Neuropsychiatric Aspects of Congenital and Genetic Disorders

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Abstract

Neuropsychiatry is an area of medicine that deals with behavioural issues caused by brain dysfunction. It is found at the intersection of neurology and psychiatry. Individuals with congenital and genetic diseases are more likely to experience neuropsychiatric symptoms (particularly mental retardation), leading to considerable disability and a lower quality of life. The most common neuropsychiatric illnesses are developmental delay, intellectual disability, autism spectrum disorders (ASDs), and cognitive dysfunction. Many intellectual developmental abnormalities are caused by complex genetic components (such as attention deficit hyperactivity disorder), pregnancy or birth complications, or environmental variables, among other things. Patients with congenital and genetic diseases with neuropsychiatric indications benefit from a multidisciplinary approach to management. Interdepartmental liaisoning may be advantageous in the absence of a multidisciplinary team.

INTRODUCTION

Psychiatric symptoms (especially mental retardation) are highly prevalent among individuals with congenital and genetic disorders, which result in significant disability and diminished quality of life.1 Developmental delay, intellectual disability, autism spectrum disorders (ASDs), and cognitive dysfunction are some of the most common neuropsychiatric illnesses. Many intellectual developmental abnormalities are caused by complicated genetic factors (such as attention deficit hyperactivity disorder), complications during pregnancy or delivery, or environmental circumstances, among other things. Many neuropsychiatric disorders follow the Mendelian pattern of genetic inheritance.2 Psychiatrists have grown more aware of the role of genetic variables in the aetiology of mental diseases in recent years. The ramifications of the Human Genome Project’s mapping of the entire sequence of human DNA for psychiatric diagnosis and therapy have piled up quickly since its discovery in 1990. Understanding the causal genes of various mental diseases is the subject of much current research.

The objective is that by identifying the genes and alleles that predispose people to mental illness, tests may be developed to identify people at risk...
of acquiring the disorder, forecast the severity of the disease, and recommend the best treatment options. According to previous studies, many individuals would accept the opportunity to undergo testing if it could predict whether or not a mental disease would impact a person. To date, progress in identifying psychiatric risk genes has been modest compared to other fields of medicine, partly because the mental illness is caused by complicated inheritance rather than Mendelian inheritance in most cases. Because the bulk of mental illnesses is polygenic, testing's potential benefit may never be realized. Many mental illnesses are due to an underlying genetic condition in which the mental disorder is a part of the larger cluster of symptoms. It is important to recognize those patients whose mental illness results from a genetic condition because a genetic disease could affect the treatment options available or influence the recurrence risk and the long-term prognosis. Therefore, the correct diagnosis of an underlying genetic disorder is essential for the proper medical management and to assess the risk to other family members. A large number of genetic conditions have a psychiatric manifestation as a feature of the condition. For example, sleep problems are extremely prevalent in patients with developmental disabilities. Some examples are Down syndrome, Prader-Willi syndrome, Angleman syndrome, Fragile X syndrome, Cri-du-chat syndrome, Rett syndrome, Adrenoleukodystrophy, Huntington disease, Velocardiofacial syndrome (VCFS), Klinefelter syndrome, Williams syndrome, Wilson’s disease, Niemann-Pick disease type C, Homocystinuria, Urea cycle abnormalities, Phenylketonuria, Maple syrup urine disease, etc.

All the above disorders have various psychiatric manifestations as a part of their clinical presentations. Figure 1 below summarizes different causes of genetic and congenital disorders.

Neuropsychiatric manifestations in congenital or genetic disorders are due to involvement of the brain (arrested or improper development) or specific deficits (sensory-motor deficits, disability, multi-systemic dysfunction) that produce psychological distress.

Individuals with congenital or genetic disorders often present with several neuropsychiatric symptoms. The neuropsychiatric manifestations can involve one or multiple domains mentioned below.

