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Partha's Current Trends in Diagnosis & Management for Pediatric & Adolescent Practitioners

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2.1 FRAGILE X SYNDROME: CURRENT INSIGHT

INTRODUCTION

Fragile X syndrome (FXS) is a very frequent cause of intellectual disability (ID) in boys. The global prevalence is around 1 in 4,000 to 1 in 7,000, even though the prevalence differs in different regions of the world.[1] It is the most common hereditary cause of ID and autism. FXS occurs due to reduced or absent levels of Fragile X mental retardation protein (FMRP).

CLINICAL FEATURES[2]

Facial features: Big and projecting ears (75%), elongated face (more common in adulthood), big head, mandibular prognathism (80% of adult men), high arched palate, cleft palate (seen in less than 5%), crowding of teeth, and malocclusion.

Ocular features: Squint (8–20%), errors of refraction (20%), nystagmus (up to 13%), and ptosis (less than 10%).

Ear features: Early onset chronic otitis media, recurrent otitis media (45–60%), deafness due to repeated infections (rare), and large ears.

Neurological features: Seizures (16%), decreased tone (common in infancy), clonus (adults), and perseverative speech.

Behavioral features: Attention deficit hyperactivity disorder phenotype (80%), reduced eye contact (90%), anxiety (70–90%), stereotypic behavior (hand flapping), anger, and tantrums.

Neurodevelopmental features: Autism spectrum disorder (ASD; 50–60%), developmental delay (90% of boys and 30% of girls), language delay, and cognitive impairment.

Orthopedic and connective tissue features: Pes planus (flat feet), hyper-extensibility in the metacarpophalangeal joints, congenital hip dislocation, scoliosis, and club foot (rare).

Thorax and cardiac features: Pectus excavatum, mitral valve prolapse (seen by adult age), and abnormalities such as aortic dilatation.

Genitourinary features: Macroorchidism (95% of adolescent and adult men).

GENETIC BASE

Fragile X syndrome is caused by decreased or absent levels of FMRP. It is caused by a full mutation (FM; >200 CGG repeats) of the gene which usually is methylated in the proximal regulatory region of Fragile X mental retardation 1 (*FMR1*) gene.[3] The severity of the FXS physical features and intellectual impairment depends on the degree of the FMRP deficit and

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the resultant decrease of FMRP produced. This in turn is related to the number of cysteine-guanine-guanine (CGG) repeats and to the degree of FMR1 methylation. FM and methylation of the cytosine bases lead to silencing of transcription which leads to either deficiency or absence of the encoded protein FMRP. FMRP is a major protein regulator of the translation of many mRNAs involved in synaptic plasticity. Fragile X can manifest as intellectual and emotional disabilities, ranging from ID to learning problems, autism, and anxiety.

The *FMR1* gene codes for the FMR1 protein. It usually has 5–40 CGG repeats in the 5'-untranslated promoter. Individuals who are carriers for FXS [premutation (PM)] have 55–200 CGG repeats. On the basis of CGG repeat length, the *FMR1* gene is classified into four allelic forms—(1) normal allele (5–44 repeats), (2) intermediate allele (also referred as gray zone, inconclusive, or borderline) (45–54 repeats), (3) PM allele (55–200 repeats), and (4) FM allele (>200 repeats). The most common repeat length in normal allele is 29 or 30 CGG repeats. FM (more than 200 repeats) is the cause of FXS.

LABORATORY DIAGNOSIS

Karyotype: The narrowing of the distal end of the long arm of the X chromosome at the band 27.3 is known as fragile site.

Gold standard: The DNA test for the confirmation of FXS is a blend of polymerase chain reaction (PCR) and Southern blot analysis. PCR uses specific primers for the *FMR1* gene. Patients with an expanded FMR1 allele in both the FM and PM range can be identified.

Southern blot analysis: Apart from identifying the alleles throughout the mutation ranges, this also determines the methylation status. Southern blot can clearly differentiate between FM and PM alleles.

