

## Perspective

# Autism: Present Scenario and Future Perspectives

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## Perspective

Usually, every parent dreams and expects that his child excels in several fields. Therefore, almost all parents despite their varying limitations attempt to provide the best possible care, amenities, and grooming to their wards. Autism spectrum disorder is a complex, lifelong, heterogeneous, multi-factorial, developmental disability with a dynamic set of metabolic, mitochondrial, immune, neuro-inflammatory, and behavioral abnormalities affecting several parts of the body. Autism Spectrum Disorder (ASD) is manifested by cognitive, behavioral, and social deficits with early childhood onset. It is only in the last eight years (DSM-5) that Autism Spectrum Disorder has been precisely recognized, its specific characteristics described and diagnostic criteria updated. Child growth-related botherations, childhood diseases, and neuro-developmental disorders are all tortuous conditions not so easy to diagnose at the right stage. The purpose of this Editorial is to highlight the Present Scenario and Future Perspectives of Autism Spectrum Disorder (ASD). The term neuro-developmental disorder reflects an abnormality in the brain during developmental years, whereas, a psychiatric disorder implies a mental disorder or imbalanced state of mind with or without any physical brain abnormality. Furthermore, neurological and psychiatric conditions are pathologically and clinically altogether distinct. Mental disorders usually develop at an advanced age and the precipitating cause (such as a serious setback at the financial or personal level) can be pinpointed. The segment of overlap among neurological, psychiatric, and neuro-developmental disorders alongside their constituent symptom dimensions is very large. Childhood neuro-developmental disorders such as Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), childhood schizophrenia, and Intellectual Disability (ID) typically are complicated conditions that not only show considerable clinical overlap but often coexist. Therefore, clinicians need to adopt an open and flexible approach while treating a child suffering from these disorders, since the kid's entire life is at stake. Experts from a wide range of disciplines (e.g. child psychiatrists, psychologists, pediatricians, neurologists, gynecologists, speech therapists, occupational therapists, etc.) need to be consulted for accurate diagnosis and treatment of children suffering from these baffling disorders. Multi-disciplinary

professional expertise and collective diagnostic facilities for children facing developmental disorders would assist to some extent in precise assessment and intervention across all neuro-developmental domains explicitly recognizing the overlaps. The management of these disorders needs to extend beyond core diagnostic criteria accounting for the limitations of formal interaction with the guardian, social inhibitions, the patient's cognitive ability, quality of parenting, family income, etc to devise a comprehensive management plan.

## Prevalence

A sharp rise in the incidence of ASD cases has been noted worldwide in recent years. ASD is presently considered one of the most commonly occurring childhood disorders with a global prevalence of 0.62%. In 2016, approximately 62 million ASD patients were reported globally. ASD prevalence was 1% in the United Kingdom (UK), whereas, in the United States of America (USA), the latest ASD prevalence estimate was 1.85%. The prevalence of ASD in European countries is almost equivalent, with 1.12% of kids afflicted by ASD. There are several reports available in the literature indicating that the incidence of ASD is almost four times higher in males as compared to females. However, ASD male: female preponderance shows substantial variation within the range of 8:1 to 2:1. Autism cases are reported to occur in all racial and ethnic groups, whether in developed or undeveloped countries. The prevalence estimates of autism in Asian patients aged 0-17 years were revealed to be around 0.09% in India, 0.5% in Bangladesh, and 1.07% in Sri Lanka. The "Centers for Disease Control" reported that approximately 1.85% in the USA, 1.52% in Canada, 1.61% in Japan, and 1% per child in France suffered from autism, whereas Italy, Holland, and Germany, showed the smallest degree of prevalence. India is a populous country of nearly 1.3 billion people out of which children from 0-15 years of age constitute nearly one-third of the population. In India, it has been estimated that more than 2 million people might be affected by ASD. The prevalence rate of autism in children (1-10 years of age) in India was found to be 1.5%. These studies were based on documented clinical evidence. It is possible that there is insufficient documentation and missed diagnosis of this complex disorder occurring in infants.