- Cognition (Intelligence, memory, attention)
- Language and communication (Speech, gestures)
- Socialization
- Motor response (Stereotypy, movement disorder, hyperactivity)
- Mood (anxiety, depression, cheerfulness)
- Behaviour (aggression, self-harm/mutilation, impulsive)
- Perception (Hallucinations)

In most congenital or genetic disorders, cognition is affected. Involvement of cognition can be global or may involve specific cognitive subdomains (e.g., reading, writing, attention). Figure 2 below mentions domains of neuropsychiatric manifestations and congenital and genetic disorders.
Down Syndrome

Down syndrome is the most common chromosome abnormality in humans.² Down syndrome has been the most researched and debated syndrome in mental retardation. It is caused by chromosome 21 trisomy, which causes overexpression of numerous genes on chromosome 21. Flat face, ear dysplasia, tongue protrusion, down-turning of corners of the mouth, hypotonia, increased nuchal thickness, epicanthic fold, and a gap between the first and second toes are all characteristics of Down syndrome. Down syndrome is characterized mostly by mental impairment. The majority of people with the condition are moderately or severely impaired. Children with Down syndrome are calm, pleasant, cooperative, and adjust well at home. The prevalence of psychiatric morbidity in individuals with Down syndrome is higher than in the normal population.⁸ Adolescence brings about a shift in the picture: children may appear with a variety of emotional issues, behavioural disorders, and (rarely) mental illnesses. Children with Down syndrome struggle with language function, exhibit scanning and environmental impairments, are more prone to fixate on a single stimulus, and have trouble perceiving ecological changes.⁹ Evidence suggests that trisomy of 21 chromosomes and deletion from 21q and 22q are associated with schizophrenia.¹⁰ Similarly, individuals with Down syndrome are at higher risk of developing Alzheimer’s disease due to increased production of amyloid-β-protein.¹¹

Fragile X Syndrome

The most frequent monogenic cause of developmental cognitive impairment is Fragile X syndrome (FXS). FXS is caused by a substantial increase of a cytosine-guanine-guanine (CGG) repeat on the X chromosome, which interferes with normal protein production from the FMR1 gene. Because males lack a second normal copy of the gene, they are more seriously impacted than females with a normal FMR1 gene on their second X chromosome. In both sexes, there is a link between the length of the expansion mutation and the severity of the disease. Psychiatric manifestations are also more prevalent in males than females.¹² The typical clinical features include a large, long head and ears, short stature, hyperextensible joints, post-pubertal macroorchidism, and mild to severe mental retardation. Attention deficit hyperkinetic disorder (ADHD), learning disorders, and pervasive developmental disorders such as autism are more common. Rapid perseverative speech with problems in combining words into phrases and sentences are examples of language difficulties. It is also linked to the development of impulsivity and anxiety. The clinical signs of fragile X syndrome may be caused by an imbalance between inhibitory and excitatory neural pathways.¹³

Angelman Syndrome (AS) and Prader-Willi Syndrome (PWS)

In humans, epigenetic imprinting causes these two illnesses. Intellectual incapacity, delayed speech, jerky walking style, and a cheerful look are all clinical symptoms of AS.¹⁴ PWS is distinguished by small height, skeletal abnormalities, vision issues, intellectual incapacity, hyperphagia, obesity, and a specific behavioural profile that includes compulsive behaviour, food hoarding, temper outbursts, mood swings, and skin picking.¹⁵ ¹⁶ Almost all children with Prader-Willi syndrome will develop a psychiatric disorder in adolescence and adulthood.¹⁶ The chromosome regions responsible are located at chromosome 15q11-13 (PWS/AS region).¹⁴ Molecular genetics indicated that the sex of the parent who donated that chromosome affected the varied manifestations of the same deletion on the same chromosome. Children with Prader-Willi syndrome acquired their father’s copy of chromosome 15, whereas Angelman syndrome children inherited their mother’s copy of chromosome 15. Disruptive behaviour disorder, obsessive-compulsive disorder, skin picking disorder, and psychotic disorder are the mental problems observed with PWS.¹⁷ Sleep disorders (circadian rhythm disturbances) are common in patients with AS.⁷ Hyperactivity, aggression, anxiety, and movement disorders are commonly reported in addition to intellectual disability in AS, in which hyperactivity decreases and intellectual disability persists with age, whereas other features worsen.¹⁸
Other Chromosomal Anomalies (Deletion or Duplication)

