DPT

DEVELOPMENTAL PEDIATRICS TODAY

February 2021

Monthly e-Newsletter of IAP Chapter of Neurodevelopmental Pediatrics

Inside

Editorial

Dear Friends and respected Seniors,

Greetings from the chapter!

Hope all of you have received 2 doses of Covid Vaccine. Our country is witnessing a resurgence of Covid cases in March after 2 months of reduced tally, with 5 states, namely Maharashtra, Punjab, Karnataka, Gujrat and Tamil Nadu accounting for 78.41 % of new infections.

Yet life seems to be returning back to normal with more and more clinics opening full time as well as physical CMEs and meetings have started happening.

Pedicon 2021 was a grand success despite the Pandemic. It was first time that conference was held in hybrid mode with online and offline registrations. There were 170000 online registrations. The onsite registrations were restricted due to the Pandemic and was held taking adequate precautions with everyone wearing mask, hand sanitization and social distancing. In any case people traveling to Mumbai from Delhi NCR, Rajasthan, Gujrat, Goa had to get their Covid RTPCR tested prior to travel.

Local Organizing committee chairperson for Pedicon 2021 was , Dr. Samir Dalwai.

There were two very meaningful preconference workshops, one was "Uday mission "which was attended by quite a few of our chapter members and the other one was a module on Covid infection. Uday mission was very well attended and will add few more dimensions to our practice as Developmental pediatricians.

The conference kick started the discussion towards "Early childhood development module" in collaboration with WHO and UNICEF , which was the theme of this conference. National coordinator for this module on Early childhood development is Dr. Samir Dalwai. Some of our chapter members were a part of the consultative meeting for the development of the module. This module will be rolled out soon.

In the symposium on ECD (WHO), Dr. Samir Dalwai and Dr. Chhaya Prasad gave very lucid and informative talk.

This Pedicon also started a "Tet a Tat "with the President which was anchored very well by our very own dynamic ex Chairperson of the Chapter, Dr. Samir Dalwai.

February has some important days related to health such as 'International prenatal infection prevention month ' and 'National eating disorders awareness week (22-26 Feb.)'. The quiz addresses questions related to prenatal infections. There is a writeup on Prenatal

infections and early brain development and one writeup on eating disorder.

I hope you all enjoy reading and gain from this issue.

Dr. Lata Bhat
Chief Editor

Chairperson's Message

Dear Readers,

Greetings for the spring season !

The lovely sunshine and the fresh leaves and budding flowers are bringing in a lot of excitement in the air. So is the Neurodevelopment Chapter brimming with ideas to celebrate the spring season.

This issue focuses on the perinatal Infections and their effects on early brain development. A healthy start in life is the focus of this year's Action Plan of the Central IAP and our contribution to the growth of the nation is to see that the incidence of Neurodevelopment disorders is reduced. This highlights the importance of keeping vigilant in the first thousand days of life.

Along with WHO-assigned Prenatal Infection Prevention Month, we are also celebrating National Dental Day and National Eating Disorder Day this month. These reinforce as a reminder for each one of us to take care of dental health and address feeding issues in every child, which is often not our focus while managing a child with disabilities.

We have added a Google feedback form in this issue. We would like to hear from you and take your suggestions for further improvement.

Happy reading,

Dr. Shabina Ahmed MD, FIAP

National Chairperson

Neurodevelopmental Pediatrics Chapter of IAP

Snippets from the Secretary

Respected Seniors and dear friends,

Seasons greetings from the IAP Chapter of Neurodevelopmental Pediatrics.

The month started with the national conference of IAP (PEDICON 2021) which was held in a hybrid mode at Mumbai on the theme - Nurturing care for Early Childhood development. The theme is in sync with the IAP president's action plan on Early Childhood Development which encompasses five important components of nurturing care - adequate nutrition, responsive caregiving, security and safety, opportunities for learning, good health. IAP has partnered with WHO, UNICEF and NNF to take this program to all over the country with the aim of empowering the parents by involving the pediatricians. The chapter is looking forward to working in close collaboration with central IAP to make this program a success.

The chapter has started online teaching activities on every tuesday of the month as part of its fellowship program from the month of January and has received a good response from all the fellowship centers. These activities are open to all chapter members for viewing. Interested members can send a request for link to the chapter email at cdgiap@gmail.com.

February month has many important health days - International prenatal infection prevention month, National children's dental health month, National eating disorder awareness week (22 -26 Feb) and Rare diseases day (28 Feb). We have some interesting articles and journal scan related to these topics. Happy reading…….

Jai Hind! Jai IAP !

Wg Cdr (Dr) KS Multani

National Secretary

IAP Chapter of Neurodevelopmental Paediatrics

Prenatal Infections and Early Brain Development

The development and maturation of the human brain occur throughout the fe-tal period and is modulated by a set of complex interactions among various signaling receptors, genetic/epigenetic factors, and environmental influences. The principal stag-es of development during the gestational period are as follows: primary neurulation (weeks 3–4), prosencephalic development (months 2–3), neuronal proliferation (months 3–4), neuronal migration (months 3–5), neuronal organization (5 months postnatal period), and myelination. Myelination of the human brain begins in the sec-ond trimester in autero and continues postnatally into adulthood with the fastest growth occurring in the immediate neonatal period. Anomalous development in any of the aforementioned stages can result in cerebral pathology.