## The interplay of protective and risk factors linked to autism

The presence of a healthy, prosperous, and caring home environment for a lady during pregnancy soothingly influences a child's personality. The actual causative factor of autism is yet not identified. The traditionally acknowledged pathological and non-pathological conditions resulting in ASD include compromised immune system, mitochondrial dysfunction, intellectual disability, prenatal, perinatal, and postnatal factors, adverse environment, gynecological interventions, and defective genes, which work independently or in conjunction to alter the functional capacity of the brain.

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## Genetics

Genetic makeup appears to play an integral role in causing autism. Several reports suggest that autism could be an inherited disorder. Selected genes such as MeCP2, DbetaH (DBH), and HOXA1 play a significant role in the monogenic heritable form of ASD. Other genes associated with autistic disorder comprise the *FMR-1* gene, *Reelin* gene, *SHANK2*, and *SHANK3* synaptic scaffolding genes, Neuroligins (*NLGN3*, *NLGN4X*), Neurexin-1 (*NRXN1*), *CNTNAP2* genes, human *SLC6A4* gene, and human *OXTR* gene. The genetic architecture of ASD is extremely diverse. Mutated genes interfere with normal physiological functions including proper development of brain parts, neuronal synapses, bones, and muscles resulting in autistic symptoms. No particular gene mutation has been established so far with ASD. Although an individual gene appears to play a very trivial role in ASD, more than 400 genes are found to be strongly associated and 200 genes are weakly associated with ASD. More recent research points to the possibility that ASD is a multi-factorial, multi-pathway genetic disorder that doesn't obey classical Mendelian inheritance. Advances in computational technologies and data mining are expected to disentangle the genetic aspects of ASD.

## Adverse environment

Adverse environment exposure at vulnerable times has attracted the attention of investigators in the area of ASD research. Cumulative neuro-toxicant exposure during sensitive periods of pregnancy disturbs the neuronal circuit formation and causes disorganization of different parts of the fetal brain consequently leading to mental retardation and abnormal behavior in the child. The adverse environment may not be a primary causative factor alone, but is emerging as a powerful precipitating element for the development of ASD in individuals having susceptible genes. However, a toxic environment could be an absolute cause of fetal brain damage and may stimulate gene mutations in sensitive individuals. Toxicants suspected to be responsible for ASD include insecticides, Polychlorinated Biphenyls (PCBs), harmful wastes, air/water pollutants, mercury, radiation, diesel exhaust, vehicular emissions, volatile organic compounds, nitrogen dioxide, and heavy metals. There seems to be a positive correlation between the cumulative presence of particulate matter in the vicinity of expecting mothers during the third trimester of pregnancy and the birth of an autistic child subsequently. Furthermore, an interconnection exists between the post-partum presence of nitrogen dioxide (a vehicular pollutant) in the proximity of the newborn and autism. The pathogenesis of ASD involves a complicated interplay between genetic factors and adverse environment, which act synergistically or laterally during vulnerable times of embryonic development thereby enhancing the probability of developing autistic symptoms in the child.

## Comorbidities

Comorbidities often associated with autism include depression, schizophrenia, schizoaffective disorder, bipolar affective disorder, epilepsy, Down's syndrome, Tourette syndrome, hypothyroidism, Attention Deficit Hyperactivity Disorder (ADHD), intellectual disorder, metabolic disorders, and hypertension. Veritably, the co-occurrence of different childhood disorders along with ASD seems to be normal rather than an exception.

## Prenatal, perinatal, and postnatal factors

ASD might be considered, at least in some cases, a disorder of fetal programming. The prenatal period represents the entire pregnancy