Indications

- Children who have either ID or developmental delay alone or with ASD with no known diagnosis must undergo FMR1 DNA testing. In the presence of characteristic facial features, a family history of ID, or macroorchidism, there is an augmented chance of the test being positive.
- In children with delay in developmental or ID but without a strong clinical suspicion of FXS, chromosomal microarray is suggested as a level one test (screening test). This will help to identify different chromosomal disorders such as DiGeorge (22q11.2 deletion) syndrome. In case chromosomal microarray is not conclusive, then Fragile X DNA test should be done because the clinical features are not well established in young children.

A PCR method named triplet repeat-primed PCR (TP-PCR) is evolving as a dependable method that can substitute Southern blot. Southern blot is

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time consuming and expensive. TP-PCR assays are displaying high promise in the field of FMR1 diagnostics due to their lesser costs and high sensitivity for large expansions. Information about the methylation pattern of FM/FMR1 alleles can also be supplemented using methylation-specific PCR, thus excluding the need of Southern blot for FMR1 diagnosis. In the near future, more advanced TP-PCR will be the only technology preferred for FMR1 analysis.

Antenatal diagnosis: PCR and Southern blot tests can be utilized for finding Fragile-X mutation in the fetus of pregnant carrier mother on chorionic villus or amniotic fluid sampling.

MANAGEMENT

Genetic counseling: The inheritance of FXS does not track a classic Mendelian inheritance pattern due to the dynamic repeat expansion. PM gets expanded to a FM when the maternal X chromosome with the PM gets passed on to the fetus. The mother's PM CGG repeat size also matters. When the repeat size is higher, larger is the risk of developing into a FM allele.

- Suggested for all affected members in the family or who may have a PM or have a child with a FM.
- Females who are carriers of a PM can transmit the FM to their offspring. The risk is based on the mother's CGG repeat size.
- PM males will pass their expanded allele to all daughters but not to their sons.
- There is a chance of developing ataxia [Fragile X-associated tremor/ataxia syndrome (FXTAS)], ovarian insufficiency [Fragile X-associated primary ovarian insufficiency (FXPOI)], anxiety, depression or other medical problems in adults who have a PM.
- If a father has FM, he will transmit only PM size alleles to their daughters. This is because the big repeat size of a FM cannot be preserved during spermatogenesis.

Specific Management

Supportive treatment: Speech therapy, occupational therapy, special educational services, and behavior therapy.

Pharmacotherapy

- *Methylphenidate:* Hyperactivity, inattention, and impulsivity
- *Alpha-2-adrenergic agonists:* Hyperactivity, hyper arousal to sensory stimuli, impulsivity, and aggressive behaviors
- *Melatonin:* Regulating sleep pattern
- *Selective serotonin reuptake inhibitors:* Mood disorders, anxiety, obsessive compulsive behaviors, and tantrums.

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What is New?

Minocycline: FMRP is a translational repressor. When it is absent as in Fragile X, there is upregulation of locally translated proteins involved in synaptic transmission and plasticity, including the matrix metalloproteinase-9 (MMP-9). The MMP-9 can interfere with appropriate synaptic connections. Minocycline lowers the increased levels of MMP-9. Minocycline in children with FXS aged 3.5 to 16 years showed improvement in their behavior.[3]

Metformin: Extracellular signal-regulated kinase (ERK) pathway is a subclass of the mitogen-activated protein kinase (MAPK) family of serine/threonine kinases, which regulate different cellular functions. ERK plays a critical role during neural development and in regulating social behaviors. ERK may be an important factor in human neurodevelopment and/or psychiatric disorders. In Fragile X, there is prolonged activation of the MEK-ERK pathway which may contribute to the behavioral features. Metformin lowers the MEK-ERK pathway. It has been shown to reduce many of Fragile-X features in animal models.

mGluR5 antagonists: FMRP is an RNA-binding protein that regulates the maturation of dendrites and modulates the plasticity of synapses by inhibition of protein synthesis by dendrites which is brought about by group 1 mGluR. Many aspects of the phenotype in FXS animal models, including the behavioral abnormalities, cognitive deficits, and dendritic spine changes, are thought to be attributable to excessive mGluR5 signaling. Fenobam, a drug that was developed originally as an anxiolytic agent, was found to be a selective mGluR5 antagonist. Trials are under way in FXS.[1] Another mGluR5 antagonist under trial is mavoglurant.