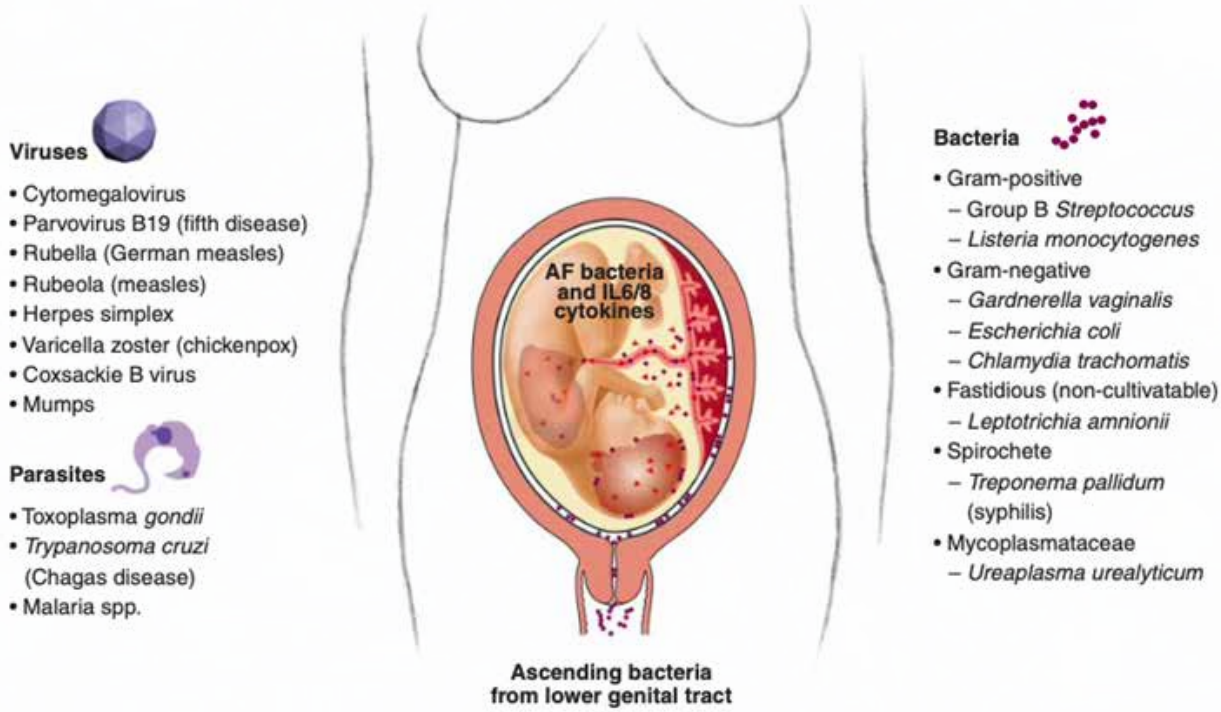


Figure 1 Bacteria, viruses, and parasites known to influence fetal development.

Fetal anomalies and long term effects on babies born to mother s who had various prenatal infections

Infection	Fetal Findings	Long Term Effects
Viral		
CMV	Periventricular calcifications, pseudocysts, and necrosis, microcephaly, subependymal cysts, ventriculomegaly, cerebellar hypoplasia, hypoplastic corpus callosum, lissencephaly, polymicrogyria	Although most infants with congenital CMV are asymptomatic at birth, about 10%–15% present with symptoms; a substantial proportion of these (approximately 40%–60%) develop long-term sequelae, such as sensorineural hearing loss (SNHL), cerebral palsy, mental retardation, and visual impairments. Sequelae are most frequent among infants with neurological signs at birth. CMV-related problems, particularly SNHL, also develop in about 10%–15% of children who are asymptomatic at birth. Cases of late-onset hearing loss have been reported, but it is unclear to what extent asymptomatic children remain at risk in the long term
Herpes simplex virus	Extensive cerebral cortical calcifications, possible microcephaly, encephalomalacia, hydrocephaly	Mental retardation, severe neurological deficits, encephalitis
HIV		Neurodevelopmental delay, especially gross motor function Poor performance on cognitive tests, decreased processing speed and visual spatial task performance Lower scores on Mental Developmental Index and Psychomotor Development Index
Influenza		Decreased IQ and Weschler Intelligence Scale information test scores at age 7 y Bipolar disorder (statistically significant in third trimester infections) Infantile autism
Lymphocytic choriomeningitis virus	Microcephaly, periventricular calcifications, pachygyria, cysts, and hydrocephalus, as well structural and functional abnormalities of the eye	Seizures Neurodevelopmental delay Nystagmus Strabismus esotropia or exotropia
Hepatatis C		Feeding difficulties or other adverse neurological outcomes
Enterovirus	Hydrocephalus	
Varicella zoster	Hydrocephalus, porencephaly, hydranencephaly, calcifications, polymicrogyria, and focal lissencephaly secondary to necrotizing encephalitis	
Rubella	Extensive cerebral cortical calcifications, microcephaly, subependymal cysts	Congenital rubella syndrome (CRS). The risk of congenital infection and defects is highest during the first 12 weeks of gestation and decreases thereafter; defects are rare after infection in the 20th week (or later) of gestation - Common congenital defects of CRS include cataracts, congenital heart disease, hearing impairment, and developmental delay. Infants with CRS often present with more than one of these signs but may also present with a single defect, most commonly hearing impairment.
Bacterial		

Syphilis	Hydrocephalus	Approximately 40% of babies born to women with untreated syphilis can be stillborn or die from the infection as a newborn. Babies born with congenital syphilis can have bone damage, severe anemia, enlarged liver and spleen, jaundice, nerve problems causing blindness or deafness, meningitis, or skin rashes
Parasitic		
Toxoplasmosis	Diffuse calcifications in the basal ganglia, periventricular calcifications, progressive hydrocephalus Increased length of cavum septum, pelucidum after midgestation influenza, toxoplasma antibody tilers, second-trimester respiratory illness, or periconceptional genital infection Ventricular enlargement secondary to brain substance loss/hypoplasia and/or cerebrospinal fluid drainage defects	Miscarriage or stillbirth. It can also cause serious and progressive visual, hearing, motor, cognitive, and other problems in a child Psychotic symptoms at age 12

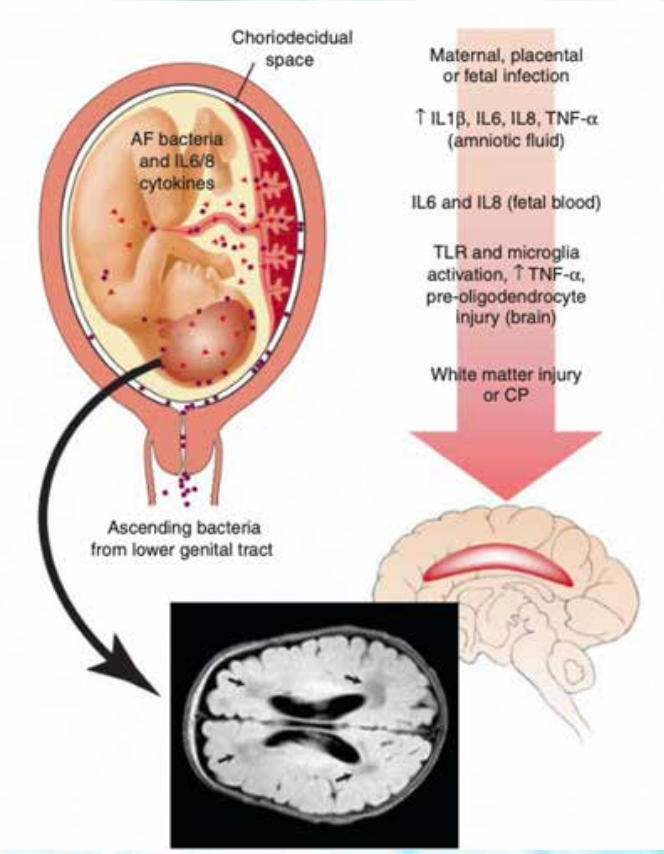
Other bacterial infections

Bacterial infections during pregnancy has been linked in a robust manner with the de-velopment of schizophrenia and ASD later in life. However , since most of these stud-ies analyse retrospective data, it is difficult demonstrate a specific causative relation-ship between maternal illness and fetal brain injury. It is not clear as yet whether this association between infection and ASDs/schizophrenia is related only to specific types of bacterial infections and/or at certain time periods in fetal development.