duration from conception till delivery of the child. Consumption of medicines (such as thalidomide, valproic acid, misoprostol, and acetaminophen) having teratogenic effects, and use of alcohol, or tobacco during pregnancy constitute important prenatal factors causing ASD. Valproic acid evokes "Fetal Valproate Syndrome" because of enhanced oxidative stress and defective gene expression, which ultimately results in slow development, motor deficits, and abnormal postnatal growth in humans as well as animals. It is a well-established fact that exposure to certain substances like alcohol, mercury, lead, polychlorinated biphenyls, phthalates, pesticides, insecticides, and radiation during the prenatal period produces autism in children. Maternal infection during pregnancy can result in behavioral abnormalities and neuropathologies in the neonate. Viral or bacterial infection in the first or second trimester of pregnancy enhances the risk of autism in children. Autistic characteristics have also been found to escalate after prenatal exposure to unusually large testosterone concentrations, produced by congenital adrenal hyperplasia. The uterine ambiance has a profound impact on the development of the fetus. The compromised mother's health can deeply affect the long-term mental and physical health of the developing embryo. Other prenatal factors, like short inter-pregnancy spacing, abnormal gestational age, multiple pregnancies, gestational hemorrhage, gestational diabetes, and advanced parental age might be linked to an increased incidence of ASD. The perinatal period is taken as the period from completion of the 20<sup>th</sup> week (end of 5<sup>th</sup> month) of pregnancy to the end of 4 weeks (1<sup>st</sup> month) after the birth of the child. Perinatal factors of ASD are conjoined with obstetric conditions such as being underweight, pre-term delivery, and birth asphyxia. Perinatal stress (fetal distress), fetal growth restriction, preeclampsia, umbilical cord complications, chorioamnionitis, acute intrapartum hemorrhage, neonatal encephalopathy, brain trauma, and cesarean delivery are all associated with a high susceptibility to autism. The postnatal period pertains to the period after the birth of the child till it is two years of age. The postnatal factors associated with a high incidence of autism include a variety of insults inclusive of auto-immune disorders, jaundice, leaky-gut syndrome, amygdale developmental arrest, vitamin-D deficiency, heavy metal toxicity, and postnatal infections.

## Gynecological interventions

Gynaecological interventions that are used in Assisted Reproductive Technologies (ART) such as hormonal stimulation, egg retrieval, in vitro fertilization, intra-cytoplasmic sperm injection, micro-manipulation of gametes, exposure to the culture medium, uterine stress could all be associated with an increased risk of developmental disorders. Children conceived using ART is at a higher risk for birth defects including a two-fold increase in epigenetic and imprinted disorders. Current research suggests that obstetric interventions, artificial insemination, advanced parental age, Cesarean Sections (CS), and/or oxytocin-induced labor appear to be closely linked to the development of ASD and other childhood disorders.

## Heavy metal toxicity

Recent ecological studies suggest a critical contribution of metal toxins in autism. Both Aluminum and Mercury appear to be the main culprits, which can penetrate the blood-brain barrier and exhibit severe adverse effects on the brain as well as the immune system. Intake of these toxic metals by ladies of child-bearing age enhances the susceptibility of a child to ASD. Elevated heavy metal concentrations

(arsenic and mercury) have been detected in the blood and urine of children suffering from autism. Lead, cadmium, aluminum, and/or arsenic toxicity has also been associated with ASD symptoms.

### Dysfunctional immune system

Weak maternal immune system and the production of pro-inflammatory cytokines are risk factors for autism. Pregnancy-induced immunosuppression makes a woman more vulnerable to infections. Besides, obese, malnourished, and underweight mothers carry an enhanced risk of ASD in newborns. Of late enhanced concentrations of maternal cytokines and chemokines during pregnancy have been linked to the development of ASD with intellectual disability in the child.

### Age of parents

The effects of aging on human genetic traits are well documented, particularly on early embryonic development. The age of parent's  $\geq 35$  years imparted a higher risk of bearing an abnormal child. The most likely underlying mechanism for older fathers to have an abnormal child can be attributed to lower sperm count due to de novo mutations, precipitated by continuous toxic environmental exposure. Whereas, the multiple reasons for older women to bear abnormal children appear to be hormonal imbalance, incompatible uterus, use of contraceptives, and adverse environment. However, the physical immaturity of parents due to younger age, inadequate intra-uterine development of the embryo, and improper maternal care also enhance the incidence of autism.

### Mitochondrial dysfunction

Recent findings suggested that mitochondrial dysfunction, impaired energy generation, dysregulated neuro-inflammation, depletion of reserve mitochondrial energy stores, and free radical accumulation as major players in the development of autism.

