Chapter 2
REVIEW OF LITERATURE

“I know of nobody who is purely autistic or purely neurotypical. Even God had some autistic moments, which is why the planets all spin”

Jerry Newport

2.1 Disability

According to WHO, “Disability is an umbrella term, covering impairments, activity limitations, and restrictions of participation”. (WHO, 2015). The National Trust Act (1999), Government of India defines that disabilities means neuro-developmental disability occurring due to insult to the developing brain, which causes damage to the central nervous system. The causative factors highlighted are mainly the various environmental factors, which deprive the brain of oxygen, occurring before, during or after birth. It may also be noted that these neuro-developmental disabilities, including autism are neither disease nor contagious nor progressive. These conditions require special mention since they cannot be cured by drugs or surgery. But there is a scope for early detection and early intervention, which will help in improving the developmental outcome of these children. The early interventional therapy offered to these children will improve the condition and will reduce the burden of disability. Early intervention services are done by utilizing the services of a multi-disciplinary team comprising of Developmental Therapists, Occupational Therapists,
Physiotherapists and Speech Therapists. Special Educators, Social Workers and Community based rehabilitation workers. The professional services in managing these children, include home based, centre based community based rehabilitation and vocational training. Among the various neuro-developmental disabilities autism, is frequently seen and this research is mainly on autism with special reference to the detection by tools and identifying the causative factors.

2.2 Neuro-developmental Disability

A neuro-developmental disability (Reynolds & Cecil, 1999) is a disorder of neural development with impairment of the growth and development of the brain and central nervous system. These disorders have their origin in infancy and childhood and include Autism Spectrum Disorders (ASD), Attention Deficit Hyperactivity Disorder (ADHD), Epilepsy, Learning Disorders (LD), Mental Retardation (MR), Neuro-motor Impairment including Cerebral Palsy (CP), Speech and Language Disorders, Hearing Impairment and Vision Impairment. These disabilities will cause varying degrees of physical, emotional, mental and economic burden to individuals, families and to the society at large.

It has been estimated that developmental disabilities are present in about 5% to 10% of children (Simeonsson, & Sharp, 1992). According to the 2011 Censes of India 2.21% of population of India is having disability (Census India, 2011). In a study done from CDC Kerala among children less than 3 years, it was observed that the prevalence of developmental delay was 2.5%. Out of a total of 32,664 representative sample of children studied from all over Kerala, the observations of
psycho motor retardation were; developmental delay (69.3%), speech delay (14.3%), global delay (5.7%), gross motor delay (5.3%) and suspected of hearing impairment (3.6%) (Nair, Princy, Leena, et. al., 2014). Autism is one of the most debated neuro-developmental disabilities in India considering the increasing nature of the condition. The burden of the disability of autism for the child and its impact on the affected parents and other stake holders is commonly highlighted.

2.3 Autism

Autism is not a very rare disease and is sometimes seen by clinicians especially pediatricians based on the clinical observation of the child. The neurodevelopmental history and clinical examination of the child will help the clinicians in arriving at a diagnosis. Clinical criterion is available for the professionals for making a diagnosis. The most common criteria used in our country is the Diagnostic and Statistical Manual for mental disorders (DSM)

As per the criteria of DSM-IV-TR (APA, 2000), the term autism or autistic disorder applies to individuals, who have social interaction impairments, communication impairments and repetitive, stereotypic and restricted interests and the impairment should have occurred before 36 months of age. Most of the children having autism have moderate to severe type of impairment and some have intellectual disability also.
2.4 Definitions of Autism

The commonly used definitions of autism include those contained in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition – Text Revision (DSM-IV-TR); (APA, 2000), the definition of the International Classification of Disease (WHO, 1993), and the educational definition of autism adopted for use in the Individuals With Disabilities Education Act (IDEA) and the National Trust for the Welfare of Persons with Autism, Cerebral Palsy, Mental Retardation & Multiple Disabilities.

2.4.1 Autism – DSM-IV

A widely used definition of autism is that of the DSM-IV-TR (APA, 2000), which classifies autism as one of the pervasive developmental disorder. Children and youth identified as having a pervasive developmental disorder “are characterized by severe and pervasive impairment in several areas of development: reciprocal social interaction skills, communication skills and presence of stereotyped behavior, interests, and activities”. These behavioural patterns will occur during the first few years of life and are significantly atypical for a child’s mental age or development level.

2.4.2 Autism – DSM-5

Even though in the DSM-IV criteria there were three domains of symptoms for qualifying for diagnosis, in the latest fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) published during 2013, there are only two domains for diagnosis like; (i) social communication impairment and (ii) restricted interests/repetitive
behaviors. In order to diagnose autism spectrum disorder there should be three numbers of social communication impairments and two impairments in the category of restricted interests / repetitive behaviours. In the second domain the new deficit of sensory sensitiveness or dysfunction or unusual sensory interests has been included (APA, 2013).

One of the most important modification in the DSM-5, is the change of nomenclature from Autism to Autism Spectrum Disorder (ASD). The revised diagnosis represents a new medically and scientifically useful method of diagnosing children with autism related disorders.

2.4.3 Autism – ICD-10

The International Classification of Disease, Tenth Revision (ICD-10: WHO, 1993) uses the term pervasive developmental disorders to refer to Autism Spectrum Disorders. With few exceptions, the ICD-10 classification system conceptualizes and defines autism in a manner similar to the DSM-IV-TR. The ICD-10 classification system includes in the autism spectrum disorders the following conditions: childhood autism, Rett syndrome, childhood disintegrative disorder. Asperger syndrome, other pervasive developmental disorders, pervasive developmental disorders – unspecified, overactive disorder with mental retardation with stereotyped movements and atypical autism. The term atypical autism is used to refer to atypical nature of age, symptoms or other characteristics of autism along with behavioural changes, such as self-
stimulatory responses and other non-functional movements and mental retardation.

### 2.4.4 Autism – National Trust, India

The National Trust for the Welfare of Persons with Autism, Cerebral Palsy, Mental Retardation & Multiple Disabilities is a statutory body under the ministry of social justice & empowerment, Government of India. The National Trust has undertaken a pioneering initiative to educate and inform citizens and parents in all parts of India on issues about Autism and other neurodevelopmental disabilities. It is hoped that these initiatives will help parents and health professionals to recognize autism, and offer help for the child as early as possible.

According to National Trust “Autism” means a condition of uneven skill development primarily affecting the communication and social abilities of a person, marked by repetitive and ritualistic behaviour, (National Trust, 1999)

### 2.5 Historical Perspectives of Autism

The term autism was coined by a Swiss Psychiatrist Eugen Bleuler in 1911, to describe cases with self-absorption due to poor social relatedness, which was seen in patients with schizophrenia (Bleuler, 1911). Meaning of autism in Greek language is “Living in Self” (i.e. ‘aut’ means self and ‘ism’ refers to a state.) He used the term, in his description of certain symptoms associated with some cases of psychosis (Oller Jr., & Oller, 2010).
Leo Kanner is credited with the first description of detailed symptoms of autism during 1943. Kanner described 11 children in the age group of 2 to 6 years, who had an apparently rare syndrome of “extreme autistic aloneness.” (Kanner, 1943). Because of the fact that the children’s symptoms started early, the condition was also known as “infantile autism.” Since Leo Kanner first described in detail about autism, the disorder is also known as Kanner syndrome.

Even though Bleuler coined the term autism in 1911, the meaning with reference to the new syndrome was described 32 years later by Leo Kanner. He was Professor and Psychiatrist at Johns Hopkins University. He applied the term “autism” in a specified manner reflecting his belief that he was reporting the discovery of an entirely new psychiatric disorder. The title of Kanner’s 1943 paper published in the journal nervous child was “autistic disturbances of affective contact”.

In 1944 Hans Asperger, a Viennese Paediatrician, described a condition similar to that described by Leo Kanner and denoted it as Autistic psychopathy (Asperger, 1944) because of severe and characteristic difficulties in social integration.

In 1952 the first edition of the American Psychiatric Associations document (APA, 1952) the diagnostic and statistical manual of mental disorders (DSM) was published and it did not categorize autism as separate category. From 1943 – 1956 autism was generally known by the clinical description of the 11 cases, first diagnosed and described in detail by Leo Kanner.

In 1956 Eisenberg and Kanner suggested two essential criteria for the disorder: inability to relate in the ordinary way to people and failure
to learn to speak or inability to convey meaning to others through language, both occurring from the beginning of life of an individual (Eisenberg & Kanner, 1956).

After reviewing the literature available it was observed that autism was unknown in ancient cultures or even in medieval times and it just “appeared” about 70 years ago. Even though the current description of autism was first documented in the 1940’s it has been described that many of the great composers, artists, scientists, writers and other famous personalities have exhibited behavioural traits similar to that of autism spectrum disorders. It can be presumed that they might have had savant skills or high functioning autism.

Many scientific contributions regarding this condition have come from individual clinicians and researchers and the concept and definition of autism have changed over the years. The ideas once held with convictions were later proved to be not true and the later research findings changed the understanding of the conditions. Similarly the care and treatment offered to the patients also changed because of varying definitions and understanding of the condition.

Various editions of DSM have been published like DSM-IV-TR in 2000 and DSM-5 in 2013. The diagnostic criteria has been changed according to the editions published.

Bernard Rimland, founder of the Autism Society of America and president of the Autism Research Institute (ARI), has thoroughly analyzed the autism database of more than 30,000 entries and reported two clear trends; (i) increasing incidence of autism (Rimland, 1999), (ii) a
distinct shift in the time of onset of autistic symptoms from late onset to early onset (Rimland, 2003).

It has been assumed that there is a sudden and exponential increase in autistic disorders in our country. It has been proposed that the sudden increase of cases of autism may be due to better diagnosis and increased awareness among parents and professionals.

Similarly, though some affected children have Fragile-X Syndrome or a family history of autism, it does not seem reasonable to insist that the present autism outbreak is solely caused by hereditary factors and genetic disorders have never occurred as epidemics. However, review of literature has indicated that the incidence of autism is increasing in our country and all over the world.

2.6 Epidemiology of Autism

There are many studies done in developed countries showing various rates of prevalence of autism. It can be seen that there are only very few studies done to find out the prevalence of autism in India. There are no methodologically sound studies done in India and review of literature shows that the prevalence of autism is not known in the state of Kerala also. There is a thinking among professionals, that autism is increasing alarmingly and public health experts and policy makers may give importance to tackle the condition since the burden of the disability is very high.
2.6.1 Autism in India – Prevalence

Majority of autistic people in India have not been diagnosed and do not receive the optimal services they need. This problem occurs in many other developing countries also, since there is lack of awareness and misunderstanding about autism among the medical professionals, who may either misdiagnose or under diagnose the condition. It can be noted that awareness about the condition among other paramedical professionals and parents are also less. Since India’s current population is 121 million, it can be extrapolated that there may be around 2 million autistic persons in the country taking into consideration the prevalence rate in Western countries. This estimate is based on the assumption that there are no significant variations in this rate worldwide.

Even though an accurate estimate of prevalence of autism in the general population in India is not available, the authors of recent case series reports of 16 and 62 autistic children from tertiary hospitals in Chandigarh and New Delhi, respectively, have stated that autism is not uncommon in India. Its diagnosis is frequently missed as there is tremendous lack of awareness and knowledge about the disorder among health professionals – trained in diagnosing autism. It is also reported in the article that due to lack of awareness of autism among professionals, many cases are being missed (Singhi, & Malhi, 2001; Kalra, Seth, & Sapra, 2005).

In a report titled “Statistical Survey of Persons with Autism, Mental Retardation, Cerebral Palsy, Multiple Disabilities In Delhi” submitted to National Trust submitted by Centre for Market Research and Social Development, it has been indicated that the prevalence rate
of disability due to autism is 10/1,00,000 persons. (National Trust, New Delhi)

2.6.2 Autism in other countries – Prevalence

Autism is prevalent in all countries of the world and epidemiological studies show various rate of prevalence.

In an epidemiological study (Hertz-Picciotto, & Delwiche, 2009) done at, University of California, USA, during the period from 1990-2006, it was observed that the cumulative incidence of autism rose consistently from 6.2/10,000 live births to 42.5/10,000.

A brief report on prevalence of autism in children born to Somali parents living in Sweden was published from the Department of Child and Adolescent Psychiatry, Sweden, to compare the prevalence of autism in children of Somali background with that in the non-Somali group. The study reviewed the records of children, born between 1988 and 1998 and with a Somali background, who had a diagnosis of autistic disorder. It was observed that the prevalence of autistic disorder was found to be three to four times higher in children of Sweden than in the non-Somali group (0.7% vs 0.19%) (Barnevik-Olsson, Gillberg, & Fernell, 2008).

The study to estimate the prevalence of autism in adolescent children with intellectual disabilities using the Autism Diagnostic Interview-Revised revealed that 28% of individuals with intellectual disabilities in the target population, were identified with autism (Bryson, Bradley, Thompson, & Wainwright, 2008).
A study to assess the degree of autism, which was done at University of Oulu, Finland using the Childhood Autism Rating Scale, showed that there were mild autistic features in 8.5%, moderate in 58.5% and severe in 33.0% of autistic children (Kielinen, Linna, & Moilanen, 2000).