Role of cytokines effect on brain development

Cytokines are molecules produced by cells involved in the inflammatory pathway. They act to modulate the immune response by binding to receptors and causing the release of additional cytokines in a cascade-like mechanism. They are defined by their primary cellular origin: T-helper type 1 (TH1), functioning in cell-mediated immunity against intracellular pathogens; TH2, functioning to promote humoral immunity against extracellular pathogens; TH17 or proinflammatory cytokines, involved in the mediation of septic shock; and T-regulatory cytokines, involved in dampening and shutting off the inflammatory response. Generally speaking, the TH1 axis includes interleukin 2 (IL-2), tumor necrosis factor [beta] (TNF-[beta]), and interferon [gam-ma]. The TH2 axis includes IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13; the T-regulatory axis includes IL-1 antagonist, transforming growth factor [beta]; and the TH17/inflammatory axis includes IL-1[beta] and IL-17.

Proinflammatory cytokines can cause (1) direct damage to oligodendrocytes and neu-rons via the activation of microglial cells, (2) neurotoxicity, and (3) neurobehavioral abnormalities. One of the most commonly studied cytokines in the context of mater-nal infection and brain development is the proinflammatory cytokine, IL-6. Inter-keukin 6 is involved in the survival of various neurons, including acetylcholinesterase-positive, catecholaminergic, cholinergic, and dopaminergic neurons. It has also been shown that IL-6 can affect the electrical mechanism by which Purkinje and enteric neuron function.



Conclusion

Various types of evidence support the theory that maternal infection and/or inflammation occurring during critical periods of fetal development could alter brain structure and function in a time-sensitive manner. Specifically, in humans, bacterial infections during pregnancy have been weakly associated with abnormal psychological and cog-nitive development in their offspring, and both bacterial and viral infections are asso-ciated with abnormal brain structure in affected individuals. Both retrospective human data and findings from animal models suggest potential causative mechanisms for the association between infection and fetal brain injury; specifically, infection induces an inflammatory cascade characterized by elevations in critical cytokines such as IL-6, ultimately resulting in altered brain structure and function. Moreover, findings linking the histological and clinical markers of fetal and maternal infection in the setting of chorioamnionitis with alterations in psychiatric and neurological development further support this theory.

References

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What is ARFID?

DR. ASHISH SAHANI

Avoidant/Restrictive Food Intake Disorder (ARFID), oftentimes characterized as "extreme picky eating," is an eating disorder impacting thousands of individuals, particularly children. The meaning of "fear food" in clients with ARFID differs from clients with anorexia nervosa and bulimia. For individuals with ARFID the fear may stem from knowing they must eat, when they have no interest in eating, fearing the temperature might not be what they like, fear of choking or becoming sick or fear of eating a new food.

ARFID is the most common eating disorder in children, affecting almost 5 % of population with boys at greater risk.

DSM 5 CRITERIA FOR ARFID

Avoidant/Restrictive Food Intake Disorder (ARFID)

- An eating or feeding disturbance (e.g., apparent lack of interest in eating or food; avoidance based on the sensory characteristics of food; concern about aversive consequences of eating) as manifested by persistent failure to meet appropriate nutritional and/or energy needs associated with one (or more) of the following:
- Significant weight loss (or failure to achieve expected weight gain or faltering growth in children). • Significant nutritional deficiency.
- Dependence on enteral feeding or oral nutritional supplements.
- Marked interference with psychosocial functioning.
- The disturbance is not better explained by lack of available food or by an associated culturally sanctioned practice.
- The eating disturbance does not occur exclusively during the course of anorexia nervosa or bulimia nervosa, and there is no evidence of a disturbance in the way in which one's body weight or shape is experienced.
- The eating disturbance is not attributable to a concurrent medical condition or not better explained by another mental disorder. When the eating disturbance occurs in the context of another condition or disorder, the severity of the eating disturbance exceeds that routinely associated with the condition or disorder and warrants additional clinical attention

Types of ARFID

1. Lack of interest: clients with this type of ARFID have a genuine lack of interest in eating and food. They also get full quickly.
2. Sensory Avoidance: clients with sensory avoidance have issues with food tastes, textures, temperature and smells.
3. Fear of Aversive Consequences; fear of illness, choking, nausea and allergies

Risks & Complications

- Co-occurring anxiety disorders
- Failure to gain weight (children)
- Gastrointestinal complications
- Malnutrition
- Weight Loss
- Developmental delays

Causes

ARFID does not have one root cause; instead, researchers and clinicians have explored a variety of potential contributing factors, such

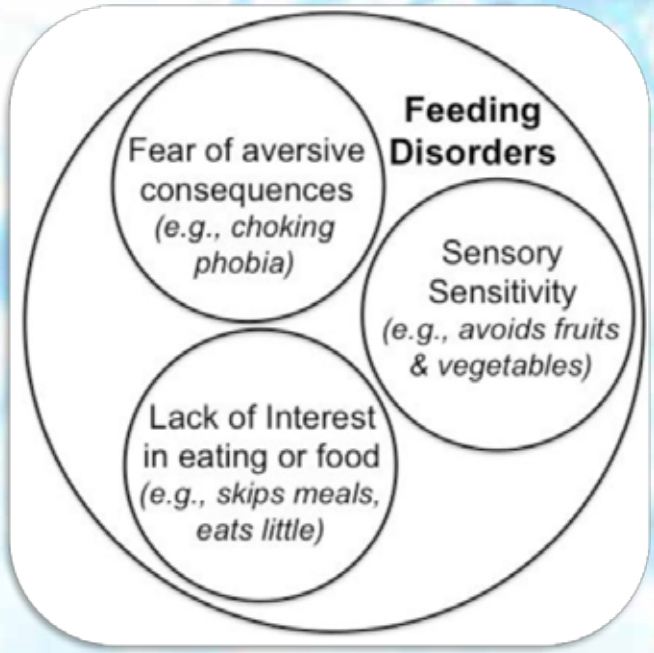
as biological, psychosocial, and environmental influences.