Lithium: Through the inhibition of inositol phosphate turnover, lithium can downregulate the phospholipase C signaling pathway. This reduces phospholipase C activity. The phospholipase pathway is used by mGluRs and other receptors to stimulate dendritic translation This action by lithium may alter the excessive dendritic protein synthesis in FXS. Lithium may provide some functional benefits in FXS.

Ampakines: In Fragile X, there is reduction in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor signaling. The impairment of cortical and hippocampal long-term potentiation thus produced are possible targets for pharmacologic management in Fragile X. Clinical trials have been done with AMPA receptor positive modulator (ampakine), CX516.

GABA agonists: GABA receptors are impaired in FXS. GABA agonists are under trial, e.g., ganaxolone, arbaclofen.

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2.2 ENZYME REPLACEMENT THERAPY

INTRODUCTION

Enzyme replacement therapy (ERT) is offered for lysosomal storage disorders (LSDs). LSDs are a cluster of infrequent inborn errors of metabolism. LSDs involve multiple system causing impaired growth, vision, ambulation, cardiac, or pulmonary function, leading to incapacitating bone and joint disease and shorten the lifespan. This happens because of deficiency of any one of the 50 lysosomal enzymes, activator proteins, or membrane transport proteins.[1] In India, incidence of LSDs is unknown. The incidence is 1 in 5,000–8,000 live births in the United States, Europe, and Australia. The common LSDs are Gaucher disease, Fabry disease, and mucopolysaccharidosis (MPS) type I.

BACKGROUND

The idea of substituting the faulty enzymes with a recombinant human enzyme in LSDs was first put forward by Christian de Duve in 1964.[2] Brady et al., at the National Institute of Health, USA, gave purified human placental glucocerebrosidase intravenously to a 15-year-old and a 51-year-old patient with Gaucher disease.[2] This product derived from the placenta and introduced in 1991 was the first ERT and was known as alglucerase.

In India, the first publication of ERT was from BARC Hospital, Mumbai. A 5-year-old boy was initiated on human placenta-derived alglucerase (Ceredase) in 1999. ERT for diseases apart from Gaucher disease was introduced in India in the following years.

What is New?

At present, ERT is manufactured using the DNA recombinant technology and is available commercially for 10 LSDs.

Current globally marketed ERT products are given in **Table 2.2.1**.

MANAGEMENT

The intravenous (IV) administrations of allowable enzymes in the LSDs usually show noteworthy clinical benefits, including improved walking capacity, ameliorated respiratory difficulties, and better life quality.

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TABLE 2.2.1: Enzyme replacement therapy products.

Disease	*Product*	*Company*	*Treatment in India*	*Dose/frequency (IV infusion)*	*Approximate annual cost (INR)—10 kg child*
Gaucher	Imiglucerase	Sanofi-Genzyme	2002	60 units/kg/EOW	40 lakhs
	Velaglucerase alfa	Shire HGT	2014	60 units/kg/EOW	70 lakhs
	Taliglucerase alfa	Protalix		60 units/kg q EOW	
Fabry	Agalsidase beta	Sanofi-Genzyme	2005	1 mg/kg EOW	20 lakhs
	Agalsidase alfa	Shire HGT	2014	0.2 mg/kg EOW	20 lakhs
Pompe	Alglucosidase alfa	Sanofi-Genzyme	2008	20 mg/kg EOW	49 lakhs
MPS§ I	Laronidase	Sanofi-Genzyme	2006	0.58 mg/kg weekly	46 lakhs
MPS II	Idursulfase	Shire HGT	2014	0.5 mg/kg weekly	1 crore
MPS IVA	Elosulfase α	BioMarin		2 mg/kg weekly	1.3 crores
MPS VI	Galsulfase	BioMarin	2017	1 mg/kg weekly	1.1 crores
MPS VII	Vestronidase α	Ultragenyx	Not available	4 mg/kg EOW	
Lysosomal acid lipase deficiency	Sebelipase α	Alexion	Not available	1–3 mg/kg weekly	3.2 crores
Neuronal ceroid lipofuscinosis type 2	Cerliponase α	BioMarin	Not available	300 mg EOW Intraventricular	4.7 crores