A prevalence study on autism among 3 – 10 year old children was done at Atlanta and found that the rate was 34 cases per 10000 for autism spectrum disorders (ASDs) (Fombonne, 2003). It was observed that the prevalence of all autism spectrum disorders was 6.7 cases per 1000 children according to a study done at New Jersy, USA in 1998 (Bertrand, Mars, Boyle, Bove, et. al., 2001)

A meta-analysis of 37 prevalence studies of autism reported from USA, UK, European countries and Japan had estimated that the prevalence of autism was 7.1 per 10,000 among individuals under 18 years of age (Williams, Higgins, & Brayne, 2006). Boys were affected more than girls and the average male: female ratio was around 4:1. (Fombonne, 1999) Studies done in USA and UK, had indicated that the prevalence of autism had increased two to three times over the last three decades (Yeargin-Allsopp, Rice, Karapurkar, Doernberg, et. al., 2003; Gurney, Fritz, Ness, Sievers, et. al., 2003). However detailed analysis of epidemiological data had revealed that the past rates underestimated true prevalence. The current higher prevalence rates most probably may be due to improved identification of autism rather than a secular increase in its incidence. (Fombonne, 2001; Heussler, Polnay, Marder, et. al., 2001)
A review article was published in 2008 from the Medical University of South Carolina, USA, and it provides an overview of the most recent developments in the literature regarding autism spectrum disorders including epidemiology, etiology, assessment, and treatment. The article states that Autism Spectrum Disorders are more common than previously believed (1 in 166), and etiology appears to be multifactorial including both heritable and non-heritable factors. State of the art treatment includes comprehensive medical monitoring as well as behavioral intervention (Charles, Carpenter, Jenner, & Nicholas, 2008).

The latest report published by Center for Disease Control and Prevention, Atlanta, during 2014, reveal that the prevalence of autism among children is 1 in 68. This estimate is around 30% higher than the estimate for 2008 (CDC - MMWR, 2014). The high value indicate that the magnitude of the problem prevailing in the world.

2.6.3 Etiopathogenesis of autism

A detailed information regarding the etiology of autism is having special importance since the disorder is seen increasing during this decade. Even though the exact etiology of autism is not known, many studies done in developed countries reveal that the cause is multifactorial in origin. There are not many published studies in Kerala or India with regard to the causative factor of autism. This disorder is cost mainly due to hereditary (genetic) and environmental factors along with a group of unknown or idiopathic factors. Most of these children present with gastrointestinal disorders like gastritis, dysbiosis, excessive intestinal permeability, yeast over growth, sensitivity to certain food and
proteins like gluten and caseins. Autoimmunity, metabolic disorders, nutritional deficiency and heavy metal toxicity like mercury, zinc are some of the postulated reasons for autism.

Most of the etiological factors can be classified as antenatal, natal and postnatal reasons. The child rearing practices of infants, toddlers and preschoolers also has got an influence for developing autism or for increasing the severity of the disorder. Some of the socio demographic factors contributing to autism have also been described in the literature.

2.6.3.1 Socio-demographic factors

Because of the increasing pattern of autism in our country the role of non-genetic factors has been highlighted like the place of residence of the child, education of parents, socio-economic status and other factors like; child rearing practices

Socio-demographic factors, particularly Socioeconomic Status (SES) have been implicated as a risk factor for Autism Spectrum Disorders (ASD). For example, in New Jersey, one of the wealthiest states in the United States, the prevalence of Autism Spectrum Disorders is 17.2 cases per 1000 children in homes with average income above $90,000 and only 7.1 cases per 1000 children in homes with median income less than $30,000 (Thomas, Zahorodny, Peng, Kim, Jani, Halperin, & Brimacombe, 2012). This lower risk is probably not due to a protective effect of lower SES but rather due to under diagnosis, a lack of surveillance by physicians, parents, and teachers, and reduced access to services. For many chronic childhood disorders and developmental disabilities, the association with SES often is found to be inverse, such
that population prevalence decreases with increasing levels of SES (Victora, Wagstaff, Schellenberg, et. al., 2003; Durkin, Schupf, Stein, & Susser, 2007).

The highest risks of autism were found in siblings of children with autism, or Asperger’s syndrome and other pervasive developmental disorders (PDDs). The relative risk of autism in the child was about twice as high if the mother had been diagnosed with a psychiatric disorder. The risk of autism was associated with increasing degree of urbanization of the child’s place of birth and with increasing paternal, but not maternal age. (Lauritsen, Pedersen, & Mortensen, 2005). The place of residence of child and the association with autism has been published in other studies also.

Seaver Center for Autism Research, New York, did a study on the relationship between advancing paternal age and autism. It was found that children of men 40 years or older were 5.75 times more likely to have autism compared with offspring of men younger than 30 years (Reichenberg, Gross, Weiser, et. al, 2006).

The risk of infantile autism was increased for mothers aged more than 35 years, with foreign citizenship, and mothers who used medicine during pregnancy. A higher risk of infantile autism was seen among children with low birth weight and with congenital malformations. (Maimburg, & Vaeth, 2006). Mother’s age at conception has been indicated as one of the risk factors for autism and also the father’s age at birth.

There was a significant association between advancing paternal age and risk of ASD. Offspring of men 40 years or older were 5.75 times
(P<.001) more likely to have ASD compared with offspring of men younger than 30 years, after controlling for year of birth, socioeconomic status and maternal age. Advancing maternal age showed no association with ASD after adjusting for paternal age (Reichenberg, Gross, Weiser, Bresnahan, et al., 2006)

Risk of Autism Spectrum Disorders increased significantly with each 10 year increase in maternal age (Relative risk, 1.31) and paternal age (Relative risk, 1.28) (Croen, Najjar, Fireman, & Grether, 2007).

Eighty-four individuals with autism spectrum disorders were enrolled in the study (Tsuchiya KJ, Matsumoto K, Miyachi T, et al., 2008) which was done at University School of Medicine, Japan to find out paternal age at birth and high-functioning autistic spectrum disorder in their offspring. It was observed that the increased paternal, but not maternal, age was associated with an elevated risk of high-functioning autistic-spectrum disorder.

The research study (Croen, Najjar, Fireman, & Grether, 2007) to find out maternal and paternal age and risk of autism spectrum disorders revealed that the risk of ASDs increased significantly with each 10-year increase in maternal age and paternal age. Associations with parental age were somewhat stronger for girls than for boys, although sex differences were not statistically significant. In this study, it was proved that advanced maternal and paternal ages are independently associated with ASD risk.

The study done at Department of Epidemiology, Denmark to document the variation in incidence of neuro developmental disorders with season of birth, it was found that there was no seasonal variation of
birth for a range of childhood neuro developmental disorders. (Atladóttir, Parner, Schendel, Dalsgaard, Thomsen, & Thorsen, 2007)

### 2.6.3.2 Nutritional and other factors

Gastrointestinal disorders are commonly seen in autistic children. The common symptoms include chronic constipation, diarrhea and abdominal pain. Chronic dueodenitis and reflux esophagitis has been seen up to two-third of autistic children (Horvath, Papadimitriou, Rabsztyn, & Drachenberg, 1999). Most of the children have a form of inflammatory bowel disease and some have food intolerance and sensitivity to food proteins including lacto globulin and casein compared to controls (Lucarelli, Frediani, Zingoni, et al., 1995).

A review (Elder, 2008-2009) article was published on the gluten-free, casein-free diet in autism at University of Florida, USA and it is indicated that the prevalence of autism and autism spectrum disorder (ASD) appears to be on the rise, and there exist no clear etiology or cure. Out of desperation, many families are turning to new therapies and interventions discovered through various media sources and anecdotal reports from other parents. Unfortunately, many of these newer, well-publicized interventions have little empirical support. One of the most popular yet currently scientifically unproven interventions for ASD is the gluten-free, casein-free (GFCF) diet.

Nutritional abnormalities are commonly seen among these children. Autistic children commonly have significantly lower plasma levels of omega-3, fatty acids than their controls (Vancassel, Durand, Barthelemy, et al., 2001). In a case control study among 70 autistic
children compared with 42 normal controls, it was found that serum vitamin-D was significantly less among autistic children (Meguid, Hashish, Anwar, et.al. 2010).

It has been suggested that fatty acid deficiencies or imbalances may cause neuro developmental disorders in children. A randomized, double-blind study done to find out the effects of 1.5 g/dl of omega-3 fatty acids (Eicosapentaenoic acid–EPA, Docosahexaenoic acid–DHA) supplementation in children with autistic disorders having severe tantrums, aggression, or self-injurious behavior revealed that omega-3 fatty acids have superiority over placebo in improving the symptoms (Amminger, Berger, Schäfer, et al., 2007)

A study was done on Behavioral effects of omega-3 fatty acid supplementation in young adults with severe autism at University of Pavia, Italy. Nineteen young adults with severe autism, aged 18-40 years, received two fish oil capsules per day containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for 6 weeks. It was observed that no significant improvements were observed with regard to the severity and frequency of problematic behaviors either during the active treatment period or during the 6 week observation period. Moreover, no effect on the number of episodes and severity of behavior aberrations was observed (Politi, Cena, Comelli, Marrone, Allegri, Emanuele, & Ucelli di Nemi, 2008).

The case study done at Post Graduate Institute of Medical Education and Research, Chandigarh, to find out the possible etiology of childhood disintegrative disorder revealed that the child had Vitamin-B12 deficiency and hyper homocysteinemia. This study illustrates the
pressing need for detailed evaluation of all such cases having regression of neurodevelopment, since Vitamin-B12 deficiency if present can be treated (Malhotra, Subodh, Parakh, & Lahariya, 2013).

Opioid Excess Theory for autism has been proposed in 1979 by Panksepp. In his article it has been described that autism is an emotional disturbance due to disturbance in the opiate systems in the brain (Panksepp, 1979). The opioid peptides (exorphins) are derived in the body from partially digested protein the food. A study done in Norway reported significantly higher levels of exorphins in urine from 315 children with autism when compared to 143 normal children. The mean level of exorphins was about two times high in autistic children (Reichelt, Tveiten, Knivsberg, & Bronstad, 2012). It has been postulated that the exorphins were formed from casein (milk proteins) and gluten (wheat proteins). This protein cross the blood-brain-barrier and cause the symptoms of the disease. This is the main justification for proposing casein free and gluten free (CFGF) diet which some parents had reported improvement in some of the symptoms of autism (Kidd, 2002).

2.6.3.3 Genetic factors

Even though autism is a multifactorial disease, it has been proved that influence of various genes has got a prime role in the causation of the disease. There is much evidence in the literature pointing that genetic factors play a major role in the etiology of autism. This evidence is derived from epidemiological studies having various research designs.

It is known from different studies that there is a multitude of genetic component, which is postulated as a reason for autism. The
study done at Department of Biological Sciences, BITS, Hyderabad, from a large population in India, revealed that consanguinity among parents increases the risk for autism spectrum disorders (OR: 3.22). This may be due to the genetic and environmental factors involved in the causation of autism (Mamidala, Kalikiri, Praveen Kumar, et. al., 2015).

It is reported in the literature that serotonergic dysfunction will cause neuro developmental abnormalities including autism and platelet hyper serotoninemia is reported as the prime endo phenotype for the causation of autism. In a study to find out the association of TPH2 limiting enzyme in the production of 5-HT biosynthesis and ITGB3 gene among ASD children in Indian population, it was proved that there is a likely involvement of ITGB3 gene and TPH2 in the causation of autism. The study was done at Biomedical Research & Diagnostic Centre, Kolkata (Singh, Chandra, Guhathakurta, et. al., 2013).

A case-study to find out nuclear transcription factor-kappa B in childhood autism was done at Osmania Medical College, Hyderabad. It was found that there was a significant increase in NF-kB binding activity in blood samples of children with autism. This genetic study has given good understanding of many of the biochemical changes occurring in autism cases (Naik, Gangadharan, Abbagani, et. al., 2011).

A study was done at Center for DNA Fingerprinting and Diagnostics, Hyderabad, to investigate whether genetic polymorphisms are the underlying causes for aberrations in folate pathway in autistic children since folic acid deficiency was postulated as a cause for autism. It was found that the MTHFR 677T-allele frequency was found to be higher in autistic children compared with non-autistic children (OR:
The frequencies of MTRR 66A allele and SHMT 1420T allele were lower in autistic group compared with non-autistic group (OR: 0.55 and 0.44 respectively) indicating reduced risk. This indicated that MTHFR C677T is a risk factor, whereas MTRR A66G and SHMT C1420T polymorphisms reduce risk for autism (Mohammad, Jain, Chintakindi, et al., 2009).

In a study, which demonstrated a link between autism and Engrailed-2 (EN2) gene, it was observed that the gene may contribute up to 40% of cases of autism in the general population. The authors suggest that mutation and disruption in the expression of EN2 gene will cause autism spectrum disorders, since the gene can alter the normal development of brain and other neural tissues (Benayed, Gharani, Rossman, et al., 2005).

A report from (Ramelli, Silacci, Ferrari, Cattaneo, Visconti, & Pescia, 2008) Department of Paediatrics, Switzerland, on a 4-year-old male child with autism with facial dysmorphism and the genetic analyses of the child demonstrated a de novo micro-duplication of the 22q11.2 chromosomal region. It is proposed that genetic evaluation of ASD should include fluorescence in-situ hybridization analysis of the 22q11.2 chromosomal region. Neuro-developmental impairment and behavioural problems are very common in patients with 22q11.2 duplication.