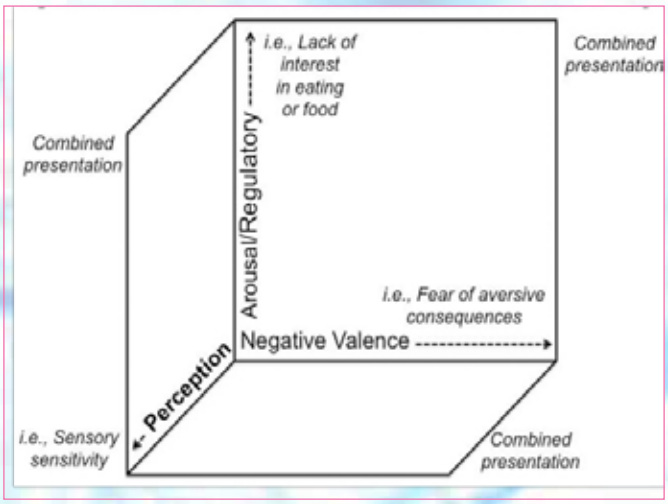
- A child who is already predisposed to ARFID due to biological or genetic makeup may be triggered by environmental or psychosocial situations, such as a traumatic event.
- Since there can be disrupted eating patterns among other mental illnesses, co-occurring diagnoses – such as anxiety disorders, developmental disabilities, and autism may exacerbate – may also be present.
- In autism and other developmental disabilities, an individual's relationship to their body and senses are already very heightened.

NEUROBIOLOGY OF ARFID

Neurobiology of ARFID though still ill defined can be comprehensively summed up in the 3 dimensional diagram shown below. It is a conglomerate of three factors

1. neurobiological abnormalities in sensory perception
2. homeostatic appetite
3. negative valence systems





WARNING SIGNS & SYMPTOMS OF ARFID

Behavioral and psychological

- Dramatic weight loss
- Dresses in layers to hide weight loss or stay warm
- Reports constipation, abdominal pain, cold intolerance, lethargy, and/or excess energy
- Reports consistent, vague gastrointestinal issues ("upset stomach", feels full, etc.) around mealtimes that have no known cause
- Dramatic restriction in types or amount of food eaten
- Will only eat certain textures of food
- Fears of choking or vomiting
- Lack of appetite or interest in food
- Limited range of preferred foods that becomes narrower over time (i.e., picky eating that progressively worsens).
- No body image disturbance or fear of weight gain

Physical

Because both anorexia and ARFID involve an inability to meet nutritional needs, both disorders have similar physical signs and medical consequences.

- Stomach cramps, other non-specific gastrointestinal complaints (constipation, acid reflux, etc.)

- Menstrual irregularities—missing periods or only having a period while on hormonal contraceptives (this is not considered a "true" period)
- Difficulties concentrating
- Abnormal laboratory findings (anemia, low thyroid and hormone levels, low potassium, low blood cell counts, slow heart rate)
- Postpuberty female loses menstrual period
- Dizziness
- Fainting/syncope
- Feeling cold all the time
- Sleep problems
- Dry skin
- Dry and brittle nails
- Fine hair on body (lanugo)
- Thinning of hair on head, dry and brittle hair
- Muscle weakness
- Cold, mottled hands and feet or swelling of feet
- Poor wound healing
- Impaired immune functioning

One major difference between anorexia and arfid is that the drive to thinness is missing in arfid unlike anorexia....though physically they can both give the same look.

TREATMENT

Treatment for ARFID is usually best tailored to the needs of the individual, based on the specific nature of the difficulties the person is experiencing and what is considered to be maintaining these. Most often, treatment can be delivered in an outpatient setting. Treatment commonly involves evidence-based treatments such as family-based treatment (for young people), cognitive behavioural therapy, behavioural interventions such as exposure work, and anxiety management training. Sometimes some medication may be suggested, most often to help with anxiety. The person's physical health should also be monitored and managed, for instance by their GP or a physician or paediatrician. Treatment may also involve nutritional management through support from a dietician, and help with sensory problems.

Hypothermia - Mechanisms of Decreasing Cellular Injury Following Hypoxic -Ischemic Injury

Riya Lukose, Shyamal Kumar, MKC Nair

Acute post-asphyxial encephalopathy occurring around the time of birth remains a major cause of death and disability. The knowledge to continue active neuroprotective treatment even after profound asphyxia (the "primary" phase), as many brain cells show initial recovery from the insult during a short "latent" phase ,typically lasting approximately 6h ,only to die hours later after a "secondary" deterioration 1 characterized by seizures, cytotoxic edema, and progressive failure of cerebral oxidative metabolism have helped to reduce mortality and morbidity. The challenge for the future is to find ways of improving the effectiveness of treatment with hypothermia2. The mechanisms by which hypothermia prevents worsening of cell injury has been elaborated ,followed by a detailed exposition of the newer treatment modalities.

Hypothermia during hypoxia – ischemia (HI) and reperfusion

Hypothermia produces a reduction in cellular metabolism, approximately 5% for every one degree fall in temperature, this delays the onset of anoxic cell depolarization. The delay in the depolarization also reduces accumulation of excitotoxic amino acids. Once blood flow and oxygenation are restored after acute HI, there is a rapid burst of NO and superoxide formation3, and EAA levels rapidly fall in parallel with resolution of the acute cell swelling,typically over 30–60min. thisrecoverycanbe acceleratedbycooling. Hypothermia also acts by suppressing nitric oxide and superoxide formation during ischemic brain injury. In addition there is a disruption of the blood brain barrier following hypoxic ischemic injury. The leakiness of the blood-brain barrier is decreased by hypothermia4

Hypothermia and cell death

Hypothermia has a particular role in suppressing the apoptosis and caspase 3 induction,and thus offers neuroprotection5 after transient ischemia in studies conducted in adult rats which was associated with upregulation of the anti-apoptotic protein bcl2 and reduced expression of the pro-apoptotic protein p53 of programmed cell death. Hypothermia also suppresses mitochondrial permeability transition pores.6 Hypothermia also reduces apoptosis by significantly reducing the activation of caspases and also reduces cytochrome c translocation Thus,all the studies indicated that hypothermia can suppress apoptosis through several pathways which include reduction of mitochondrial permeability 7and reduced activation of extrinsic pathway of apoptosis. Hypothermia has been shown to reduce apoptotic cell death but not necrotic cell death ..

Hypothermia and inflammatory second messengers

There is increased release of cytokines and interleukins following brain injury. These compounds exacerbate cell injury either directly or via apoptosis. Cooling suppresses this inflammatory reaction. for eg: in vitro, hypothermia inhibits microglia proliferation, chemotaxis, induction of pro-inflammatory cytokines, and attenuates microglia neuro- toxicity, during and critically, after exposure to both hypoxia and lipo polysaccharide8. The decrease in inflammation protects the mitochondria and also has an effect on suppressing the microglia formation.