(EOW: every other week; IV: intravenous; HGT: human genetic therapies; MPS: mucopolysaccharidosis)

Drawbacks

- Continuous treatment is needed for improved clinical outcome in the LSDs. Hence, it may not be cost-effective. Availability of treatment is also a major shortcoming since it is available only in certain centers.
- The body's immune response results in IgG antibody generation against the infused enzymes. This can be dangerous to the patient and it can also reduce the efficacy and success of the treatment.
- The biodistribution of the enzymes into the specific sites of pathology [especially into central nervous system (CNS), bone, cartilage, cornea, and heart] is a prominent challenge.
- The enzymes do not cross the blood–brain barrier (BBB) and hence the CNS manifestations are not rectified.

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What is New?

- ERT often does not provide the anticipated clinical consequences due to its nonspecific biodistribution, low bioavailability, and high rate of degradation. Development of safe and effective targeted enzyme delivery systems (EDSs) may offer a hopeful substitute to the presently used treatments in LSDs.
- Increasing the existence of mannose 6-phosphate receptors (M6PRs) residues on the recombinant enzyme or increasing the expression rate of the M6PRs on the target cells can make the cellular uptake of the enzyme through targeting mechanism more efficient. M6P targets the lysosomes.
- Development of enzyme-loaded nanosystems (ENSs) is under research. Here advanced nanobiomaterials are used to improve the efficacy of ERT while minimizing the side effects. The different nanocarriers that have been tried include biodegradable nanomicelles, nanoliposomes, and polymer- and lipid-based nanoparticles.
- Enzyme encapsulation is another research process in which unsought immunologic reactions and biodegradation can be decreased. It also safeguards the recombinant enzymes from undesirable biological influences, nonselective biodistribution, and improves the pharmacological response by increasing the drug absorption, controlled release of enzyme supply, and the pharmacokinetics.
- Targeted nanosystems such as polymeric/lipid nanoparticles, attached with homing agents (e.g., aptamers or antibodies), can be used in going across the biological barriers such as BBB and blood-ocular-barrier.
- Engineered cells can be enclosed by biocompatible devices and they can be rooted into different sites in the host body, particularly in difficult-to-access sites such as the brain and eye, to distribute constant amounts of the enzyme for lengthy periods of time.
- The final therapy of LSDs in the future would be based on the gene and/or cell therapy.

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2.3 STEM CELL TRANSPLANT IN NEURODEVELOPMENTAL DISORDERS

INTRODUCTION[1]

Stem cells have two defining characteristics—(1) perpetual self-renewal and (2) the ability to differentiate into a specialized adult cell type. The two major classes of stem cells are—(1) pluripotent that can become any cell in

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the adult body, and (2) multipotent that are restricted to becoming a more limited population of cells.

Pluripotent stem cells are present for a very brief duration of time in the embryo. These cells differentiate into multipotent stem cells which are highly specialized. They eventually produce the specialized body tissues. Pluripotent stem cells come from embryos. They are also called "embryonic stem cells". The "inner cell mass" of a few days old preimplantation embryos comprise about 10–15% pluripotent cells. These pluripotent cells can be removed and cultured.

The plasticity of the multipotent stem cells enables them to change into various progenitor cells for a particular germ layer or can be restricted to a few specialized cell types of a specific tissue. In the embryo, the multipotent stem cells are seen during gastrulation (day 14–15). These cells do not have the ability to change into all the three germ cell layer cells, hence they are not pluripotent.

The unipotent cells change into any one specialized cell type (e.g., skin stem cells or muscle stem cells). They are restricted to the specific organ and their capacity to differentiate is limited. It is the role of these limited progenitor cells to maintain tissue integrity by replacing aging cells or cells which have sustained damage.