2.6.3.4 Antenatal Risk factors

Many antenatal risk factors have been indicated as the causative factor for autism, which are mainly due to environmental toxins,
infections and certain diseases occurring during pregnancy. Some of the antenatal risk factors and the related studies are:

Review of Literature which was mainly based on interview schedule administered among parents of autistic children revealed the association between autism and many antenatal risk factors. The review article to find out the presence of prenatal and perinatal factors that affect the risk of autism and autism spectrum disorders was done by searching MEDLINE. Seven epidemiological studies were reviewed and it was observed that there was an increased risk of autism and autism spectrum disorders due to advanced maternal age, advanced paternal age, and maternal place of birth outside Europe or North America. The natal and perinatal conditions that were significant are birth weight, duration of gestation and intrapartum hypoxia. There was evidence to suggest that parental age, antenatal and perinatal conditions were associated with an increased risk of autism and autism spectrum disorders. (Kolevzon, Gross, & Reichenberg, 2007)

In a case-control study conducted at Early intervention clinic at SSKM Hospital, Kolkata, among 31 autism cases and 100 controls to find out the perinatal complications associated with autism, significant correlation was found between presence of ante partum hemorrhage, pregnancy induced hypertension, preterm delivery and autism in the baby (Nath, Roy & Mukherjee, 2012).

A case-control study was done by Mamidala (2013) in Hyderabad among a retrospective cohort of 942 children under the age of 10 to find out prenatal, peri-natal and neonatal factors involved in etiology of autism. Advanced maternal age, fetal distress, respiratory infections
during pregnancy were found to be associated with autism (OR: 1.8). Labor complications, preterm birth, neonatal jaundice, delayed birth cry and birth asphyxia were also associated with autism (OR: 1.5). This is the first study of its kind in Indian population done in this area of possible risk factors of autism (Mamidala, Polinedi, P T V, et. al., 2013).

In a case control risk factor study done at Denmark, the logistic regression analysis showed that breech presentation, low Apgar score at 5 minutes, gestational age at birth less than 35 weeks, and parental psychiatric history, and affective disorders were the common risk factors. There was no statistically significant association between risk of autism and weight for gestational age, parity, number of antenatal visits, parental age, or socioeconomic status. The results pointed out that prenatal environmental factors and parental psychopathology were also associated with risk for autism (Larsson, Eaton, Madsen, et. al., 2005).

The case-control study on prenatal, perinatal and neonatal factors responsible for autism in children was done on 74 participants. 28 prenatal, perinatal and neonatal factors were examined and it was observed that many factors showed statistically difference from the control group. Significantly high incidence of uterine bleeding, lower incidence of maternal vaginal infection, less maternal use of contraceptives and higher incidence of hyperbilirubinemia was seen among ASD group (Juul-Dam, Townsend, & Courchesne, 2001).

Increased duration of education among mothers of children with autism, perinatal factors like breech presentation and primary cesarean delivery were observed in a study done to investigate 23 numbers of prenatal, perinatal and neonatal risk factors of autism spectrum
disorders. There were no significant association between autism and neonatal factors (Bilder, Pinborough-Zimmerman, Miller, & McMahon, 2009).

The case control study to find out Perinatal risk factors for infantile autism done at Karolinska Institute, Sweden, done among 408 autism cases and 2040 controls, revealed that the risk of autism was associated with daily smoking in early pregnancy, maternal birth outside the country, cesarean delivery, small for gestational age, five minute Apgar score below 7, and congenital malformations. These findings suggest that certain intrauterine and neonatal factors which lead on to restricted intrauterine growth and fetal distress are important cause for autism (Hultman, Sparén, & Cnattingius, 2002)

The association between maternal characteristics and autism risk done at Department of Health Services, California, among 4381 children with autism found that increased risk were observed for males, multiple births, and children born to black mothers. The risk also increased as maternal age and maternal education increased. (Croen, Grether & Selvin, 2002)

In a study done at Denmark to find out the familiar risk factors of autism from a National Registry of follow-up of 943,664 children less than 10 years, who developed autism (818 children), it was found that the risk of autism in the child was about two times high if the mother had a psychiatric disorder. The risk for autism was associated with increasing degree of urbanization of place of birth of the child and increasing paternal age (Lauritsen, Pedersen & Mortensen, 2005).
The study (Kolevzon, Gross, & Reichenberg, 2007) to review the evidence for the presence of prenatal and perinatal factors that affect the risk of autism spectrum disorders done at Mount Sinai School of Medicine, New York, proved that an increased risk of autism spectrum disorders included advanced maternal age, advanced paternal age, and maternal place of birth outside Europe or North America. The obstetric conditions that were significant for the causation of autism spectrum disorders were birth weight and duration of gestation and intra partum hypoxia.

A population study on perinatal factors and the development of autism done at University of Western Australia revealed that autism is unlikely to be caused by a single obstetric factor. In the study it was observed that the parents of autism cases were older and is mostly first born than the controls. Threatened abortion, labor induction, fetal distress, emergency caesarian section and Apgar score less than 6 at one minute were some of the findings associated with autism (Glasson, Bower, Petterson, et. al., 2004).

The study on prenatal and perinatal risk factors of autism done in North Dakota, using multivariate analysis revealed that decreased birth weight, low maternal education, previous termination of pregnancy, late onset prenatal care were the significant factors (Burd, Severud, Kerbeshian, & Klug, 1999).

The prevalence, correlates and antecedents of autism spectrum disorders in extremely preterm children less than 26 weeks of gestation was studied in U.K. and Ireland in 1995, among 307 children at11 years of age using social communication questionnaire (SCQ). It was observed
that higher scores of SCQ were observed in those pre terms than peer classmates. The findings suggest that extremely preterm children are at increased risk for autism spectrum symptoms in middle childhood. An analysis of the summary of discharge from the hospital data revealed that male sex, lower gestation, vaginal breech delivery, abnormal cerebral ultrasound scanning results, and not having had breast milk were independently associated with autism spectrum symptoms (Johnson, Hollis, Kochhar, Hennessy, Wolke, & Marlow, 2011).

It was proposed that autism may be caused by mercury. Several epidemiological studies failed to find a correlation between mercury exposure through thimerosal, a preservative used in vaccines, and the risk of autism. Recently, it was found that autistic children had a higher mercury exposure during pregnancy due to maternal dental amalgam and thimerosal-containing immunoglobulin shots. It was hypothesized that children with autism have a decreased detoxification capacity due to genetic polymorphism. It has been indicated that repetitive doses of thimerosal lead to neurobehavioral deteriorations in autoimmune susceptible mice. Promising treatments of autism involve detoxification of mercury, and supplementation of deficient metabolites (Mutter, Naumann, Schneider, Walach, & Haley, 2005).

In a study done at Karolinska Institute, Sweden (Buchmayer, Johansson, Hultman, Sparén, & Cnattingius, 2009) to find the association between preterm birth and autism, it was found that the increased risk of autistic disorders related to preterm birth is mediated primarily by prenatal and neonatal complications that occur more commonly among preterm infants. It was observed that compared with infants born at
term, the odds ratios for autistic disorders among very and moderate preterm infants were 2.05 and 1.55 respectively. When controlled for maternal, pregnancy, and birth characteristics, odds ratios were reduced to 1.48 and 1.33 respectively. When controlled for neonatal complications, odds ratios were 0.98 and 1.25, respectively. Reductions in risks of autistic disorders related to preterm birth were primarily attributable to pre-eclampsia, small-for-gestational age birth, congenital malformations, low Apgar scores at 5 minutes, and intracranial bleeding, cerebral oedema, or seizures in the neonatal period. Neonatal hypoglycaemia, respiratory distress, and neonatal jaundice were also associated with increased risk of autistic disorders for term but not in preterm infants.

The study (Lee, Harrington, Chang, & Connors, 2008) to find out increased risk of injury in children with developmental disabilities done at School of Public Health, USA, revealed that among Children with autism, ADD/ADHD, and other psychopathology there were about 2-3 times more likely to experience an injury that needs medical attention than unaffected controls.

Harvard Medical School, USA, did a study on increase in paternal age and risk for autism in an Iranian population sample among 179 autism cases and 1611 matched cohort children (Sasanfar, Haddad, Tolouei, Ghadami, Yu, & Santangelo, 2010). It was observed that there was a significant association between higher paternal age, but not maternal age, and an increasing risk of autism.

The study done at King's College Hospital, London, to find out the association between prenatal exposure to influenza and occurrence of
autism, revealed that the relative risk of developing autism, for exposure to influenza during gestation indicated that exposure to influenza epidemics during gestation is not associated with autism (Dassa, Takei, Sham, & Murray, 1995).

The case control study (Burd, Severud, Kerbeshian, & Klug, 1999) to identify pre- and perinatal risk factors for autism done at University of North Dakota, USA, among 78 cases and 390 controls identified five risk factors and the factors were decreased birth weight, low maternal education, later start of prenatal care, having a previous termination of pregnancy and increasing father's age.

In a population-based, case-control study of infantile autism done at Institute of Public Health, Denmark, the findings were; the risk of autism was increased for mothers aged more than 35 years, with foreign citizenship, and mothers who used medicine during pregnancy. A higher risk of infantile autism was seen among children with low birth weight and with congenital malformations. (Maimburg, Vaeth, 2006).

The study to investigate prenatal, perinatal and neonatal risk factors for autism spectrum disorders done at University of Utah School of Medicine, USA, revealed that the significant prenatal factors more frequently seen among children with autism spectrum disorders were advanced maternal age and parity. Increased duration of education among mothers of children with autism spectrum disorders was small but statistically significant. Significant perinatal factors were breech presentation and primary caesarean delivery. There were no significant associations found between autism spectrum disorders and neonatal factors (Bilder, Pinborough-Zimmerman, Miller, & McMahon, 2009).
In a study (Dodds, Fell, Shea, Armson, Allen, & Bryson, 2011) to find out the role of prenatal, obstetric and neonatal factors in the development of autism, among 924 children with an autism diagnosis, it was observed that among those children with low genetic susceptibility, some maternal and obstetric factors had an independent role in autism etiology whereas among genetically susceptible children, these factors appeared to play a lesser role. The role of pre-pregnancy obesity and excessive weight gain during pregnancy on autism risk require further investigation.

A case-control study (Zhang, Tian, Miao, et al., 2010) among 190 children with and without autism, to investigate prenatal and perinatal risk factors for autism in China, observed that nine risk factors showed significant association with autism like maternal second-hand smoke exposure, maternal chronic or acute medical conditions unrelated to pregnancy, maternal unhappy emotional state, gestational complications, oedema, abnormal gestational age (<35 or >42 weeks), nuchal cord, gravidity more than 1, and advanced paternal age at delivery (>30 year-old).

In a comprehensive meta-analysis study done at University of Miami Miller School of Medicine, USA, it was observed that the factors associated with risk for autism were advanced parental age at birth, maternal prenatal medication use, bleeding, gestational diabetes, being first born Vs third or later, and having a mother born abroad. The factors with the strongest evidence for autism risk included previous fetal loss, maternal hypertension, proteinuria, pre-eclampsia and swelling. (Gardener, Spiegelman, & Buka, 2009)
The study (Williams, Helmer, Duncan, Peat, & Mellis, 2008), done at Australia to find out the Perinatal and maternal risk factors for autism spectrum disorders, revealed that there were statistically significant trend towards gestational age, multiple birth and maternal age and mother's country of birth. The groups with the highest risk were children of mother's born in south-east or north-east Asia.

The study (Haglund, & Källén, 2011) to find out risk factors for autism and Asperger syndrome among 250 children born in Sweden, revealed that obstetric sub-optimality viz., prematurity, low Apgar scores, growth restriction, or macrosomia was positively associated with autism but not with Asperger syndrome. Maternal birth outside the country was positively associated with autism and negatively associated with Asperger syndrome. The highest risk estimate for autism was found among children to women who were born in sub-Saharan Africa, or in East Asia.

The study (Bilder, Pinborough-Zimmerman, Miller, & McMahon, 2009) to investigate prenatal, perinatal, and neonatal risk factors for autism spectrum disorders done at University of Utah School of Medicine, USA, revealed that the prenatal factors that occurred significantly more frequently among children with autism spectrum disorders were advanced maternal age and parity. Increased duration of education among mothers of children with autism spectrum disorders was small but statistically significant. Significant perinatal factors were breech presentation and cesarean delivery. There were no significant associations found between autism spectrum disorders and neonatal factors.
A study done to find out the association of family history of autoimmune diseases among 3325 children with autism revealed that there is an increased risk of autism for children with a maternal history of rheumatoid arthritis and celiac disease. There was an increased risk of infantile autism occurrence, if there is family history of type-1 diabetes. This study is relevant since familial autoimmunity and pathogenesis of autism was suggested (AtladAttir, Pedersen, Thorsen, Mortensen, Deleuran, Eaton, & Parner, 2009).

A retrospective analysis of 428 children diagnosed with autism-spectrum disorders was done to examine the hypotheses that maternal ethnicity and/or immigration are linked to the rate of childhood autism-spectrum disorders. It was observed that mothers born outside Europe had a significantly higher risk of having a child with an autism-spectrum disorder compared with those born in the UK, with the highest risk observed for the Caribbean group mothers of Black ethnicity. Analysis of ethnicity and immigration factors together suggested that the increased risk is predominately related to immigration. It was observed that maternal immigration is associated with substantial increased risk of autism-spectrum disorders with differential risk according to different region of birth and possibly ethnicity (Keen, Reid, & Arnone, 2010).