Hypothermia and excitotoxicity

It was shown that antiexcito toxic agents (glutamate antagonist) had neuroprotective role only when there is associated hypothermia.Pathological hyperexcitability of glutamate receptors has been reported in rats for many hours after HI, with improved neuronal outcome after receptor blockade. Neuronal death after ischemia has been associated with a selective,delayed change in the composition of the (AMPA)receptor.

Hypothermia following ischemia can be associated with increase in growth factors such as BD NF (brain-derived neurotrophic factor) which help protect injured cells10. Hypothermia is also seen to maintain an intact mitochondria, though the exact mechanism is unclear.

All the experimental findings indicate that to achieve optimal neuroprotection therapeutic hypothermia should be initiated as soon as possible after resuscitation, Ideally within 6 hours of life, should involve cooling by approximately 3-5 degree Celsius, and continued for approximately 48 to 72 hours until resolution of the secondary phase of injury.

Newer Modalities of detection of cellular injury and treatment modalities following Hypoxia-ischemia

Therapeutic hypothermia has not definitively changed outcomes in severe HIE of the following treatment modalities listed below,only erythropoietin and analogues are currently being evaluated in large randomized controlledtrials (RCTs). Exogenous therapies such as argon and xenon, allopurinol, monosialogangliosides, and magnesium sulfate continue to be investigated. The recognition of tertiary mechanisms of brain damage has opened up new research into therapies not only to attenuate brain damage but also topromote cell repair and regeneration in a developmentally disorganized brain long after the perinatalinsult. These alternative modalities may be especially important in mild HIE10 and in areas of theworld where there is limited access to expensive hypothermia equipment and services.

Specific Biomarkers of Brain Injury

Due to the varied clinical presentation of HIE, it is difficult to predict outcomes early during the course, when intervention with targeted therapies would have maximal effect. Hence, biomarkers that could help detect presence and severity of HIE are being evaluated .

These brain-specific proteins may be useful immediate biomarkersof cerebral injury severity but still need to be independentlyvalidated in large cohorts before they are ready for clinical implementation in practice11.

1. S100B is a calcium binding protein released by brain glial cells in response to injury. Increased levels of S100B have been evaluated in cord blood, urine, CSF, as well as amniotic fluid for newborns with HIE or encephalopathy. A recent study detected elevated umbilical cord blood levels of this protein in neonates suffering from HIE stages II-III, suggesting that this biomarker may correlate with the severity of disease and the risk of adverse neurodevelopmental outcomes and/or death12. If S100B protein in plasma is seen elevated within 24 h after birth it is associated with increased brain injury as detected by MRI

2. Neuron specific enolase (NSE) is a glycolytic isoenzyme that is released after neuronal death. Celtik et al. has identified the NSE cut off values that could help differentiate mild moderate and severe encephalopathy 13 NSE levels in the early postnatal period can indicate

poor outcomes at two years of age . However, NSE levels may be affected by hemolytic process, Massaro et al. have shown that elevated serum S100B and NSE levels measured during hypothermia are associated with neuroradiographic and clinical evidence of brain injury in NE.

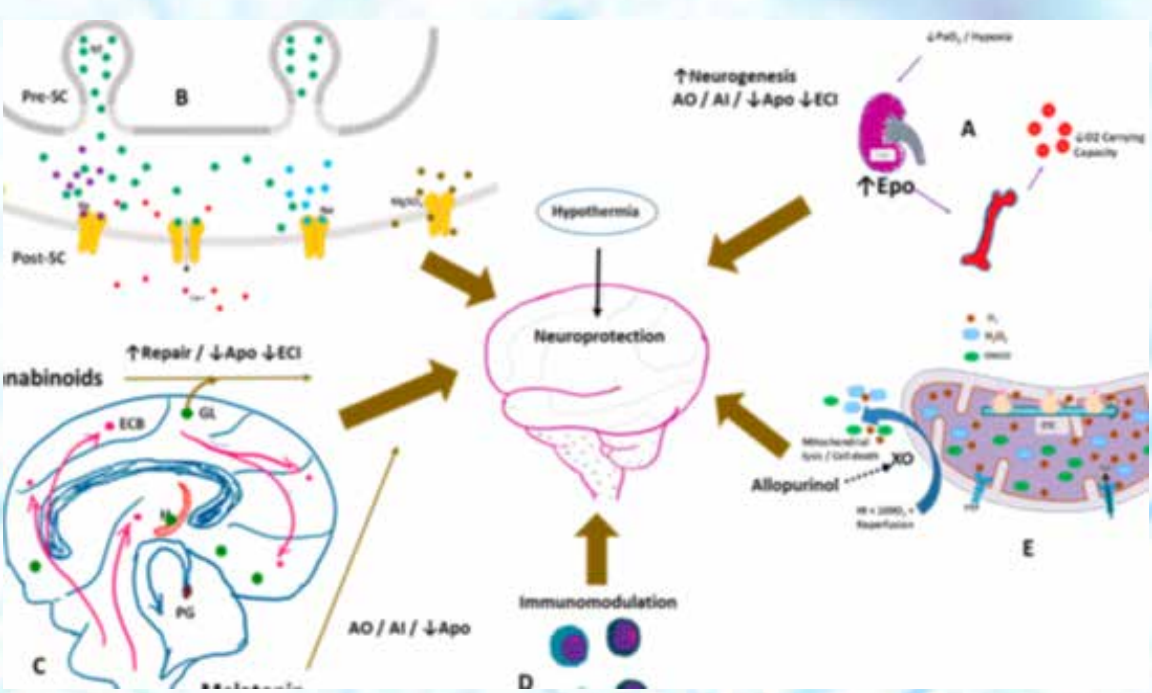
3. Glial fibrillary acidic protein (GFAP) is released when there is damage to astroglial cells and levels in blood and CSF have been seen to correlate with severity of HIE, MRI changes, and developmental outcomes in small studies14. However, the normal values for GFAP values in various body fluids is not clear, and levels in newborns with HIE found very low GFAP levels, below the assay lower limits for detection. Chalak et al. were able to stratify HIE into mild, moderate and severe based on cord blood GFAP and ubiquitin carboxy-terminal hydrolase15.

Other biomarkers of brain injury including ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1) and total tau protein also hold promise as early biomarkers of brain injury in HIE that are being studied further16.

4. Inflammatory markers: Many cytokines are released following ischemic insult,especially IL-6 and IL-16 seen in the cord blood and was associated with electrographic and clinical HIE severity in a study of full term infants. Plasma levels of IL-6, IL-8, and vascular endothelial growth factor was associated not only with severity of HIE but also predicted abnormal neurological outcomes17. However, inflammatory cytokines are not specific and may be elevated with other causes of inflammation.