### Protective factors

Protective factors when identified precisely would play a crucial role in preventing the occurrence of ASD. Impressive Intellectual Quotient (IQ), excellent social skills, and extrovert nature acquired or inherited by the individual were hitherto considered to be positive attributes against the backdrop of restricted interests and defective communication skills exhibited by autistic children. A healthy environment coupled with proper maternal care and diet during pregnancy helps in the normal growth of neonates and plays an important role in preventing ASD-like symptoms. The increased consumption of Polyunsaturated Fatty Acids (PUFA), especially omega-3 fatty acids, during the prenatal phase by expecting mothers lowered the risk of giving birth to an abnormal child. Vitamin D supplements during the prenatal phase and adequate iron and calcium intake during the perinatal and postnatal phases of pregnancy reduced the incidence of developing ASD in the offspring. Breast milk offers the best protection to the child against developing ASD symptoms. Some components of breast milk such as bifidobacteria, lysozyme, lipoxins, glutathione, and anti-inflammatory cytokines provide good protection against developing ASD symptoms. Another factor that could play a role as a protective agent is the hormone melatonin. Melatonin synthesis is frequently impaired in children with ASD and their mothers. Therefore, consumption of this hormone during pregnancy could act as a neuroprotective factor, decreasing the risk of neuro-developmental disorders including ASD. In addition to the above factors, a healthy environment, family support, optimal age of parents, adequate inter-pregnancy spacing, limited gynecological

interventions, proper maternal care, natural delivery (as opposed to cesarean section), and specified vaccination schedule provide a protective shield against the development of ASD. The author recommends that focusing on these protective factors during pregnancy might prove to be an effective strategy for bearing a normal child.

### Strategic management of autism spectrum disorder

Over the last century, research in Autism Spectrum Disorder (ASD) has undergone a revolutionary change. The established treatments for ASD core symptoms are still lacking. Pharmacotherapy has shown limited benefits in addressing the core symptoms of ASD.

### Drug therapy

The goal of the management of autism is to improve the quality of life of the patient and diminish family distress. Pharmacological treatment of basic symptoms of ASD is by and large intricate, owing to the complexity of the appearance of ASD, co-morbid conditions, and age-related response variation. Despite the urgent need for a satisfactory remedy, there are no US-FDA-approved medicines, which ameliorate the core symptoms of ASD, particularly the deficits in reciprocal conversation and defective social skills. ASD-associated secondary symptoms and Co-morbid conditions are targeted since a satisfactory therapeutic regimen is not available for the treatment of core symptoms of ASD. To date, aripiprazole and risperidone are the only medicines approved by the US-FDA, for controlling ASD-associated behavioral disturbances, such as aggression, self-harm, severe tantrums, agitation, irritability, and outbursts of ASD subjects. However, these allopathic medicines show rewarding benefits only when applied in conjunction with complementary therapies. Different drugs that have been prescribed for the treatment of various ASD-associated symptoms include antipsychotics (Aripiprazole, Risperidone, Clozapine, Olanzapine, Ziprasidone, Paliperidone), serotonin reuptake inhibitors (Fluoxetine, Fluvoxamine, Venlafaxine), Mood stabilizers (lithium), anticonvulsants (Divalproex, Oxcarbazepine) Alpha 2 agonists (Clonidine, Guanfacine), Acetylcholinesterase (AChE) inhibitors (Donepezil), glutamate antagonists, GABA-ergic agonists (Acamprostate), Hormones (Melatonin, Oxytocin), CNS-stimulants (Methylphenidate), NMDA glutamate receptor modulators (Memantine, Ketamine), Na-K-Ca co-transporter-1 (NKCC1) inhibitor (Bumetanide), and Vasopressin 1a (V1a) receptor antagonist (Balovaptan). A few medicinal herbs like *Asparagus racemosus* (Shatavari), *Ginkgo biloba*, *Panax ginseng*, Immuno-modulatory agents (immunoglobulin i.v., corticosteroids), Memory enhancers (Piracetam, lamotrigine, and dextromethorphan) and antidepressants (Clomipramine) have shown promising results to a varying degree. Stem cell therapy being highly invasive is not likely to be adopted by the caretakers for a child suffering from ASD. The endocannabinoid system appears to mediate social interaction and emotional responses impaired in ASD. A well-designed clinical investigation in children suffering from ASD showed beneficial results after the administration of cannabidiol and tetrahydrocannabinol (present in cannabis).

### Non-drug therapies

Autism is such a disorder for which there is no cure in allopathy thereby making therapeutic management of patients suffering from ASD challenging. Usually "where there is no cure, one thousand approaches seem to be useful." Patients suffering from Autism Spectrum Disorder (ASD) experience difficulties in social

communication and interaction in addition to involuntary stereotypic behaviors. Complementary interventions are available and may prove beneficial when applied with adequate frequency and intensity by a professional therapist tailored to the needs of the individual child. No single therapy fits exactly into all kinds of patients.