Autism occurs in children reared in all types of cultures and countries. It can be noted that most of the published research articles come from Western countries. Very little information about its clinical correlates and co morbidity are available from African and Middle Eastern countries. A study was done at King Fahd Medical City Hospital, Riyadh, Saudi Arabia, to find out G6PD deficiency in autism. Two cases of
G6PD deficiency was reported in children with autism recruited in the cohort of a large study to find out the occurrence of autism in Saudi Arabia. The findings suggest that a different set of medical conditions may be associated with autism in developing countries. (Al-Salehi, & Ghaziuddin, 2009)

The study on association between parental age at birth and the social functioning of their adolescent male children was done at Israel. The findings revealed that compared with offspring of parents aged 25-29 years, the prevalence of poor social functioning was increased both in offspring of fathers younger than 20 years and in offspring of fathers more than 45 years. The evidence indicated there is an association between higher age of parents of children at their birth and increased risk for schizophrenia and autism. (Weiser, Reichenberg, Werbeloff, et al., 2008)

After adjustment for maternal factors, only one autoimmune condition, psoriasis was significantly associated with Autism Spectrum Disorders (adjusted odds ratio, 2.7. A greater than 2 fold elevated risk of ASD was observed for maternal asthma and allergy diagnoses recorded during the second trimester of pregnancy (Croen, Grether, Yoshida, Odouli, Van de Water, 2005)

As per the study done by Hultman and colleagues (2002) it was observed that the risk of autism was associated with daily smoking in early pregnancy (OR = 1.4), cesarean delivery (OR = 1.6), being small for gestational age (OR = 2.1), a 5 minute Apgar score below 7 (OR= 3.2), and congenital malformations (OR=1.8) (Hultman, Sparén, & Cnattingius, 2002)
In a research done by Larsson et al. (2005) the observation with regard to the association of antenatal risk factors and autism was published. The risk of autism was associated with breech presentation (risk ratio-RR) = 1.63), low Apgar score at 5 minutes (RR =1.89), gestational age at birth less than 35 weeks (RR=2.45), and parental psychiatric history -schizophrenia like psychosis: (RR=3.44), affective disorder (RR=2.91) (Larsson, Eaton, Madsen, et al., 2005)

Compared with control subjects, cases of autism had significantly older parents and were more likely to be first born. Autism mothers had greater frequencies of threatened abortion, epidural caudal anesthesia use, labour induction, and a labour duration of less than 1 hour. Cases were more likely to have experienced fetal distress, been delivered by an elective or emergency caesarean section, and had an Apgar score of less than 6 at 1 minute. Cases with a diagnosis of autism had more complications than those with pervasive developmental disorder not otherwise specified or Asperger syndrome (Glasson, Bower, Petterson, de Klerk, Chaney, & Hallmayer, 2004).

It was revealed in a study published in 2007 that among specific diagnoses, upper respiratory infections were significantly less frequently diagnosed and genitourinary infections more frequently diagnosed in children with autism. In the first 30 days of life, the frequency of having an infection was slightly higher among children with autism (22.6% vs 18.7%) (Rosen, Yoshida, & Croen, 2007).

The autism group was found to have a significantly higher incidence of uterine bleeding, a lower incidence of maternal vaginal infection, and less maternal use of contraceptive during conception
when compared with the general population. Similarly, the PDD –NOS group showed a higher incidence of hyperbilirubinemia when compared with the general population (Juul-Dam, Townsend, & Courchesne, 2001).

2.6.3.5 Natal and Neonatal Risk factors

Some of the natal and neonatal risk factors have been indicated as the causative factor for autism and the related studies are;

Compared with the controls, the children who had experienced newborn encephalopathy were 5.9 times more likely to have been diagnosed with an ASD (Badawi, Dixon, Felix, Keogh, Petterson, Stanley, & Kurinczuk, 2006) as per the study published in 2006.

Birth asphyxia and hypo perfusion to brain was highlighted as one of the reasons of autism. A case-control study was done in ten children with autism and mental retardation at SDM Hospital, Jaipur, titled “Cerebral perfusion abnormalities in children with autism and mental retardation”. The cases were evaluated using single photon emission computed tomography (SPECT) and it was observed that there was generalized hypo perfusion of brain in all ten cases compared to the controls. The maximum hypo perfusion was in the frontal and prefrontal regions of brain. It was also concluded that children with autism have varying degrees of abnormalities in perfusion of brain that will cause neuro developmental dysfunction (Gupta & Ratnam, 2009).

The University of Aarhus, Denmark conducted a study (Maimburg, Vaeth, Schendel, Bech, Olsen, & Thorsen, 2008) to find out risk factor for infantile autism. The study was done among 473 cases and an equal number controls born from 1990 to 1999 in Denmark. It was observed
that almost fourfold risk for infantile autism in infants had hyperbilirubinaemia after birth (OR 3.7). A strong association was also observed between abnormal neurological signs after birth and infantile autism, especially hyper tonicity (OR 6.7). No associations were found between infantile autism and low Apgar scores, acidosis or hypoglycaemia.

A population based case-control study of 473 children with autism and without autism that were born between 1990 and 1999, was done at University of Aarhus, Denmark, on Neonatal jaundice and its association with infantile autism. Logistic regression analysis revealed that four-fold risk for infantile autism was observed in infants who had hyperbilirubinaemia after birth. A strong association was also observed between abnormal neurological signs after birth and infantile autism, especially hypertonicity. There was no association between infantile autism and low Apgar scores, acidosis or hypoglycaemia at birth. The findings suggest that hyperbilirubinaemia and neurological abnormalities in the neonatal period are important factors to consider in studies to find out the etiology of infantile autism (Maimburg, Vaeth, Schendel, Bech, Olsen, & Thorsen, 2008).

2.6.3.6 Environmental risk factors including child rearing practices

It has been reported in the literature that many of the environment toxins, pollutants are the culprits for the causation of autism. Lead, methyl mercury, polychlorinated biphenyls, arsenic, toluene, manganese, DDT, fluoride, ethanol are some of the environmental toxins that are involved. Electromagnetic radiation from
cellphones, cell towers, Wi-Fi devices, microbial toxins, Vitamin-D deficiency, is also indicated as risk factors for autism. Review of literature does not give much convincing evidence for this association. Favorable early child care practices that foster child development is postulated as a protective factor for autism. In this research special reference has been made in this direction regarding the influence of favorable early child care practices.

2.6.3.7 Vaccines and autism

The connection between MMR Vaccine and Autism is based on two theories. One is based on the fact that some fraction of the vaccine will cause entropathy due to malabsorption which will cause absorption of toxic neuro-peptides into brain to cause Autism. The other theory involves the role of a preservative used in vaccines the thimerosal. This is a combination of ethyl mercury and thio salicylate. There have been many legal battles in USA with regard to claims filed for compensation by parents of Autistic children (Artigas-Pallarés, 2010).

There have been some reports that MMR vaccine is the culprit for autism among children. But it has been proved that MMR vaccine is not a causative factor for Autism. In a study done at Denmark from 1991 to 1998 done among 537,303 children it has been disproved the hypothesis that MMR vaccination causes Autism. (Madsen, Hviid, Vestergaard, et. al., 2002)

Many of the vaccines given to children contain thimerosal. This contains ethyl mercury and is used as a preservative in vaccines. In the research studies done by Geier (2005) they could found that there could
be an association between thimerosal and autism (Geier, & Geier, 2005). But further studies in this direction have refuted the association between thimerosal and autism (Honda, Shimizu, & Rutter, 2005).

In a population-based study (Madsen, Hviid, Vestergaard, et. al., 2002) of measles, mumps, and rubella vaccination done at Denmark among 537,303 children the relative risk of autistic disorder in the group of vaccinated children, as compared with the unvaccinated group, was 0.92. The study provided strong evidence against the hypothesis that MMR vaccination causes autism.

The study on relationship between thimerosal and autism was published in Pediatrics. (Nelson, & Bauman, 2003). It highlights that there is no evidence, which indicate that children exposed to vaccines containing mercury will cause autism than children with no exposure. It is also stipulated that on the basis of current evidence it is not possible to infer that thimerosal and autism are linked.

In a sound epidemiological study done at Department of Psychiatry, Montreal, it was proved that there is no association between autism spectrum disorders and immunizing the child with measles or MMR vaccine (Zingg, 2005).

A review (Cave SF, 2008) done at Louisiana, USA, revealed that the number of autistic children has increased over the last decade. The cause of this epidemic has remained unknown, but several hypotheses have been studied. Most of these studies suggest an environmental trigger, such as the ethyl mercury contained in the preservative thimerosal, which has been used in vaccines since 1931. Other possible triggers associated with vaccinations are chemical toxins due to live
viruses. The Hannah Poling vaccine decision was a landmark case. Poling’s family was awarded compensation for medical care of autistic child, who had mitochondrial dysfunction thought to be exacerbated by vaccines. Several studies have emerged supporting the fact that a significant number of autistic children do have mitochondrial dysfunction.

A study was done at California to find out whether autism is caused by exposure to the preservative thimerosal, which contains ethyl mercury, during the period from 1999 to 2007. The data did not support the hypothesis that exposure to thimerosal during childhood is a main cause of autism. (Schechter, & Grether, 2008)

In a case control study done in Poland with the objective to find out whether there is a relationship between MMR vaccination and autism in children it was proved that there is evidence against the association of autism with either MMR or a single measles vaccine (Mrozek-Budzyn, Kieltyka, & Majewska, 2010)

In a case control study (Mrozek-Budzyn, Kieltyka, & Majewska, 2010) to find out lack of association between measles-mumps-rubella vaccination and autism in children done at Poland, among 96 cases with autism and 192 control group, it was proved that there was no association of autism with either MMR or a single measles vaccine.

On the basis of the current evidence it is known that thimerosal, vaccine and autism have no link.
2.7 Clinical features of Autism

Autism is a neurodevelopmental disorder of multifactorial etiology and the diagnosis is essentially clinical. Making a diagnosis of autism is very important considering the role for early intervention. Clinicians should think of the possibility of the disorder in all children, when they report for routine check-up, including for immunization or for treatment for some other diseases, where impairment in social development, impairment in communication and presence of pervasive behaviour is manifested in them. Clinicians especially pediatricians and psychiatrist, speech therapists and clinical psychologists are usually the primary professionals, who commonly encounter these children.

The clinical features of Autism can be observed in infancy itself on close tracking of the developmental milestones and observing the behavioural pattern of children. The aberrations in various domains of neuro development like personal social and language development are commonly observable in infancy and toddler period itself.

Social Smile at 2 months, laughing with sound at four months, locating sound with eyes, following a moving object at four months, reaching out for toys with hands around 4 to 6 months, transferring objects with hands at 6 months, turning to sound at 8 months, producing speech like sounds at 8 months, speaking one or three words like amma, appa, waving tata – bye bye and pointing to objects at one year of age are the some of the important developmental mile stones in the area of personal social and language development normally seen during infancy. On close observation it can be seen that these mile stones may not be well developed in autistic children.
Regression of attained milestones is commonly seen in certain autistic children. Absence of Interactive play, not responding to sounds, avoiding eye contact are seen in these children. Absence of joint attention, proto declarative pointing and proto imperative pointing are some of the red-flag signs observed in autism. The other features are poor emotional bonding with parents, not maintaining eye contact with others, not initiating or speaking to others, abnormal repetitive behaviours. Apart from this, abnormal sensitiveness and reaction to sound, light, smell, and touch are seen as part of sensory dysfunction in these children.

Some children will have abnormal posturing as part of abnormality in position sense. Abnormal taste sensation whereby they have abnormal liking for certain foods having typical texture is also encountered. Abnormal interest for certain musical tones, smell are seen as part of the obsessive behaviour. They like to move around an object frequently and repeatedly or and spin by themselves and this is a behaviour observed as part of abnormal repetitive behaviour. All these symptoms can be put together into the following categories of domains like - abnormalities of social development, language development, abnormal – repetitive behavioural pattern and sensory dysfunction

2.7.1 Comorbid conditions associated with autism

Apart from the three major symptom complex of autism these children commonly have certain co morbid conditions like mental retardation, epilepsy, visual impairment, hearing impairment, hyperactivity, obsessive compulsive disorders, behavioural problems,
hypothyroidism, gastro intestinal problems, sensory dysfunctions like
tactile, olfactory, auditory, gustatory, proprioceptive.

The following are some of the studies with regard to comorbid
conditions associated with autism.

In a group of 112 ten-to-fourteen year old children from
Department of Child and adolescent psychiatry, King’s College London, it
was observed that 70% of children had at least one comorbid disorder
and 41% had two or more. The most common comorbid conditions were
social anxiety disorder (29.2%), ADHD (28.2%) and ODD (28.1%).
(Simonoff, Pickles, Charman, Chandler, Loucas, & Baird, 2008)

Kanne and colleagues (2009) did a study on the report by parents
and teachers of children with autism spectrum disorders at Columbia,
USA, and observed that the following co-morbidities were present; (i)
affective-26%; (ii) anxiety-25%, (iii) attentional-25%, (iv) conduct-16%,
(v) oppositional-15% and (vi) somatic problems-6% (Kanne, Abbacchi, &
Constantino, 2009).

The association between depression and anxiety in high
functioning children with autism spectrum disorders and maternal mood
symptoms were studied. It was observed that 32% had depressive
symptoms and 39% had anxiety disorders among autistic children
(Mazefsky, Conner & Oswald, 2010)

Attention deficit hyperactivity disorder (ADHD) is a common
comorbid condition commonly seen among children with autism. In a
review study done at Netherlands, it was indicated that 30 to 80% of
children with autism had ADHD (Rommelse, Franke, Geurts, Hartman & Buitelaar, 2010).

In a clinical sample of 89 children with autism and 258 controls studied at University Hospital, Denmark, it was observed that 22.5% had epilepsy against 4.3% in the control group. (Mouridsen, Rich, & Isager, 2011) highlighting that epilepsy is a co-morbid condition seen among autistic children.

The study to determine whether children with autism have an increased incidence of gastrointestinal symptoms compared with matched control subjects (Ibrahim, Voigt, Katusic, Weaver, & Barbaresi, 2009), observed that no significant associations were found between autism cases and controls with regard to the incidence of gastrointestinal symptoms. However, gastrointestinal problems have been reported in children with autism in other studies.