5. Metabolomic Analysis and Metabolites: Metabolomic analyses are being used in various conditions to identify its presence in time for appropriate therapy. Eight metabolites (arachidonic acid,butanoic acid, citric acid, fumaric acid, lactate, malate, propanoic acid, and succinic acid) were noted to correlate with adverse neurodevelopmental outcomes18. Much research needs to be done in this field before, considering the practical implications.

6. Magnetic resonance spectroscopy (MRS) has significantly improved our understanding of



the changes in brain metabolism and evolution of brain injury after a hypoxic ischemic insult. It could help define the severity of injury if done during the treatment window (within 6 h) by estimating phosphocreatine (PCr) and cerebral lactate or inorganic phosphate. High PCr has been associated with a favourable outcome19, while high lactate and Pi may indicate a poor outcome. MRS after 6 h continues to provide useful clues to help the clinician prognosticate HIE insult. Low cerebral PCr/Pi, high cerebral lactate, and decreased nucleoside triphosphate are associated with poor outcomes.

Persisting brain lactic acidosis on MRS is seen in infants with poor neurodevelopmental outcomesthrough the first year after birth20.

NEWER TREATMENT MODALITIES

1. Erythropietin/Analogues (Endogenous)

Erythopoietin (Epo) is an endogenous protein,that is synthesized in the fetal liver and has many roles. The main action of Epo is stimulating erythropoiesis, Epo also influences the body's immune response, and is also neuroprotective Epo receptors (EpoR) are present throughout the many cells of the central nervous system like progenitor cells, astrocytes, oligodendrocytes and microglia etc. Epo and EpoR are upregulated following hypoxic ischemic injury and Epo has an anti-oxidant as well as anti-inflammatory effect. It causes reduced apoptotic21 and excitotoxic cell injury .

A Phase I trial evaluatingeffective dose and safety22 demonstrated that a moderately high dose of 1000 U/kg achieved levels(based on animal studies) that would protective maximal neuroprotection and minimize risks of excessive Epo.

Darbepoietin (darbe) is a long acting erythropoietin analogue that offers the additional benefit of once weekly administration

2. Stem cell therapy

The two main sources of stem cells are—bone marrow derived mesenchymal stem cells (BM-MSC) and umbilical cord blood derived mesenchymal stem cells(UCB-MSC)23. Cord blood stem cell therapy has been shown to have protective effects mainly on inflammation, apoptosis, oxidative stress, and may enhance regeneration [46]. Unlike hypothermia, cell based therapy may provide a longer therapeutic window as repair and regeneration take place over longer periods of time. Donor MSCs do not last for a long time in the brain, but do have paracrine action.

Phase-I clinical trial evaluating UCB cells to neonates with HIE showed that collection, preparation, and infusion of autologous, volume- and RBC-reduced, non-cryopreserved cord blood cells within the first few postnatal days was feasibleand relatively safe in their cohort

3. Remote Ischemic Postconditioning (Endogenous) (RIPC)

The concept of remote ischemic conditioning (RIPC) involves delivery of sub-lethal small ischemic insults, remote from the area of injury, that activate endogenous repair pathways which potentially help in reducing the extent of original ischemic injury. RIPC, as it applies in neonatal HIE, would involve conditioned ischemic insults to the limb soon after the initial hypoxic ischemic insult. The ischemic skeletal

muscle releases several endogenous compounds that activate not only the neuronal and humoral pathways, but also the systemic inflammatory response25. And thus improves long term sensory motor deficits. Delayed RIPC has significantly improved long term sensory motor deficits in a neonatal HI(in rat model)

4. Endocannabinoids (Endogenous)

The endocannabinoid system has been recognized as an important neuroregulatory mechanism that could help in protection from brain injury. Activation of this system has been shown to decrease glutamate excitotoxicity and activation of microglia and cell death pathways. Use of a cannabinoid agonist WIN 55212-2 in a rodent model of neonatal HIEdemonstrated protective effects by prevention of glutamate release, TNF alpha accumulation, and iNOSinduction, resulting in decreased cell death26. Additionally, use of CBR agonists promotes oligodendrocyte generation, survival, and differentiation, thus contributing to repair from white matter injury27.

5. Melatonin

Melatonin is an endogenous neuroendocrine moiety secreted by the pineal gland and well known for its role in modulating the circadian rhythm. Besides this, melatonin has several other mechanisms that suggest an important role in recovery and repair from brain injury. Melatonin plays an important role in normal glial development28 and has anti-apoptotic29 anti-inflammatory, and anti-oxidant effects. Melatonin has a good safety profile with low risk for toxicity and thus holds tremendous promise in management of infants with HIE.

6. Gangliosides

Gangliosides are sphingolipids that serve an important function in maintaining cell membrane integrity. There is reduced ganglioside, phospholipid,and cholesterol contents in the hippocampus in rats following ischemic injury30. Monosialoganglioside therapy thus seems to protect against apoptotic injury and attenuate brain injury

7. Xenon

Xenon inhibits NMDA signalling and thus may play a role in reducing the acute cell injury. A clinical trial (TOBY-Xe)31 in 92 neonates concluded that xenon is unlikely to enhance the neuroprotective effects of cooling after birth asphyxia. Moreover, xenon is a noble gas that is costly and requires a specialized delivery system. Due to these factors, alternative therapies are currently being evaluated.

8. Argon

Argon demonstrated reduced brain cell death, MRS, and a EEG improvements with combined argon hypothermia treatment32. Additionally, both xenon and argon have good blood brain barrier penetration

9. Allopurinol

Oxidant injury by free radicals and superoxides formed through activation of the xanthine oxidase pathway contribute to the damage caused by a hypoxic ischemic insult. Allopurinol is a xanthine oxidase inhibitor that is being investigated as a potential agent for use in treatment of HIE33.

10.Magnesium sulfate

Magnesium sulfate is an NMDA receptor antagonist believed to reduce excitotoxic damage after a hypoxic ischemic insult. It is now being widely used antenatally for neuroprotection in preterm deliveries. The incidence of low magnesium levels in infants with HIE actually sparked the idea of Magnesium as a treatment modality A prospective, longitudinal, placebo-controlled trial of MgSO4 use in infants with severe asphyxia, without hypothermia therapy, revealed encouraging short term outcomes compared to standard supportive treatment., MgSO4 is thought to be an easily initiable therapy in low resource settings due to its low cost and ease of delivery, in spite of its side effects34.

11. Topiramate

Topiramate blocks the voltage-dependent sodium and calcium channels and also inhibits the excitatory glutamate pathway while enhancing the inhibitory effects of gamma-aminobutyric acid (GABA). All these effects would work favorably in the pathophysiology of HIE. In newborns, it has been extensively studied in the management of HIE in combination with hypothermia35.