### Complementary Therapies

Complementary therapies include Cognitive-Behavioral Therapy (CBT), Applied Behavior Analysis (ABA), mindfulness-based interventions, educational therapy like speech exercises, communication training, and vocational training, and support, Animal-Assisted Therapy (AAT), occupational therapy, psychotherapy etc. Complementary therapies aim at decreasing destructive and depressive episodes, alleviating anxiety, improving self-expression, and encouraging conversation, thereby facilitating sensory integration. Best results are obtained when complementary therapy intervention is tailor-made for each child and applied from the initial stage of ASD presentation soon after a confirmed diagnosis. At present, Behavioral therapy remains the mainstay for the management of the core symptoms of ASD. There are several types of behavioral therapies such as CBT, Aversion therapy, Applied Behavior Analysis (ABA), system desensitization, etc. for treating mental health disorders. Applied Behavior Analysis (ABA) is administered to address difficulties in communication and social interaction as well. The goal of Behavioral therapy is positive reinforcement of desired behavior and breaking down tasks into simple steps with frequent rewards and corrections. Behavioral interventions are highly effective in improving IQ scores, communication, and social skills in children with ASD. Cognitive-Behavioral Therapy (CBT) is a type of psychotherapeutic intervention that teaches patients to identify and change destructive thought patterns that have a negative influence on behavior. CBT is based on the concept that one's thoughts, feelings, physical sensations, and actions are interconnected. The negative thoughts and feelings trap one in a vicious cycle. CBT aims to help one and all in dealing with overwhelming problems in a positive way by breaking them down into smaller parts. CBT is a talking therapy, which deals with one's current problems rather than focusing on issues from the past. CBT is very helpful in improving the mental health of a child diagnosed with ASD. CBT encourages the engagement of the patient with surrounding people and events. Mindfulness appears to have broadly positive impacts on human functioning. Mindfulness deals with focused attention to and awareness about present events and experience". The Mindfulness intervention helps in reducing distractions and improving attention, audio and visual focus, cognition, stability of mind, and efficiency. Interventions based on mindfulness attempt to improve self-awareness, emotional quotient, positive outlook and create optimistic thoughts about life. Cognitive-Behavioral Therapy (CBT) and mindfulness-based interventions are two primary intervention approaches of immense benefit to children suffering from autism. Furthermore, the facilitation of parent-child interaction through language and communication therapy produces excellent outcomes in developing communication. Children having symptoms of ASD show substantial benefits from educational interventions. Education therapy is used to treat individuals with learning difficulties/disabilities. ASD children differ in their capabilities to learn new things relative to their intellect and the efficiency of sensory organs. Education therapy helps in overcoming learning problems and improving academic performance. Speech therapy is applied for the treatment of speech disorders and communication problems. It is administered by speech therapists. Speech therapy helps in improving

aphasia, dysarthria, expressive disorder, limited vocabulary, language disorder, fluency disorder, articulation disorder, and receptive disorder. Animal-Assisted Therapy (AAT) is a new intervention through which many children can develop a relationship with animals. One form of AAT is Equine-Assisted Activities and Therapies (EAAT). Children get an opportunity to communicate in a complex nonverbal manner with horses (equine) in addition to developing a bond with them. Preliminary evidence with EAAT indicates that there are reductions in problematic behaviors such as irritability, hyperactivity, self-injury, etc. and a calming feeling is experienced by children after riding a horse. However, EAAT is an expensive therapy. Psychotherapy when administered by a professional therapist has the potential to counter psychiatric symptoms such as obsessions, anxiety, minor or major depression, intellectual disability, and aphasia. The transition to adult life is one of the most important stages in an individual's life. Since ASD children exhibit defective social skills and compromised cognitive abilities, they face a lot of problems in coping with the new phase and responsibilities of life while transitioning to adulthood. Vocational training offers great help in developing life skills in such individuals. Social organizations have developed programs for the vocational training of such adults with Autism Spectrum Disorder (ASD). Vocational training refers to instructional courses that focus on the skills required for a particular job, trade, or career rather than an academic subject. Occupational therapy including sensory integration (massage, pressure, and brushing) and auditory integration therapies are also used by families to help develop skills needed for daily living. Improvement in the cooperative attitude of the patient indicates the effectiveness of the therapy. The quality of the health care provider, the duration, and the intensity of the intervention also play an important role in the effectiveness of the intervention.