A study was done at New York, to find out gastrointestinal symptoms in children with autism spectrum disorders and language regression (Valicenti-McDermott, McVicar, Cohen, Wershil & Shinnar, 2008) and it was found that, autistic children with language regression more frequently exhibited an abnormal stool pattern. They also had increased family history of celiac disease or inflammatory bowel disease and rheumatoid arthritis. An association was observed between autistic children with language regression, and a family history of autoimmune disease.

In a case control study to find out whether there were more bowel symptoms in children with autism compared to normal children and children with other developmental and neurological disorders, it
was observed that there was a significant difference in the reporting of certain bowel symptoms (constipation, diarrhoea, flatulence) and food faddism between the autism group and the control group. (Smith, Farnworth, Wright, & Allgar, 2009).

The study to find out Savant skills in autism among 137 individuals with autism (mean age 24 years) revealed that 28.5% met criteria for either a savant skill or an exceptional cognitive skill. No individual with a non-verbal IQ below 50 met criteria for a savant skill and, contrary to some earlier hypotheses, there was no indication that individuals with higher rates of stereotyped behaviours/interests were more likely to demonstrate savant skills (Howlin, Goode, Hutton, & Rutter, 2009).

A study was done on Autism at All India Institute of Medical Sciences, New Delhi, with the main objective to establish the diagnosis of autism among children with derangements of language, communication and behaviour; among 75 referred patients, who fulfilled the DSM criteria for autism. Evaluation included a detailed history, clinical examination, IQ assessment; Connor's scoring for hyperactivity and Fragile-X screening. It was observed that the male: female ratio was 8:1. The important co-morbidities found were mental retardation (95%), hyperactivity (53%) and seizures (10%) (Kalra, Seth, & Sapra, 2005)

Many researches indicate the presence of macrocephaly or large head circumferences in children with autism compared with their typically developing peers. A study done at Texas revealed statistically non-significant differences in the head circumferences of children with autism spectrum disorders, compared with children without autism spectrum disorders. These results may be considered highly
generalizable, because they were derived from a nationally representative, community-based sample of children with and without autism spectrum disorders (Barnard-Brak, Sulak, & Ivey Hatz, 2011).

The increased prevalence of macrocephaly in relatives of children with autism compared with control children suggests that this characteristic may be familial risk factor in the pathogenesis of autism (Fidler, Bailey, & Smalley, 2000).

Autism is frequently seen in tuberous sclerosis and fragile-X syndrome, but these two disorders account for a small minority of cases. Diagnosable medical conditions, cytogenetic abnormalities, and single gene lecdefects together account for less than 10% of cases of Autism. There is convincing evidence that “idiopathic” autism is a heritable disorder. More prevalence of autism among males is seen and this increase of autism in males remains unexplained, but autism associated with certain X-linked disorders contribute to a small percentage. The recurrence rate in siblings of affected children is approximately 2% to 8%, much higher than the prevalence rate in the general population but much lower than in single-gene diseases. (Muhle, Trentacoste, & Rapin, 2004).

A study was done at Neurodevelopmental Disorders Research Center, University of North Carolina, USA, to examine the structure of restricted repetitive behaviors (RRBs) in autism using relevant items from the tool, the Autism Diagnostic Interview-Revised in a sample of 316 individuals with autistic disorder. (Lam, Bodfish, & Piven, 2008). It was observed that RRBs is a core feature of autism and consist of a variety of behaviors, ranging from motor stereotypies to complex
circumscribed interests. Using exploratory factor analysis, three distinct factors were identified: Repetitive Motor Behaviors, Insistence on Sameness, and Circumscribed Interests. The repetitive behaviour is commonly seen in all children with varied presentation.

A clinical and neurodevelopmental profile of 51 children with Autistic disorder, from a referral population was done at Maulana, Azad Medical College, New Delhi (Juneja, Mukherjee, & Sharma, 2005). It was observed that a correct diagnosis had been made in only 5.8% of children prior to referral. The mean age of presentation was 3.28 years. Among this 96% of the autistic children had developmental delay. Qualitative impairment in social interaction and communication was more commonly observed than restricted interests and activities. Forty-seven (92.15%) children were severely autistic and 4 (7.84%) were in the mild to moderate autistic category. On follow up it was observed that all children诊断e before two years, were confirmed to have Autistic disorder at a later stage.

The patterns of development in young children with autism was studied at Post Graduate Institute of Medical Education and research, Chandigarh to determine the extent to which the developmental profile of children less than 4 years can help in distinguishing children with autism from children with developmental delay. The study was done among 32 children with autism and 32 children with developmental delay using the assessment by Developmental Profile-II. The two groups showed significantly different developmental profiles and these differences were accounted for mainly by significantly lower social skills and superior motor skills in the autistic group as compared to the
developmentally delayed group. It was inferred that Developmental Profile II may help in distinguishing young children with autistic disorder from non-autistic children with developmental delays (Malhi, & Singhi, 2005).

A pilot study explored activity patterns in children with and without ASD and examined the role of sensory responsiveness in determining children's level of competence in activity performance. Twenty-six children with high functioning ASD and twenty-six typically-developing children of 6 to 12 years old were assessed using the Sensory Profile and the Child Behavior Checklist. Significant differences were seen in overall level of competence in activities, social, and school performance among the both groups. ASD Children had more frequent Sensory Sensitivity and Sensory avoiding and had significantly lower competence scores than children without ASD (Reynolds, Bendixen, Lawrence, & Lane, 2011).

The study (Mosconi, Cody-Hazlett, Poe, et. al., 2009) done at University of North Carolina, USA on longitudinal study of amygdala volume and joint attention among 2 to 4 year-old children with autism, revealed that amygdala enlargement was seen in children with autism at both 2 and 4 years of age. A significant association between amygdala volume and joint attention suggests that alterations to this structure may be linked to a core deficit found in autism.

A study on Screening for autism in extremely preterm infants was done at UK. All babies born less than 27 weeks gestational age in England during 2006 were recruited for the study. Parents of 559 (55%) survivors were included in the research to study the cognitive disability,
motor and sensory impairment at 2 year corrected age using M-CHAT. It was observed that cognitive impairment was present in 340 (61%) children, motor impairment in 71 (13%), visual impairment in 10 (2%) and hearing impairment in 6 (1%). 216 (41%) were screened positive for autistic features. (Moore, Johnson, & Marlow, 2010).

Family history data showed that motor tics, obsessive-compulsive (OCD) and affective disorders were significantly more common in relatives of autistic children and individuals with OCD were more likely to exhibit autistic-like social and communication impairments. Direct interview data confirmed the increased rate of affective disorders (especially major depressive disorder) in the first-degree relatives. (Bolton, Pickles, Murphy, & Rutter, 1998). Thus it can be seen that there exist many comorbid conditions associated with autism. All these comorbidities should be assessed and treated so that there will be targeted improvements for the total development of the child.

2.8 Diagnosis of Autism

Diagnostic and Statistical Manual (DSM) of Mental Disorders of American Psychiatric Association is the manual used by clinicians and researchers to diagnose and classify mental health related disorders. During 2013, the latest version DSM-5 was published after a long process of 14 years of revision. Similarly the manual of World Health Organization, the International Classification of Diseases (ICD), is being used in certain countries for the diagnosis of autism and similar disorders.
Clinical criteria, the DSM and ICD-10 are available for clinicians to record and diagnose autism all over the world. But in our country usually DSM criteria is being used for the diagnosis. This classifies autism as a pervasive developmental disorder characterized by severe and pervasive impairment in several areas of development; (i) reciprocal social interaction skills, (ii) communication skills, and (iii) presence of stereotyped behavior, interests, and activities. The recent DSM-V criteria for autism made available from 2013 include; (a) persistent deficits in social communication and social interaction, not accounted for by general developmental delays and manifest by 3 of 3 symptoms, (b) restricted, repetitive patterns of behavior, interests, or activities as manifested by at least 2 of 4 symptoms, (c) symptoms must be present in early childhood (but may not become fully manifest until social demands exceed limited capacities) and (d) symptoms together limit and impair everyday functioning. However the diagnosis of autism is usually made by Childhood Autism Rating Scale (CARS), which is a behavior checklist completed by an examiner and using cut off scores 30 and above. However, an Indian study from CMC Vellore has suggested a more appropriate CARS cut off score of 33 or more for the diagnosis of autism (Russell, Daniel, Russell, et. al., 2010).

The term Pervasive Development Disorder (PDD) described in International Classification of Diseases and Diagnostic and Statistical Manual includes the five conditions viz., Autistic disorder, Asperger’s Disorder, Rett’s Disorder, Childhood Disintegrative Disorder and Pervasive Developmental Disorder not otherwise specified (PDD-NOS).
In the new DSM-V criteria – autistic disorder, Asperger’s disorder and pervasive developmental disorder – not otherwise specified have been combined and included as a single entity known autism spectrum disorder (ASD)

Even for many clinicians, the diagnosis of autism can be difficult especially when trying to distinguish between autism spectrum disorders and other neurodevelopmental disorders. The common diseases or disorders like mental impairment, expressive and receptive language disorders, anxiety disorders, and attention-deficit hyperactivity disorder, as well as genetic disorders, such as fragile-X syndrome, share many features with autism. Making diagnostic distinctions in very young children is therefore a difficult task. However, an experienced clinician can diagnose autism even before the age of one year. Not able to say “ta ta”, not pointing to objects, avoiding eye contacts, not attaining speech are ‘red flag signals’ for autism at one year of age. Absence of proto-declarative pointing and proto-imperative pointing and pretend play at 12 to 18 months of life are almost sure signs of autism.

Apart from the above signs some children may develop regression of attained development milestones. In addition to early regression, there are some other behavioral markers that have been established as indicators of autism during infancy and toddler period. Retrospective analysis of videotapes of children in their first year of life have indicated that those who later receive a diagnoses of autism exhibit poor visual orientation and attention, limited response to calling names, lack of socially directed gaze, excessive mouthing of objects, and inappropriate behaviour to social touch, in relation to the comparison groups of
typically developing children (Baranek, 1999; Osterlin, Dawson, & Munson, 2002).

The specific diagnostic criteria of DSM-IV-TR for identification of autism is detailed below;

I. Total of six (or more) items from (A), (B), and (C), with at least two from (A), and one each from (B) and (C) should be present for making a diagnosis of autism.

A. Qualitative social interaction impairments as shown by at least two of the following characteristics; (i) significant impairment in the use of nonverbal behaviours, including eye-to-eye contact, facial expression, body posture and social interaction gestures, (ii) inability to establish developmentally appropriate peer relationships, (iii) failure to spontaneously seek opportunities to interact with other people (eg. by lack of identifying objects of interest) and (iv) poor social and emotional reciprocity.

B. Qualitative communication impairments as shown by at least one of the following characteristics; (i) delay in, or total lack of, spoken language development (not accompanied by an attempt to use alternative modes of communication such as gestures), (ii) Marked impairment in the ability to initiative or sustained a conversation with others, (iii) stereotyped and repetitive language use or idiosyncractic language and (iv) lack of varied, developmentally appropriate spontaneous make-believe play or social imaginative play.

C. Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following;
(i) encompassing preoccupation with one or more stereotyped patterns of interest that is abnormal either in intensity or focus, (ii) apparently inflexible adherence to specific, nonfunctional routines or rituals, (iii) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements) and (iv) persistent preoccupation with parts of objects

II. Delays or abnormal functioning in at least one of the following areas with onset prior to age 3 years
   i. Social Interaction
   ii. Language as used in social communication
   iii. Symbolic or imaginative play

III. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder.

Even though the diagnosis of autism is by clinical observation and assessments, screening or diagnostics tools have to be administered to confirm the diagnosis. Many tools are available for use in the community or clinical settings.

2.9 Early Detection and Early Intervention of Autism

It has been proved that even though there is no complete cure for autism, early intervention programs will reduce the undesirable behavioural symptoms of the disorder. Complete therapeutic cure is not possible because of the reason that the exact etiology of autism is not known and the proposed one is a multifactorial etiology. However
multidisciplinary intervention is the answer for treatment. Concerted effort by pediatricians, developmental therapists, occupational therapists, speech therapists, clinical, psychologists and special educators along with continued support-care and intervention by parents at home will help in reducing the burden of the disability. This will help in improving the quality of life of the affected individual. Early detection of autism can be made before 3 years by experienced clinicians and professionals. It may also be noted that the early detection process will be augmented and confirmed by availability of screening and confirmatory tests for detection of autism.

Some of the studies done in our country have proved that early intervention is effective in improving the symptoms of autism. In a study done at Child Development Centre, Kerala, during 2012, among 39 cases of autism, it has been proved that a clinic based low intensity, early intervention given for children has helped in amelioration of the severity of autism after intervention and the effect was clinically and statistically significant. (Nair, Russell, George, Prasanna, Mini, Leena, Russell, & Minju, 2014)

In order to find out the effectiveness of low intensity home based early intervention for autism spectrum disorders among 52 children less than 6 years of age, a study was done at Child Development Centre, Kerala, during 2012. It was found that the intervention was statistically significant and there was clinical improvement in the severity of autism especially in acquiring social and language skills. The study had policy implications for clinicians, administrators and other stakeholders, since this model of early intervention is feasible and can be adopted in
developing countries with low disability resources (Nair, Russell, George, Prasanna, Bhaskaran, Leena, Russell, &Mammen, 2014).

Many studies done in other countries of the world also have proved that early intervention is effective in improving the problems of autism. Early intervention is possible through screening in the community and diagnosing in clinical setting at an early age possibly below 2-3 years.