12.Azithromycin

Preclinical studies in models of ischemic stroke have revealed that azithromycin has a neuroprotective effect36. Recent abstracts have investigated the possibility of using azithromycin in neonatal HIE alone and as an adjunct to hypothermia. This is another easily available drug.

TH is being explored for mild HIE, as neurological deficits have been noted in these infants as well . Melatonin, epo, darbe, xenon, and topiramate are all being studied as adjuncts to TH (Clinicaltrials. gov NCT02071160, NCT01913340, NCT01471015, NCT00934700, NCT01241019). Stem cells and Epo have actions that extend into the tertiary phase and thus may prove to be complementary to TH37. Creative ways of combining pharmacological and cell based therapies in secondary and tertiary phases of injury would be exciting and would especially benefit infants with HIE that evolved over time and missed the window for TH.

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Quiz

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1) In Prenatal CMV infection, following fetal findings are there:

a) Periventricular Calcification
b) Microcephaly
c) Hypoplastic Corpus Callosum
d) All the above

2) Hearing loss can be seen in which of the following congenital infections (there can be more than one answer):

a) CMV
b) Toxoplasma
c) Rubella
d) HIV

3) Fetal microcephaly is seen in which of the following congenital infections:

a) CMV
b) Congenital Rubella Infection
c) Toxoplasma
d) Varicella Zoster

4) Diffuse calcifications in the Basal Ganglia are seen in which of the following congenital infections

a) Toxoplasmosis
b) Congenital Rubella
c) CMV
d) Herpes Simplex Infection

5) When does Myelination of the human brain begin:

a) Second Trimester
b) Frist trimester
c) After birth
d) After 1 year

**Please send answers to lata2207@gmail.com / Kawaljit000@gmail.com.
Correct answer will be published in next issue**

Answers - JANUARY 2021

1) a
2) a
3) a and d
4) a
5) a,b,c,d
6) a,b,c,d
7) d
8) a,b,c,d
9) a,b,c,d
10) d

**The winner of the ped ortho quiz was Dr Haneesha.
She is doing her IAP Neurodevelopment Fellowship from CCDD Bengaluru**

Dental Care in Children with Downs Syndrome

DR. ASHISH SAHANI

In this article we would be highlighting the difference of dentition in children with downs syndrome, the problems faced because of this and the necessary inputs before visiting a dentist for treatment.

What is Different About the Teeth of children with Down Syndrome?

DELAYED ERUPTION

The teeth of people with Down syndrome, both baby teeth and permanent teeth, may come in late compared to children without Down syndrome. On average, babies with Down syndrome get their first teeth at 12 to 14 months, but it may be as late as 24 months of age. Babies without Down syndrome typically get their first teeth between 6-12 months. It is typical that a child with Down syndrome may not get all 20 baby teeth until he or she is 4 to 5 years of age, rather than 2-3 years of age, which is typical for children without Down syndrome. The front permanent teeth and permanent 6 year old molars may not erupt until 8-9 years of age. It is also common for the teeth of children with Down syndrome to erupt in a different order than in children without Down syndrome.

SMALL AND MISSING TEETH

Frequently, people with Down syndrome have smaller than average teeth and missing teeth. It is also common for the teeth of people with Down syndrome to have roots that are shorter than average.

LARGE TONGUES

People with Down syndrome may have large tongues or they may have an average size tongue and a small upper jaw that makes their tongue too large for their mouth. It is also common for people with Down syndrome to have grooves and fissures on their tongues.

PROBLEMS WITH BITE

People with Down syndrome may have small teeth, which can cause spacing between the teeth. They also tend to have a small upper jaw. This may cause crowding of the teeth and may result in the permanent teeth being "impacted" because there is no room in the mouth for them to come in. The small upper jaw may create a situation where the top teeth do not go over the bottom teeth the way they are meant to; instead, the bottom teeth may be out further than the top teeth in the back of the jaw, the front of the jaw, or both. It is also common that the front teeth of people with Down syndrome do not touch.

Orthodontics (braces) may be able to improve some of these issues. Orthodontics require a lot of cooperation and make the teeth even more difficult to keep clean, so it may not be possible in all people. It may be a good idea to wait until a child is older and able to tolerate it a bit better. Having orthodontic appliances in the mouth can also pose challenges to speech. Children without Down syndrome typically adapt their speech quickly; however, in a child with Down syndrome, where speech may already be an issue, adapting to the appliances may be very difficult. Therefore, it may be a good idea to delay orthodontic treatment until a child is older and his or her speech is further along.

GUM DISEASE

People with Down syndrome are at an increased risk for gum disease (periodontal disease). Even when individuals with Down syndrome do not

have a lot of plaque and tartar (calculus), they get periodontal disease more frequently than others. This is because people with Down syndrome have an impaired immune system and do not have some of the natural protections against the disease that people without Down syndrome have. To prevent gum disease brush twice daily, focusing the bristles along the gum line, floss daily and be sure to visit the dentist regularly to have gum health monitored and to take X-rays to monitor bone levels. If the gums bleed that means that they are inflamed. Brushing and flossing should not be stopped because of this. In fact, brushing and flossing will keep the gums clean and help to minimize the inflammation.

CAVITIES

Some research says that people with Down syndrome are at less of a risk for cavities; however, much of that research was done when people with Down syndrome lived in institutions and had very restricted diets. People with Down syndrome do get cavities, so brushing with fluoride toothpaste, flossing between any teeth that touch, and limiting the amount and frequency of sugar and refined carbohydrates eaten will help to prevent the development of cavities.

• Visit the dentist regularly; it is typically recommended that you go every 6 months, but some people may need to go more often.

"What Should be Done for Dental Care in Down's Syndrome Children?".

A- Teach her how to brush. Use the doll to do this or do yourself and ask him to repeat it. Parents are better to brush their teeth with a Down's syndrome and let them see it while doing it. He should see that his parents brush twice a day and they care about it.

B- - If possible, use clear images that clearly show the process of brushing, and preferably put it in the toilet on the wall.

C - Starting with a toothbrush is the best way. Use a soft toothbrush. Brush his teeth with fluoride toothpaste twice a day. Brush teeth twice daily with a soft toothbrush and fluoride toothpaste. Children less than 2 years should get a thin "smear" of fluoride toothpaste, and children 2 to 5 years should get a small "pea-sized" amount Tooth brushing on the tongue should not be forgotten.

D- For dry mouth, rinse patient mouth with water several times during the day

E- If the person cannot spit out the toothpaste, talk to the speech therapist.