Multipotent stem cells seen in bone marrow have been used for treatment since the 1960s. New sources for multipotent stem cells identified are placenta and umbilical cord blood. Recently, in the heart, stem cells with the capability of becoming cardiac myocytes have been detected. Neuroprogenitor cells are seen in the brain.

Differentiation of stem cells into specific cell types is brought about by different incubation factors, different growth factors, and chemicals and complex substrates used for cells growth. For example, in order to cause stem cells to differentiate into cardiac myocytes, the chemical activin A and the growth factor BMP-4 are utilized. Pluripotent cells are exposed to these factors in a rigidly controlled method—both the concentration and temporality are rigidly controlled. Stem cells under these conditions are efficiently changed into cardiac myocytes, but even then, only 30% of cells are likely to evolve into cardiac myocytes.

CLINICAL USE

Pluripotent stem cells are yet to be used for treatment in human beings. The reason being unwanted teratoma formation in animal studies. Teratomas are composed of all cell types from the early germ layers. Cells derived from pluripotent cells have been used to treat diabetes, acute spinal cord injury or visual impairment in animals. Other animal studies which are going on are in Parkinson's disease, muscular dystrophy, and heart failure.

Since 1960s, multipotent stem cells collected from bone marrow have been made use of in the treatment of leukemia, myeloma, and lymphoma.

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Stem cell therapies are probable treatments for spinal cord injury, heart failure, retinal and macular degeneration, tendon ruptures, and diabetes type 1.

What is New?

In 2006, scientists Shinya Yamanaka and Kazutoshi Takahashi discovered reprograming of multipotent adult stem cells to the pluripotent state. This was based on animal studies where they reprogrammed mouse fibroblasts with four transcription factors (Oct-3/4, Sox2, KLF4, and c-Myc) and made them pluripotent. These stem cells are called induced pluripotent cells (iPSCs). After a year, the experiment was effectively done with human cells. iPSCs avoid the need for embryos in stem cell therapy. They are autologous because they are obtained from the patient's own cells. Hence, there is no risk of immune rejection. Fibroblasts are most excellent stem cell source since they can be stimulated in a rapid and controlled manner.

Stem Cell Therapy in Autism[2]

Due to their paracrine action, stem cells may prove to be useful for ASD therapy. The cytokines, chemokines, and growth factors released by stem cells can repair/restore injured tissues. Stems cells also have immunomodulatory properties. Immune system abnormalities and strong pro-inflammatory cytokine production are seen in ASD subjects **(Table 2.3.1)**.

Different types of stem cells along with their mechanism of action have been discussed in **Table 2.3.1**.

Stem Cells and Autism: Clinical Trials

- Sharma et al. conducted an open-label proof-of-concept study on the use of autologous bone marrow-derived mononuclear cell (BMMNC) transplantation. The selected ASD children were given intrathecal cellular therapy and later occupational therapy, sensory integrative approach, speech therapy, psychological intervention, and specific dietary recommendations. Multipotent adult bone marrow cells were used intrathecally. Following therapy, Indian Scale for Assessment of Autism (ISAA) was performed to demonstrate improvement. The domains of social relationships and reciprocity (improved eye contact, social smile, and reaching out to others), cognitive aspects (attention, concentration, and time of response), and speech and language patterns (reduction in echolalic speech, reduced stereotyped repetitive use of language, decrease in infantile squeals or unusual noises, better ability to initiate or sustain conversation with others, and improved ability to grasp the pragmatics of the conversation) were noted. Positron emission tomography (PET) scan showed improved functioning of areas of frontal lobe, cerebellum, amygdala, hippocampus,

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TABLE 2.3.1: Stem cells and their mechanism of action.