In the review article on “Autism Spectrum Disorders” it is specifically described that there is no single best treatment package for all children with Autism Spectrum Disorder. Decisions about the best treatment, or combination of treatments, should be made by the parents with the assistance of a trusted expert diagnostic team. The major treatment modalities are Pharmacotherapy, Sensory Integration Therapy, Auditory Integration Therapy, Diet Therapy, Mega Vitamin Therapy, Behavioural modification Therapy, Speech and Language Therapy. Lovaas Behavioural modification, Applied Behaviour analysis are some of the Behavioural modification techniques used in some countries. (Nair MKC, 2004)

2.10 Screening and Diagnostic tools for Autism

Early identification of children with Autism is important in the primary care setting and Pediatricians are the best informed professional with whom many families have contact during the first 2 – 5 years of life. Pediatricians are not only an expert on childhood illnesses, but also are on child’s development.
There is a great role for screening toddlers for autistic spectrum disorders because of a perceived increase in the prevalence of the condition and for instituting early diagnosis and intervention. The American Academy of Neurology has published “A Practice Parameter” that recommends the use of developmental screening tools with good sensitivity and specificity at every possible preventive services. The use of specific questions for early signs of Autism and use of specific autism screening tools as and when needed are also warranted. (Filipek, Accardo, Ashwal, et al., 2000)

Many centres use various tools depending on the various factors including availability, preference of clinicians and trained manpower. Tools like CHAT, M-CHAT are being used as screening tools. Tools like Childhood Autism Rating Scale (CARS), Autism Diagnosis Observation Schedule (ADOS) (Lord, Rutter, DiLavore, &Risi, 1999), Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994) are being used in our country as diagnostic tools. In Kerala many clinicians use CARS for the diagnosis of autism. Most of the tools are designed in western countries and are not standardized for Indian population. Further the above mentioned tests require in-depth training for administration and interpretation is also not very easy. The tool has got copyright and has to be purchased. Certain tools like ADOS and ADI-R are expensive and require mandatory international accreditation.

2.10.1 Screening Tools for Autism

Screening for diseases and disorders are usually done in normal population to identity diseases or conditions. Screening can be done
even by the trained health workers using screening tools. The cases identified by screening tools are to be confirmed by clinicians with the help of diagnostic tools. Thus Screening is a brief assessment procedure, designed to identify children who should receive more intensive diagnosis or assessment (Meisels, & Provence, 1989). Many screening tools are available in our country.

**Trivandrum Autism Behavioral Checklist (TABC):** TABC is a simple screening tool developed and validated at Child Development Centre (CDC) Kerala. TABC is essentially developed based on DSM-IV-TR criteria and can be administered by trained health workers as it has easily observable criteria with total 20 questions in 4 domains with minimum score of 20, and maximum score of 80. Validation study of TABC among 100 less than 6 year old children showed that it has 57.1% sensitivity, 94.2% specificity, 61.5% positive predictive value, 93.1% negative predictive value against another international autism screening tool the Checklist for Autism in Toddlers (CHAT). Similarly TABC showed 80% sensitivity, 91% specificity, 36.4% positive predictive value, 98.6% negative predictive value against the gold standard the Childhood Autism Rating Scale (CARS) (Nair, George, Purandare, Akhila, et. al., 2013)

**The Checklist for Autism in Toddlers (CHAT):** The checklist for Autism in Toddlers was initially introduced in the United Kingdom as a population screening measure for Autism Spectrum Disorders (Baron-Cohen, Allen, & Gillberf, 1992). The CHAT is mainly used for screening children for autism at 18 months of age. This tool is freely available for screening autism among normal population.
Modified Checklist for Autism in Toddlers (M-CHAT): This is a modified American version of the original CHAT published from United Kingdom. The M-CHAT has 23 questions using the original nine from the CHAT as its basis. The M-CHAT is available for clinical and research use. The tool consist of 23 yes/no items and is a promising instrument for the early detection of autism. The M-CHAT was designed as a simple, self-administered, parental questionnaire for use during regular pediatric visits. The more questions children failed, the higher their risk of having autism. This tool has a better sensitivity than the original CHAT (Robins, Fein, Barton, & Green, 2001)

The Screening Test for Autism in Two-Year-Olds (STAT): STAT is a simple screening tool, which is brief and can be administered without extensive training (Stone, Coonrod, & Ousley, 2000) and is available for using in children less than 2 years.

The Social Communication Questionnaire (SCQ): The Social communication Questionnaire (Rutter, Bailey, & Lord, 2003) is designed to identify children with Autism spectrum disorders less than 3 years old. This is mainly used for research purposes and is used for children with suspected autism. Most of the diagnostic tools are developed and validated in Western countries and is detailed below.

2.10.2 Diagnostic tools for autism

The Childhood Autism Rating Scale (CARS): CARS is a widely used tool for diagnosing autism (Schopler, Reichler, & Renner, 1988). It was designed to help to differentiate children with autism from other developmental delays, such as mental impairment. The CARS has strong
psychometric properties and is available for clinical and research work in India. Among the various tools for diagnosing autism CARS is commonly used as a diagnostic measure, because of its simplicity, conceptual relevance, high concordance agreement with DSM criteria. CARS has been validated for Indian population and found that it is acceptable and can be used among different populations in India. (Russell, Daniel, Russell, et. al., 2010).

In India CARS is widely used and has got strongest and best documented psychometric properties for diagnosing autism. The scale is designed for use with children 2 years and older. Advanced training is necessary for administrating the tool and requires about 30 minutes to complete the test. CARS is used all over the world and has been translated into many languages.

CARS consist of 15-items and the layout of the tool is on a 4 point scale. The standard cut-off score of 30 and above has been suggested as positive for autism. Minor modifications have been suggested where by the cut-off scores are moved up a few points for very young children and down for high functioning adolescents and adults (Lord, & Corsello, 2005).

The scale was developed using the diagnostic criteria based on (Kanner, 1943; Creak, 1961; Rutter, 1978) the diagnostic and statistical manual of mental disorders – DSM-III. The scale focus on behaviour of people affected with autism under 14 domains and a single category of general impression of autism. These 15 items are as follows; (1) Relating to people; (2) Imitation; (3) Emotional response; (4) Body use; (5) Object use; (6) Adaptation to change; (7) Visual response; (8) Listening
response; (9) taste, smell, and touch response and use; (10) Fear or nervousness; (11) Verbal communication; (12) Nonverbal communication; (13) Activity level; (14) Level and consistency of intellectual response; (15) General impressions.

The total score varies from 15 – 60 and the cut-off point for autism is 30. Using CARS the children can be differentiated into mild to moderate from severe autism. (Schopler, Reichler, & Renner, 1988). CARS is considered as the gold standard or reference standard for the diagnosis of autism. (Matson, & Bamburg, 1998; Morgan, 1988; Sturmey & Sevin, 1994).

**Gilliam Autism Rating Scale (GARS):** The Gilliam Autism Rating Scale (GARS), consists of 56 items divided into four subscales (Social Interaction, Communication, Stereotyped Behaviors, and Developmental Disturbances). The items are rated on a four-point scale. Some workers have challenged the accuracy of GARS for diagnosis of children with milder presentation of autism, but the GARS does have a method for grading the severity of disease. The GARS could be sensitive to subtle changes, but, it is unclear whether it would miss important autistic symptoms. The design of the scale is appropriate for repeated use, but some items do not appear to be appropriately sub grouped (e.g., play and repetitive behavior appear in Social Interactions subscale). GARS has good potential, but additional sensitivity and further psychometric data are needed (Gilliam, 2006).

**INCLEN Diagnostic Tool for Autism Spectrum Disorder (INDT-ASD):** INDT-ASD is a simple validated diagnostic tool for identifying autism spectrum disorders in India. This tool has got high diagnostic
accuracy, adequate content validity and criterion validity. The tool was validated against Childhood Autism Rating Scale and is available for diagnosing autism among 2 to 9 years old children (Juneja, Mishra, Russell, et. al., 2014).

**Indian Scale for Assessment of Autism (ISAA):** The ISAA was jointly developed by the National Trust, Ministry of Health and Family Welfare, and Ministry of Social Justice and empowerment (ISAA, 2009). ISAA is psychometrically acceptable and reliable but has sub-optimal validity in 3-9 year-old children. It was developed essentially to establish diagnosis of autism and to rate the severity. It can be used for certification of disability and thereby availing disability pension from Government.

Autism Diagnostic Observation Schedule (ADOS) and Autism Diagnostic Interview (ADI) are the two diagnostic tools which require extensive training for administration and is available only in very few centres in India.

Some of the studies published in literature regarding the use of the tools for identification of autism are;

In a review article on Screening for autism in young children using M-CHAT published from University of Connecticut, highlighted that increased prevalence of autistic spectrum disorders has fostered research efforts on the development and validation of autism-specific screening instruments for use with young children. It was indicated that many such autism-specific screening tools are to be used with young children in various stages of development for early identification. Data from a few of the screening instruments have been published, and they
include the Checklist for Autism in Toddlers (CHAT), Pervasive Developmental Disorders Screening Test (PDDST), Screening Tool for Autism in Two year olds (STAT), Checklist for Autism in Toddlers-23 (CHAT-23), and the Modified Checklist for Autism in Toddlers (M-CHAT). In this review, these five tools designed for use with children under three years old was mentioned in detail. (Dumont-Mathieu, Fein, 2005)

A comparative analysis study (Oosterling, Swinkels, van der Gaag, Visser, Dietz, & Buitelaar, 2009) of screening instruments for autism spectrum disorder in toddlers at Child and Adolescent Psychiatry University Centre, Netherlands using Early Screening of Autistic Traits Questionnaire, Social Communication Questionnaire, Communication and Symbolic Behavior Scales-Developmental Profile, Infant-Toddler Checklist and Checklist for Autism in Toddlers was done among 238 children (mean age =29.6 months, SD = 6.4) at risk for Autism spectrum disorder (ASD). It was observed that no instrument or individual item showed satisfying power in discriminating ASD from non-ASD.

The study (Kuban, O'Shea, Allred, Tager-Flusberg, Goldstein, Leviton, 2009) done at USA, to test the hypothesis that children born preterm are more likely to screen positive on the M-CHAT for an autism spectrum disorder, it was observed that motor, cognitive, visual, and hearing impairments appear to account for more than half of the positive M-CHAT screens in extremely low gestational age newborns.

A study was done which investigated the early detection of autism and pervasive developmental disorders using the Modified Checklist for Autism in Toddlers (M-CHAT) at University of Connecticut, USA. The results revealed that autism, is difficult to detect in very young children.
The M-CHAT was used to screen 1,293 children. Of the 58 children offered developmental evaluation, 39 were diagnosed with a disorder on the autism spectrum. Six items pertaining to social relatedness and communication were found to have the best discriminability between children diagnosed with and without autism. Results indicated that the M-CHAT is a promising instrument for the early detection of autism. (Robins, Fein, Barton, & Green, 2001)

2.11 Psychometrics of Tool Development and Validation

In India many of the tools both screening and diagnostic are used for identifying various mental health and behavioural disorders. Many of the tools are developed and validated in western countries. Since socio-cultural and socioeconomic factors of countries like India is different from developed countries, many of the tools are not ideal for our clinical use. In this context, the requirement of new tools, which is culturally appropriate for our nation, is essential.

There are many screening tools and diagnostic tools for autism. Screening tools are mainly used for identifying diseases in normal population and diagnostic tools are usually used in clinic settings for confirming the diagnosis from among the screened population. The psychometric properties of screening tools and diagnostic tools are also different. The screening tools should have high sensitivity whereas diagnostic tools should have high specificity. The detail of the most commonly available tools for autism is described previously.
When construction of a tool is planned it may be considered whether the proposed measure is for diagnosis or screening. The basic difference between the two is that diagnostics tool is administered on patients who have symptoms, whereas screening tool administered on subjects who does not have symptoms of the disease.

2.11.1 Concepts of screening and diagnosis

There are many tools available in our country for screening or diagnosis of autism among children. Many centers use various tests depending on the various factors. Tools like CARS, CHAT, ADOS, ADI-R, etc are being used in our country. In Kerala many clinicians use CARS for identification of cases. All the tools are designed in western countries and are not standardized for Indian population. Further the above mentioned tests require in depth training and the interpretations of results are not very easy. Further many tools have got copyright and has to be purchased for using the same in our country. Certain tools like ADOS and ADI-R are expensive and need advanced training for the testers to administer the test. The following are some of the screening and diagnostic tools for identification of autism.

Checklist for Autism among toddlers (CHAT), Autism Behavior Checklist (ABC), Social Communication Questionnaire (SCQ), Autism Research Institute’s Form E-2 Checklist, Autism Treatment Evaluation Checklist (ATEC), Childhood Autism Rating Scale (CARS), Gilliam Autism Rating Scale (GARS), Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedules (ADOS).
Diagnostic tools are tests that clinician use in the process of making the diagnosis of a particular disease. It is done to confirm the disease in a person suspected of having the disease, usually following the report on signs and symptoms, or based on the results of other medical tests (Al-Gwaiz, & Babay, 2007). The most accurate tool for determining a disease is a “gold standard tool” or reference standard tool, since it represents the best of the existing tests for diagnosing a specific disease (Spiegelman, Schneeweiss, & McDermott, 1996). Some of the diagnostic tools are invasive or expensive and some may not be available in our country. In case of developmental and behavioural tools cultural difference may exist and has to be standardized for our population. Hence some other diagnostic tests may be used and necessitates the requirement of newly designed tests which has to be validated by comparing its results with a gold standard tools.

The selection of Gold standard of reference standard tools may change depending on various situations and the clinician is the best person to select the one for making the correct diagnosis. Sometimes combination of tests can be considered for diagnosing a particular disease when one tool has not enough psychometric properties.