F- Once parents finished training the person's oral hygiene habits; they need to make sure that his child is in his routine daily schedule. Even if the person might not engage in this work, let him see that oral health is part of the parent's daily schedule. Eventually, he will join parents as well.

G- Encourage him if he is doing the correct person's oral health instructions. Be sure to encourage the action of this work all the time, and always remind him of the importance of oral hygiene. In this way, patience is the most important tool.

H- Some people with Down syndrome have instability in the neck joints. When checking her mouth, be sure to move her head slowly.

I- If he is not able to handle the tooth brushing and has a gag reflex, look for consulting.

J- Use antibacterial mouthwash to prevent bacterial growth and bad breath.

K- Beware of excessive consumption of sweet food and snacks.

L- Due to the specific circumstances of people with Down's syndrome, an examination is recommended every 3 to 4 months by the dentist.

M- Sometimes oral and dental illnesses in these people can exacerbate their physical (heart) problems. Consult a paediatric cardiologist before any dental procedure for any prophylaxis medications.

N- Dental floss is the hardest job to help children's Down syndrome oral hygiene. If the patient is not interested in doing so, do not force him. But parents can show them that they do it for

themselves. This may be a motive for breaking his resistance.

O- The use of mouthwashes can also be as challenging as the application of the dental floss. It has often seen in patients with Down's syndrome that have difficulty with spitting out. If this is a problem for the child, parents should not use mouthwash for them because they might swallow it.

Dental recommendations for parents

The first dental visit should be within 6 months of the first tooth erupting or by 1 year of age.

Visit the dentist regularly; it is typically recommended that you go every 6 months, but some people may need to go more often.

1. Find a dentist with experienced and knowledgeable dental problems for people with disabilities. 2. Before the visit, discuss the problems and medications with the dentist.

3. Coordinate with the dentist's secretary to appoint a visit at the private time.

4. In the case of an uncooperative child, ask about anesthesia. At the same time, the flexible appointment is also worth asking.

5. Ask the dentist about the things Down's child may need before starting the dental procedures.

6. At the same time, check the condition of the office. If the child is a Wheel chaired person, it is required the office to be equipped with a ramp or an elevator.

7. Ask your dentist if there is a virtual tour of his clinic which can be shown to the child

8. If your child has any sensory issues or hypersensitivity pre inform the dentist.

9. If the child has atlanto axial instability then the dentist needs to be informed beforehand

10. Take your childs favourite toy of music along, when visiting a dentist

11. It would not be a bad idea to make him visit the dentist one or two times without doing any procedure to make him comfortable with the surroundings and try to bond with the dentist.

A small post script on tooth brushing in children with downs syndrome. (a detail discussion with a dentist will be advisable)

Stabilize your child's head. Your child can rest their head in your lap while brushing the first teeth. Toddlers can sit in a high chair or the corner of the couch. You can also lay your child on the bed with their head at the foot end and kneel behind them. You will have a better view to brush teeth efficiently. Start brushing teeth. Brush teeth as soon as they erupt, using a tiny smear of fluoride toothpaste across the toothbrush. Wipe the teeth with a dry washcloth after brushing. When more teeth come in brush one area at a time as outlined below.

1. Brush the outside of the bottom teeth from one side of the mouth to the other. Make small circles with the brush where the teeth and gums come together with moderate pressure for chewing surfaces. Then move to the inside to brush the tongue side of the teeth.

2. Brush the upper teeth in the same manner. • Make tooth brushing a routine. Make tooth brushing part of the daily morning and bedtime routine. • Brush morning and night even if only for a short period. Some brushing is better than none. Once a routine is established, brushing will get easier.

Supervise tooth brushing for children. Most children with Down syndrome will learn how to brush and floss independently but some will continue to need partial or total assistance. A good rule is to brush your child's teeth until they can tie their shoelaces.

• Once your child accepts brushing, start flossing. Use the same step-by-step approach as brushing. Try floss holders if easily available

Glimpses from Pedicon 2021

Glimpses from Pedicon 2021

Dr.Samir anchoring the musical evening during Pedicon

Month in pics

Indian Academy of Pediatrics (IAP)

GUIDELINES FOR PARENTS

Care of a Child with Down Syndrome

Convener: **Neerja Gupta**
Members: **Kausik Mandal, Nina Piyush Vaidya, Reena Gulati**

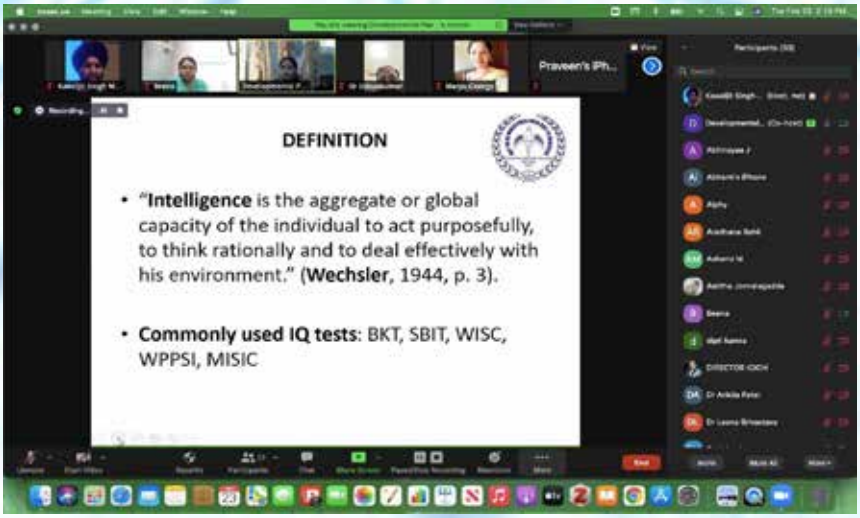
9 FAQs on CARE OF A CHILD WITH DOWN SYNDROME

1. What is Down syndrome?
2. How is my child with Down syndrome different from other children?
3. If Down syndrome is a genetic disorder, how did my child get it?
4. What are the common medical issues that a child with Down syndrome has?
5. Which health checkups should be done and how frequently?
6. Is there a cure for Down Syndrome (DS)? What do you mean by early intervention program?
7. How can I help my child with Down syndrome?
8. What is the risk that my next child will have DS?
9. Can the birth of a child with Down syndrome be prevented? How can it be done?

Under Auspices of IAP Action Plan 2020–2021

Piyush Gupta	**Bakul Parekh**	**GV Basavaraja**	**Deepak Ugra**
IAP President 2021	IAP President 2020	IAP HSG 2020–2021	National Co-ordinator

Month in pics



Online Teaching activities for IAP Fellowship program in Neurodevelopment Pediatrics

Month in pics