### Healthy lifestyle practices

A healthy lifestyle can improve the mood and behavior of any person. Healthy lifestyle practices include proper nutrition, regular exercise, adequate sleep, listening to music, and good relationships. High-fat diet and food additives present in packed foods are found to aggravate the symptoms of ASD.

### Challenges ahead

Right estimates of the incidence of ASD are critical for any nation to evaluate the economic burden and allocate adequate funds and health services to children with ASD and their families. Regular epidemiological surveys are being carried out to measure the prevalence of ASD over the last three decades globally for this reason. Despite the positive role played by the organizations supporting ASD patients and awareness attempts by the media, there is a huge scope for better coordination between healthcare systems, service providers, and the special training schools, available for disabled ASD children.

ASD male: female preponderance shows substantial variation within the range of 8:1 to 2:1. The reason for this heterogeneity is poorly understood. A 'female protective effect' is being supported by recent studies as an explanation for the higher prevalence of ASD in males as compared to females. There is insufficient documentation of female cases suffering from autism because ASD cases may go unnoticed, misdiagnosed, or under diagnosed in girls. However, this discrepancy in prevalence may be because females camouflage their symptoms. The pathogenesis of autism has oscillated from the sole "uterine factors", singular "environment" approach through the "solitary genetic" approach to the uterine-gene-environment interplay of modern times. Besides, forethought is imperative for developmental

changes associated with the child's growth, maturity, middle age, and old age, while finalizing the treatment schedule. Autism is currently the most visible and widely discussed developmental disorder with no clue about the biomarkers. Although research in the area of Autism Spectrum Disorder (ASD) has constantly grown, the neurochemistry and causative factors of this disorder are still a matter of speculation. Furthermore, there is no perfect animal model to study ASD pathogenesis. At present, ASD is being recognized based on discernible symptoms, unusual behavior of the patient and the observations revealed to the physician by the guardian. Nevertheless, the recent advances in comprehending the kind of gene-environment interactions might eventually throw open new doors leading to the effective management of this incurable disorder. It is anticipated that the crucial advances in the area of high-risk genes and aberrant neuronal circuitry commonly found in ASD children would lead to innovative break-through. Advances in computational technologies and data mining are expected to disentangle the genetic aspects of ASD. Large and heterogeneous sample sizes are needed to identify the interconnection between the effects of adverse environmental exposure during critical (conception, prenatal, perinatal and postnatal) phases of an embryo within the uterus, outside the uterus, and the dynamic role of protective factors. The perplexing mystery of ASD appears to be linked to the dynamic meshwork of precipitating and protective factors involving culprit genes, adverse environment, and uterine adaptation. In recent times, there has been an emphasis on shifting behavioral observations to mechanistic investigations to establish a cause-effect relationship. No single therapy fits exactly all

kinds of patients. An integrated strategy comprising psychotropic medications and complementary therapies appears to be quite effective given the scenario that there is no US FDA-approved medicine for the treatment of autism as yet. The author advocates that focusing on and consolidating the protective factors antepartum and post-partum might prove to be an effective method for the prevention of ASD. A wise selection of diet, during the antepartum and post-partum phase, can help reduce the challenges of ASD-associated neuro-cognitive impairments. Personal Attention, Assurance, and Reassurance given to the child are the essential components of counseling yielding the best possible results. Most importantly compassionate care is crucial. An integrative approach combining drug therapy and non-drug therapy aimed at ameliorating the primary and secondary symptoms of ASD is more likely to help the unfortunate child and improve the quality of life of concerned families. Future challenges include a better understanding of the influence of gender, and the best application of what we know about the dimensions that significantly impact the lives of pregnant ladies and ASD patients in different countries, cultures, and populations. Furthermore, management strategies based on "Autistic voices" and inputs from adolescents suffering from Autism and their families would surely go a long way in improving the quality of life of the ASD community. We have crossed several stumbling blocks so far and are placed in a much better position today as compared to yesterday nonetheless; we still have many obstacles to overcome and a long expedition ahead.