). N Eng J med 310 : 1462

Yuwiler A, Ritvo E, and et al(1971) : Examination of circadian rhythmicity of blood serotonin and platelets in autistic and non-autistic children. J Aut Child Schiz 1 : 421-435

ABSTRACT

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FRAGILE X SYNDROME AND IT'S ASSOCIATION WITH AUTISM

Moon Bong Yang, M.A.

Director, New England Institutes for Autistic Behavior Research

The fragile X syndrome, which is considered to be synonymous with the Martin-Bell syndrome, is a relatively common form of X-linked mental retardation. The syndrome seems to occur in many different ethnic groups and its prevalence among mentally retarded males has been estimated to be in the order of 2 to 6%. The karyotypic hallmark of the syndrome is made up with a pronounced constriction near each tip of the long arm of the X chromosome (fragile site), shown in vitro only under conditions in which thymidylate production is blocked (lowered folate levels). Special culture media are needed to demonstrate this constriction site. Major clinical features associated with the syndrome include macroorchidism, large or prominent ears, significant emotional and behavioral dysfunctions such as hyperactivity, self-injury, lack of eye contact and social interaction, schizophrenia, autism, etc., and speech and language dysfunctions ranging from nonverbal to verbal speech with moderate to severe expressive language delays. Some have minor clinical features in common such as an increase in birth weight, high forehead, prognathism, increased head circumference in infancy and childhood which did not persist into adult life.

The recent research findings have shown that the fragile X syndrome is associated with infantile autism. Many patients with the fragile X syndrome fulfill the diagnostic criteria for infantile autism. Therefore it is recommendable that any patient with developmental delays and autism or autistic manifestations should have a chromosomal analysis, including fragile X examination.

In the present review, historical aspects, incidence, and clinical features are presented. Recent anecdotal reports of the association with autism and the clinical improvement following high dose folic acid treatment will be discussed.

KEY WORD : fragile X Syndrome · Autism.