The selection of an appropriate diagnostic test depends upon the intended use of the results. If the intention is to rule out a disease, reliable negative results are required for which a test with high sensitivity (i.e. few false negatives) is used. If it is desired to confirm a diagnosis or find evidence of disease (i.e. to "rule in" the disease) we require a test with reliable positive results (i.e. high specificity). As a general rule of thumb, a test with at least 95% sensitivity and 75%
specificity should be used to rule out a disease and one with at least 95% specificity and 75% sensitivity used to rule in a disease (Pfeiffer, 1998).

2.11.2 Tool development and validation

The tool development and validation require elaborate procedure to undertake the various statistical principles and techniques involved. Review of available literature does not reveal any model for the tool development and validation. But many of the models follow similar steps. However, the developed tool should have good psychometric properties measured in terms of sensitivity, specificity, positive predictive value and negative predictive value ensuring good reliability and validity.

The tool developed can either be a new tool or a cultural modification of the existing tool. However to have better psychometric stability including criterion validity, the new developed tool should be validated against a gold standard tool or reference standard tool. The standard guidelines available in the literature for tool development are detailed below:

Tool development and items for the tool: The initial step in tool development is formulating the items required for the tool. The items for the tool can be obtained from review of literature, in depth interview of consultants, focused group discussions of patients, care givers and consultants and experts. The concepts of the disease will be converted to items. From the derived items of the tool, item selection will be done. This process of item reduction will be based on endorsement rate by the clinicians based on the clarity, frequency and
importance of the items for the tool. More details of tool development are given in chapter on methodology.

**Sample size for tool validation:** A wide range of recommendations regarding sample size of subjects required for analysis have been published in the literature. These are usually stated in terms of either the minimum sample size \( N \) for a particular analysis or the minimum ratio of \( N \) to the number of variables, \( p \) i.e. the number of items in the tool being subjected to factor analysis (MacCallum, Widaman, Zhang, & Hong, 1999). Gorsuch (1983) recommended five subjects per item, with a minimum of 100 subjects, regardless of the number of items. Guilford (1954) argued that \( N \) should be at least 200, while Cattell (1978) recommended three to six subjects per item, with a minimum of 250. Comrey, and Lee (1992) provided the following guidance in determining the adequacy of sample size: 100 = poor, 200 = fair, 300 = good, 500 = very good, 1,000 or more = excellent. More demanding recommendations for sample size require a minimum of 10 subjects per item (Everitt, 1975).

The developed tool should have good psychometric properties including validity and reliability.

**2.11.3 Reliability of measurement tools**

Reliability is the degree of consistency and accuracy with which an instrument measures the attribute for which it is designed to measure. This is the ability of an instrument to create reproducible results and is concerned with consistency of the tools. A tool only can be
considered reliable if it measures an attribute with similar results on repeated use and with different persons.

Unfortunately, it is impossible to calculate reliability exactly, but there are different ways to estimate the reliability. Consistency is the hallmark of reliability and in order to estimate the following three tests are used:

**Test-retest reliability** is a measure of reliability obtained by administering the same test twice over a period of time to a group of individuals. The scores from Time 1 and Time 2 can then be correlated in order to evaluate the test for stability over time. The minimum permitted test-retest interval is 3 days, and the maximum is 1 month.

**Inter-observer reliability** is a measure of reliability of a tool and is used to assess the agreement between two raters regarding the result of the tool to find out the presence or absence of disease.

There are mainly two types of measures to find out the Test-retest and inter observer reliability. One is the intra class correlation coefficient (ICC) the measure for calculating the reliability of continuous data and the other is kappa coefficient which is the measure for nominal data.

ICC values are between -1 and +1. Values nearing to +1 show high repeatability of the tool. Values, more than 0.75 is generally considered enough to infer that there is good agreement and the tool has good test-retest reliability and inter observer reliability (Indrayan, 2012). Minimum acceptable values of an intra-class correlation coefficient have been indicated in the literature. Fleiss describes values from 0.40 to 0.75 as “fair to good” (Fleiss, 1986); Streiner and Norman recommend values
more than 0.75 for continuous scales used in health research (Streiner & Norman, 1995). However if a psychometric test is used as a diagnostic tool, it should have a ICC reliability of at least 0.9 (Nunnally, 1978)

**Internal consistency reliability** is a measure of reliability used to evaluate the degree to which different items of the tool or parts of tool are consistent with other parts of the tool. This reliability is measured by the Cronbach's alpha reliability coefficient and it is suggested that if the score is higher the consistency is high. Nunnaly (1978) has indicated that a value of 0.7 is an acceptable reliability coefficient. However, lower thresholds have been accepted and used in the literature. Alpha can also be used to identify poor items that can be dropped, and those items that do not contribute significantly to homogeneity of the tool can be dropped to make the scale shorter.

Cronbach’s alpha reliability coefficient normally ranges between 0 and 1. Cronbach’s alpha reliability coefficient if closer to 1.0 the internal consistency of the items in the tool is greater. George and Mallery (2003) provide the following rules of thumb: “≥0.9 – Excellent, ≥0.8 – Good, ≥0.7 – Acceptable, ≥0.6 – Questionable, ≥0.5 – Poor and ≤0.5 – Unacceptable”. It is indicated that an alpha of 0.8 or above is probably a reasonable goal for good internal constituency of the tool (Cronbach, 1951).

### 2.11.4 Validity of measurement tools

Validity of an instrument refers to the degree to which an instrument measures what it is supposed to be measuring. For example, an instrument for measuring blood pressure of an individual is supposed
to measure only the blood pressure. It cannot be considered a valid tool if it measures an attribute other than hypertension, hypotension or normal blood pressure. Similarly, if a researcher developed a tool to measure the pain, and if it also includes the items to measure anxiety, it cannot be considered a valid tool. Hence, a valid tool should only measure what it supposed to measure. The validity of a tool can be measured in terms of face validity, content validity, construct validity and criterion validity.

**Face validity:** Face validity refers to the overall appearance and look of a tool regarding its appropriateness to measure a particular attribute or construct to be measured. Face validity is the weakest form of validity measure and is not considered as an important and essential type of validity of a tool. This validity refers to the face value or the outlook of a tool. However for completion sake face validity may also be done since it also contributes to the validity measurement in some cases.

**Content validity:** The content validity is one of the measures of validity and ensures that the items chosen in the tool had included all the items that can measure the construct of the disease to be measured. It refers to the degree that the instrument covers the content that it is supposed to measure. This validity will give confidence to the readers, users and researchers about instruments regarding the construct of the disease. Content validity is also known as content related validity, intrinsic validity, relevance validity, representative validity and logical or sampling validity. Content validity is an important step in the development and validation of a new tool since, it is an important step
for linking abstract concepts with measurable indicators (Wynd, Schmidt, & Schaefer, 2003).

According to Burns and Grove content validity is obtained from three sources: literature, representatives of the relevant populations and experts (Burns & Grove, 1993).

There are no specific objective methods for determining the content validity of a tool. Similarly there are no statistical approaches or designated tools (Polit, 1991). However content validity is a subjective judgment of experts about the degree of appropriate construct included in a tool. Among the suggested methodology it is indicated that at least five to ten experts in the field should judge the content validity. There are many subjective methods to record the content validity of a tool. It has been indicated that the measurement by a four point Content Validity Index (CVI) developed by Waltz and Bausel is a useful one (Waltz, & Bausell, 1983). Experts will be asked to rate each item based on relevance, clarity, simplicity and ambiguity of the tool on a four-point Likert-type scale. The details are:

I. Relevance

1 = not relevant

2 = item need some revision

3 = relevant but need minor revision

4 = very relevant
II. Clarity

1 = not clear
2 = item need some revision
3 = clear but need minor revision
4 = very clear

III. Simplicity

1 = not simple
2 = item need some revision
3 = simple but need minor revision
4 = very simple

IV. Ambiguity

1 = doubtful
2 = item need some revision
3 = no doubt but need minor revision
4 = meaning is clear

The items that have CVI over 0.75 will be retained and rest will be discarded. If the researcher feels that the discarded items are important considering the concept and construct of the disease to be assessed the discarded items may be modified based on experts’ opinion.

**Construct validity:** The construct validity measures the underlying constructs of the disease and the developed tool will be divided into factors and the statistic which is used for this validation is known as factor analysis.
**Factor analysis:** Factor analysis is an essential step in scale development. It is done to determine the number of factors underlying a set of items. In addition, it can provide us with insights into the nature of the latent variables underlying the items. There are measures available to researchers to help to determine the appropriate number of factors to retain. The Kaiser criterion recommends that researchers can select factors with Eigen values greater than 1.0 (Kaiser, 1958). The next measure is the scree test, which examines the scree plot, which is a plot of the eigenvalues along an x-y axis. The point at which the curve decreases and straightens out (i.e., the “elbow” of the graph) is the point where researchers should include all factors before the elbow. By applying various tools and statistical principals, the items of the tool can be reduced so that the tool will be shorter. Among the various techniques the most important ones are exploratory factor analysis and confirmatory factor analysis. Exploratory factor analysis is used when the underlying factors are not known and confirmatory factor analysis is used to confirm the underlying construct if already known.

The extraction of the factors is usually done by principal component analysis (PCA). After reduction of the tool, during each step cumulative variance and internal constituency of the tool should be measured. The cumulative variance should ideally be above 60. The final tool has to be subjected to varimax or promax rotation for better interpretation of the factors. Eigen value of above 1 is taken as the cut off value for identifying factors. Factor loadings are used for enabling whether to delete or retain the items. Factor loading above 0.4 is taken as cut of value for retaining the items of the tool. Cross loadings and
wrong loadings are also used as a measure for deleting the items of the tool.

**Convergent validity:** Convergent validity refers to the degree of relationship of scores of the indexed tool to the scores of other tools having similar theoretical concepts. This will ensure that the new developed tool can correlate with other similar test.

**Divergent validity:** Divergent validity refers to the degree of relationship of scores of the indexed tool to the scores of other tools having dissimilar theoretical concepts. This will ensure that the new developed tool can negatively correlate with other test used for diagnosis of other diseases.

**Criterion validity:** This validity is estimated mainly by two objective measures: the sensitivity and specificity.

**The sensitivity** is defined as the proportion of people with disease who have a positive test (True positive). A test which is very sensitive will rarely miss people with the disease. It is important to choose a sensitive test with high value if there are serious consequences for missing the disease.

**Specificity** of a test is defined as the proportion of people without the disease who have a negative test result. (True negative). A specific test will have only few false positive results and it will rarely misclassify people without the disease as being diseased. If a test is not specific, it may be necessary to order additional tests to rule in a diagnosis. The ideal diagnostic test should correctly identify all tested people with or without disease with 100% of accuracy, which is practically impossible.
Sensitivity and specificity are inversely proportional, meaning that as the sensitivity increases, the specificity decreases and vice versa. The formula and other details of calculation of sensitivity, specificity and other measures are given in the chapter on methodology.

The cut-off point is determined based on a trade-off between sensitivity and specificity. This trade-off can be represented graphically as a Receiver Operating Characteristic Curve (ROC). The ROC analysis was originally developed during World War-II to analyse classification accuracy in differentiating signal from noise in radar detection (Lusted, 1971). This statistical technique has been used in clinical settings especially the development of screening and diagnostic tools. ROC analysis is an important tool for evaluating the performance of diagnostic test to classify subjects into diseased or non-diseased. ROC curves are also used to determine cut-off points for mild, moderate and severe categories of disease by calculating the sensitivity and specificity of the scale for mild and moderate groups and severe groups respectively.

The Area under the ROC curve (AUC) provides a measure of the overall performance of a diagnostic test. The greater the AUC, the better the test discriminates between patients with or without disease. AUC greater than 0.7 is usually considered acceptable and it can be inferred that the tool is a standard tool. (0.9-1.0 Excellent; 0.8-0.9 Very good; 0.7-0.8 Good; 0.6-0.7 Sufficient; 0.5-0.6 Bad; < 0.5 Test not useful). If a test is designed to confirm a disease, a cutoff point with greater specificity and lower sensitivity is selected. If a test is designed to screen for disease, a cutoff point with greater sensitivity and lower specificity is selected.
Youden's index is one of the oldest measures for diagnostic accuracy (Youden, 1950). It is used for the evaluation of overall discriminative power of a diagnostic procedure and for comparison of this test with other tests. Youden's index is calculated by deducting 1 from the sum of test’s sensitivity and specificity expressed not as percentage but as a part of a whole number: (sensitivity + specificity) – 1. For a test with poor diagnostic accuracy, Youden's index equals 0, and in a perfect test Youden's index equals 1.

**Positive Predictive Value (PPV):** It is the percentage of patients with a positive test who actually have the disease. PPV indicates regarding how many of test positives are true positives. If this number is higher (as close to 100 as possible), then it suggests that the new test is doing as good as ‘gold standard.’

**Negative Predictive Value (NPV):** It is the percentage of patients with a negative test who do not have the disease. NPV indicates regarding how many of test negatives are true negatives. If the number is higher (should be close to 100), then it suggests that this new test is doing as good as ‘gold standard.’

**Likelihood ratio positive (LR +ve) and Likelihood ratio negative (LR -ve):** As the Likelihood ratio positive (LR +ve) becomes larger, the likelihood of the disease increases; as the LR- approaches zero, the disease becomes much less likely. Positive likelihood ratios greater than 10 or negative likelihood ratios less than 0.1 are sometimes judged to provide convincing diagnostic evidence (Deeks, 2001).
2.11.5 Related Studies

Some of the studies done in tool validation are discussed below;

The psychometric properties, development and related validation studies of the tools which have been published are;

Childhood Autism Rating Scale (CARS) was developed to discriminate between children with autism and those with other developmental disorders. Each CARS item is scored on a 7-point continuum from 1 to 4 (including mid points), with scores of 1 indicating that behavior is appropriate for the child’s chronological age and scores of 4 indicating that behavior is severely abnormal for the child's chronological age. A total score is calculated by summing all item scores, and total score of 30 or above are in the autism range. Scores of 30 to 36.5 suggest mild to moderate autism, while scores of 37 to 60 suggest severe autism.