Type of stem cells	*Source*	*Mechanism of action*
Fetal stem cells	Fetus, fetal blood, placenta, amniotic membrane, amniotic fluid, umbilical cord	Secretion of neurotrophic factors, immunomodulatory capacities, suppression of proinflammatory processes
Mesenchymal stem cells	Bone marrow, umbilical cord	• Paracrine secretion of several anti-inflammatory and survival-promoting molecules (i.e., VEGF, HGF, BDNF, NGF) • Neuroprotective effects • Hypoimmunogenic and immunosuppressive properties
Neural stem cells	Brain (subventricular zone of lateral ventricles and subgranular zone of hippocampus)	• Secretion of neurotrophic factors • Maintenance of homeostasis • Neuroprotective effects • Differentiation into neural-type cells
Adipo-derived stem cells	Adipose tissue	• Secretion of trophic factors • Immunosuppressive and hypoimmunogenic effects
Umbilical cord and amniotic fluid-derived stem cells	Umbilical cord, placenta, amniotic fluid	• In vitro growth capacity • Low immunogenicity and immunomodulation properties
Hematopoietic stem cells	Blood, bone marrow, umbilical cord	Paracrine activity
Induced pluripotent stem cells	Any cell type	Differentiation capacity

(BDNF: brain-derived neurotrophic factor; HGF: hepatocyte growth factor; NGF: nerve growth factor; VEGF: vascular endothelial growth factor)

parahippocampus, and mesial temporal lobe after 6 months of cellular therapy. The study had limitations such as small sample size, lack of randomization, and absence of a control group.[2]

- Lv et al. performed a Phase I/II trial to investigate the safety and efficacy of combined transplantation of human cord blood mononuclear cells (CBMNCs) and umbilical cord-derived mesenchymal stem cells (UCMSCs) in treating children with autism.[2] 37 autistic children including one female patient were randomly classified into control (mean age 5.60) and experimental groups. This group was again separated into CBMNC group (mean age 7.4) and combined group (mean age 6.2) who benefited from both types of cells. In both groups, administration was done four times at an interval of 5–7 days. Transplantation was done intravenously and/or intrathecally (2 mL) per treatment. Marked improvements were seen in stereotypic behaviors and lethargy/social withdrawal. After a 24-week follow-up, the combination group showed better improvement than CBMNC group, with respect to control group. Among limitations, registered subjects were not characterized on disease severity. The long-term usefulness (beyond 24 weeks) was not estimated.

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- In one more open-label pilot study, 45 autistic children (39 males, 6 females, mean age 6.9) were registered to evaluate the safety of the use of fetal stem cells (FSCs) in ASDs. FSCs were collected from 5- to 9-week-old human fetuses (one donor sample for each transplantation process) resulting from pregnancy terminations done willingly. The cells were intravenously transplanted on day 1. On the second day, the fetal cells were inoculated into the subcutaneous abdominal adipose tissues. The early post-cellular transplantation consequences detected were better eye contact, appetite, and socialization. Autism Treatment Evaluation Checklist and ABC scores at follow-up of 6 and 12 months displayed advances in sociability, cognitive ability, and behaviors, particularly at 12 months.
- Clinical trial was done as Phase I/II on autologous umbilical cord blood (AUCB) transplantation in idiopathic ASD children. One was a crossover study. ASD children (age 2–7 years), with umbilical cord blood cryopreserved and kept aside and transplanted with either AUCB or placebo (0.9% saline solution). They were assessed at starting point, 12 and 24 weeks. The subjects were randomly separated into two groups. The first group was given cord blood infusion and then saline injection. The second group received saline infusion first, then cord blood infusion. Since it was a crossover study, each subject serves as its own control. Expressive/Receptive One Word Picture Vocabulary Tests scores reported minimal evidence of clinical effectiveness of AUCB therapy.

The limitations of all the studies were:

- Comparatively trivial number of subjects.
- Absence of long-term outcomes studies.
- The efficiency of cell therapies in ASDs should be assessed by internationally validated, standardized, and, if possible, harmonized scales. Use of diverse scales and scores may not show the effective result of cell transplantation.
- Better description of cell types should be done so that the right selection of cell can be done.
- There should be an agreement about the effective cell dosage and the optimal stem cell type for cellular grafts.

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