The CARS diagnostic tool was developed and refined on a sample of more than 1500 children, more than half of whom were under the age of 5 (Schopler, Reichle, & Renner, 1988). It is widely used in both clinical and research contexts and studies indicate that it demonstrates many strong psychometric properties. Though interobserver reliability coefficients for individual items are somewhat variable rating from 0.10 to 0.93, most are above 0.50 (Sevin, Maston, Coe, Fee, et al., 1991). Reliability coefficients for the CARS total score have been strong, ranging from 0.68 to 0.80 and above (Garfin, McCallon, & Cox, 1988; Sevin, Maston, Coe, Fee, et al., 1991)
However, results of factor analytic studies with CARS suggest that it may be multidimensional, with factors measuring social behavior, sensory behavior, emotional responses, and cognitive and behavioral consistency (DiLalla & Rogers, 1994; Stella, Mundy, & Tuchman, 1999)

During the development phase of Gilliam Autism Rating Scale (GARS) the author contacted school personnel and parents and asked them to complete the GARS, resulting in a normative sample of more than 1000 children, adolescents, and adults with autism. The internal consistency of the GARS subtests ranged from 0.88 to 0.93, with a coefficient of 0.96 for autism quotient. The Inter observer reliability coefficients ranged from 0.83 to 0.99 for the autism quotient and from 0.55 to 0.99 for the subtest scores. Two-week test-retest coefficient ranged from 0.81 to 0.86 for the subset and the autism coefficient was 0.88. The GARS autism quotient and the Autism Behaviour Checklist total score were also found to be significantly correlated at 0.94.

Thus GARS has strong psychometric properties. However, the GARS tool was designed for individuals age 3 and older and its utility as a screening measure for younger children has not yet been examined. In addition, the only independent study evaluating psychometric properties of the GARS indicates that its use as a screening measure for preschool and school and school-age children is questionable (South, Williams, McMahon, et al., 2002).

The Social Communication Questionnaire (SCQ)-formerly known as the Autism Screening Questionnaire is a 40 item parent report questionnaire designed to screen for PDDs in individuals age 4 and older. Item were taken from the ADI-R. The SCQ demonstrates many strong
psychometric properties. A cutoff score of 15 or above was derived empirically using receiver operating characteristic analyses. Comparing participants with PDDs to those with other diagnoses, the sensitivity of the SCQ was 0.85 specificity 0.75 PPV 0.93 and NPV 0.55. Comparison autism to other diagnoses excluding mental retardation, the sensitivity and specificity were .96 and .80, respectively; comparison autism to mental retardation, the sensitivity and specificity were .96 and .67, respectively. Thus far, test-retest and inter observer reliability have not been evaluated for this instrument, but internal consistency using coefficient alpha was .90 for the total scale (Berument, Rutter, Lord, Pickles, & Bailey, 1999).

The Checklist for Autism in Toddlers (CHAT) is a simple screening tool for identification of autistic children at 18 months of age in the United Kingdom. A 6-year follow-up study of more than 16,000 children screened with the CHAT at 18 months in the United Kingdom showed a sensitivity of only 0.40 and a specificity of 0.98, with a positive predictive value (PPV) of 0.26. Rescreening using the same instrument at 19 months for those who failed the 18-month screening yielded a higher PPV of 0.75. Because of the poor sensitivity of the original CHAT for autism, a Modified Checklist for Autism in Toddlers (M-CHAT), consisting of 23 questions, with 9 questions from the original CHAT and an additional 14 questions addressing core symptoms present among young autistic children, was designed in the United States (Baron-Cohen, Allen, & Gillberg, 1992; Wong, Hui, & Lee, 2004).

The Modified Checklist for Autism in Toddlers (M-CHAT), the modified American version of the original CHAT published from United
Kingdom has 23 questions using the original nine from the CHAT as its basis. The M-CHAT is available for clinical and research use and is a promising instrument for the early detection of autism (Dumont-Mathieu, & Fein, 2005).

The study done at Ohio State University, USA, assessed the psychometric properties of the Modified Checklist for Autism in Toddlers (M-CHAT) and the Social Communication Questionnaire (SCQ) in a sample of 82 preschool children of ages of 18 and 70 months. The diagnostic agreement of both instruments were compared and it was observed that the M-CHAT and SCQ appear to more accurately classify children with pervasive developmental disorders, who have lower intellectual and adaptive functioning (Snow, & Lecavalier, 2008).

A study was done to translate the Childhood Autism Rating Scale into Brazilian Portuguese and to determine the initial psychometric properties of the resulting version (CARS-BR) (Pereira, Riesgo, & Wagner, 2008). In order to determine its psychometric properties (internal consistency, validity and reliability), the CARS-BR was administered to 60 consecutive children with autism. It was observed that the internal consistency was high, with a Cronbach's alpha of 0.82. Convergent validity, in comparison with the Autistic Traits Assessment Scale, exhibited a Pearson's correlation coefficient of $r = 0.89$. When correlated with the Global Assessment of Functioning Scale in order to evaluate divergent validity, the CARS-BR exhibited a Pearson's coefficient of $r = -0.75$. Test-retest reliability exhibited a kappa coefficient of 0.90. The result suggested that the CARS-BR is a valid and reliable instrument for evaluating autism severity in Brazil.
The study done at Vanderbilt University, USA, examined the properties of the Screening Tool for Autism in Two-Year-Olds (STAT) for children less than 24 months. STAT was administered in 71 children between 12 and 23 months of age. A follow-up evaluation was also done. All had an older sibling with an autism spectrum diagnosis (n=59) or had been referred for evaluation for concerns about autism (n=12). The analysis showed that there was a sensitivity of 0.95, specificity of 0.73, positive predictive value of 0.56, and negative predictive value of 0.97. STAT screening properties were improved when the sample was limited to children of age 14 months and older. Thus STAT can be considered as a screening tool for identifying autism in children above 1½ years of age (Stone, McMahon, & Henderson, 2008).

The need for autism-specific screening during visit for immunization at well baby clinics was studied at Department of Psychology, Georgia State University, USA. The study used the Modified Checklist for Autism in Toddlers (M-CHAT) to screen 4797 children during toddler checkups. Of the 4797 cases, 466 were screened positive on the M-CHAT; of the 362 who completed the follow-up interview, 61 continued to show risk for autism spectrum disorders (ASDs). It was observed that the positive predictive value of M-CHAT plus interview was 0.57. The findings suggest that the M-CHAT is effective in identifying ASD in primary care settings. (Robins, 2008)

In the 6 year follow-up study done at London, using a screening instrument for autism at 18 months of age, 16,235 children aged 18 months were screened using the Checklist for Autism in Toddlers (CHAT) to identify childhood autism. Two further screening procedures were
conducted at age 3 and 5 years. The population was followed up at 7 years of age in order to establish the sensitivity, specificity, and positive predictive value of the instrument. It was observed that 19 cases of autism were successfully identified by the CHAT at 18 months and CHAT had a sensitivity of 38% and a specificity of 98% for identifying childhood autism. It is suggested that CHAT can be used to identify cases of autism and related pervasive developmental disorders at 18 months of age. It is emphasized that the CHAT is not a diagnostic instrument but can identify potential cases of autism spectrum disorders (Baird, Charman, Cox, Baron-Cohen, Swettenham, Wheelwright, & Drew, 2001).

A validation study of the repetitive and restricted behaviour (RRB) scale in autism spectrum disorders was done on 145 children with autism spectrum disorders, who were assessed using the RRB scale. It was observed that the new RRB scale has good inter-rater reliability, internal consistency and content validity. Factorial analysis produced four clinically meaningful factors, i.e. "sensorimotor stereotypies", "reaction to change", "restricted behaviours" and "modulation insufficiency". The RRB scale has good psychometric qualities. This gave an insight towards the construct of the repetitive and restricted behaviour of autistic children (Bourreau, Roux, Gomot, Bonnet-Brilhaut, & Barthélémy, 2009).

A study was done to find out the interrelationship between the Autism Diagnostic Observation Schedule-Generic (ADOS-G), the Autism Diagnostic Interview-Revised (ADI-R) and DSM-IV clinical diagnosis, in a sample of 77 children and adolescents, referred for the assessment of pervasive developmental disorder. It was observed that the agreement
of the ADOS-G and the ADI-R with the clinical diagnosis was estimated as satisfactory and moderate, respectively, while both instruments. Thus the tools have excellent sensitivity for the diagnosis of autistic disorder along with satisfactory specificity. ADOS-G/ADI-R agreement was fair. The results confirm the divergent validity of ADI-R and ADOS-G in diagnosing pervasive developmental disorders in children and adolescents. (Papanikolaou, Paliokosta, Houliaras, Vgenopoulou, Giouroukou, Pehlivanidis, Tomaras, & Tsiantis, 2009).

A study was done to see the diagnostic utility of the Social Communication Questionnaire in screening for Autism Spectrum Disorder (ASD) and assessed in extremely preterm children at 11 years of age. All babies born at less than 26 weeks gestation in UK and Ireland during 1995 were studied. Of 307 survivors, 219 (71%) were assessed at 11 years. Parents of 173 children completed the SCQ to screen for autistic features. The study revealed that using the established SCQ cut-off score, 16% of extremely preterm children were screened positive for ASD. 6% were having a confirmed diagnosis of ASD. Thus SCQ had 82% sensitivity and 88% specificity for identifying ASD in this population. However, the positive predictive value was relatively low (31%) resulting in numerous over-referrals. It was observed that the SCQ has good diagnostic utility for identifying ASD in extremely preterm children and is a useful screening tool (Johnson, Hollis, Hennessy, Kochhar, Wolke, & Marlow, 2011).

A study was done to screen 18 to 24 month old children for Autism in a Semi-Urban Community in Sri Lanka in a defined geographical area and who were initially screened for autism, using ‘Red
“Red Flag” criteria. All the children with one or more positive ‘Red Flag’ signs were further screened using Modified Checklist for Autism in Toddlers (M-CHAT) translated to Sinhala, followed by a comprehensive clinical assessment. Of a sample of 374 children, ‘Red Flag’ signs were positive in 28 (7.4%). Four children received a diagnosis of autism on clinical assessment and it was observed that the sensitivity of M-CHAT was 25%, and specificity was 70%. It is also suggested that a culturally sensitive screening tool needs to be developed for Sri Lanka. (Perera, Wijewardena, & Aluthwelage, 2009)

The study on Agreement with diagnosis of autism was done at Vancouver, Canada. The screening measures to identify very young children at risk for autism spectrum disorders included the Modified Checklist for Autism in Toddlers (M–CHAT) and the Social Communication Questionnaire (SCQ). The M–CHAT was given to 84 parents of 2 to 3-year-olds and the SCQ to 94 parents of 4 to 6-year olds. Sensitivity was higher than specificity in both tools with positive predictive values of 0.63–0.68 respectively. It was also suggested that M-CHAT and SCQ could be recommended for screening for autism among children (Eaves, Wingert, Ho, Mickelson, 2006).

Georgia State University, USA, did a study on Screening for autism spectrum disorders in primary care settings (Robins, 2008) using Modified Checklist for Autism in Toddlers (M–CHAT) among 4797 children of toddler age group. It was observed that 466 were screened positive on M-CHAT and 61 continued to show signs of autism. Among these children 21 had autism spectrum disorder. The positive predictive
value of M-CHAT was 0.57. It was inferred that M-CHAT is effective in identifying autism spectrum disorders in primary care settings.

The Childhood Asperger Syndrome Test (CAST) is a parental questionnaire to screen for autism spectrum conditions. The diagnostic accuracy study of the tool was done at University of Cambridge, UK. The tool was distributed to 1925 children of age 5 – 11 years. It was observed that the sensitivity of CAST at a cut-off point of 15 was 100%. The specificity was 97% and the positive predictive value was 50%. It was also suggested that CAST is useful screening test for autism spectrum disorders in epidemiological research (Williams, Scott, Stott, Allison, Bolton, Baron-Cohen, & Brayne, 2005).

Childhood Autism Rating Scale (CARS) and Autism Behavior Checklist (ABC) are tests widely used for screening and diagnosis of autism. The study on Childhood Autism Rating Scale (CARS) and Autism Behavior Checklist (ABC) and its conflicts with DSM-IV criteria in diagnosis of autism was verified. The sample consisted of 65 children, aged 18 months to 11 years. It was observed that there was complete agreement between DSM-IV and CARS. The number of false negatives is high (46%) with ABC as opposed to 0% with CARS (Rellini, Tortolani, Trillo, Carbone, & Montecchi, 2004).

A study on psychometric properties of Tamil version of impact of event scale for adolescents was done among 100 adolescents attending an adolescent clinic who had been exposed to diverse traumatic events completed the Impact of Event Scale (IES) along with the Child Behaviour Checklist. It was observed that the tool had adequate face and content validity. In addition to adequate face and content validity, the scale has
satisfactory internal consistency, moderate convergent validity and high divergent validity. Factor analysis revealed a two-factor structure, explaining 68.4% of variance. A threshold IES score of 17 was associated with 93% sensitivity and 85% specificity. It was inferred that the Tamil IES for adolescents has satisfactory psychometric properties and should be useful in international studies as well as clinical care (Russell, Subramanian, Russell, 2004).