Many other relatively rare chromosomal abnormalities manifest with neuropsychiatric symptoms resulting from duplication or deletion. Developmental delay (intellectual disability) is reported with deletion of 1p, 4p, 5p, 9p, 13q, 18p, 18q and trisomy 9p. Inverted duplicated 15 chromosomes is associated with developmental delay as well as autistic features.

Rett Syndrome

Rett syndrome is a neurodevelopmental condition of the brain’s grey matter. Mutations cause it in the methyl CpG binding protein two genes (MECP2). Approximately 4% of people with autism have MECP2 gene mutations. MECP2 gene mutations may affect the structure or result in lower levels of MeCP2 protein, which binds to methylated DNA and suppresses gene expression. There is diminished pigmentation of the substantia nigra and brain atrophy, indicating dopaminergic nigrostriatal system abnormalities. The fact that most Rett syndrome patients are female raises the hypothesis that this is a male-lethal illness. Clinically, children with Rett syndrome are only identified after 6-18 months because growth is normal until approximately six months, after which there is a decline in intellectual ability. Early indicators of regression in speech and motor function abilities are commonly observed. Some children have growth retardation and cognitive and motor disability (such as repeated, stereotyped hand movement, dystonia, ataxia, and so on). Children with Rett syndrome frequently exhibit characteristics of autism spectrum disorder.

Adrenoleukodystrophy (ALD)

Mutations in the ATP-binding cassette transporter D1 gene cause X-linked adrenoleukodystrophy (ABCD1). The ABCD1 gene encodes a peroxisomal membrane transporter protein, and mutations build up very long-chain fatty acids in organs throughout the body. The adrenoleukodystrophy gene is found on the distal end of the long arm of the X chromosome. Myelin-containing white matter is the most seriously impacted brain area. Adrenoleukodystrophy is characterized by diffuse demyelination of the cerebral white matter resulting in visual and intellectual impairment, seizures, spasticity, and progression to death. The clinical onset is generally between 5 and 8 years of age. Seizures, disturbances in gait, and mild intellectual impairment are early clinical presentations. Clinical presentation of ALD varies greatly. The childhood-onset type ALD affects only boys, and girls carrying this gene mutation will become symptomatic in adulthood but will be less severe. Due to the white matter changes, patients with ALD may present with schizophrenia-like symptoms.

Velocardiofacial/DiGeorge's Syndrome

Velocardiofacial syndrome is an autosomal dominant congenital disorder caused by a 1.5–3 Mb deletion of chromosome 22. Although the clinical manifestation of the VCFS genetic anomaly is very varied, common clinical symptoms of this syndrome include typical facies, cleft palate, cardiac anomalies such as ventricular septal defect, and learning difficulties. There is an increased incidence of ADHD, oppositional defiant disorder, phobias, obsessive-compulsive disorders, generalized anxiety disorder, schizotypal disorder, mood disorder, and autism in patients with VCFS. In addition, there is an increased risk for bipolar disorder, schizophrenia, and schizoaffective disorder in adults with VCFS. Golding-Kushner et al. discovered that patients had dull average or lower IQs, limited abstract reasoning skills, delayed speech onset, immature language use, blunt affect, monotonous voice, and poor social interaction with extremes of disinhibited or shy behaviour, but no identifiable psychiatric disorders in childhood.

Huntington's Disease (HD)

Huntington's disease (also known as Huntington's chorea) is a neurological disorder that causes damage to the neuronal cells in the caudate nucleus and the parts of the brain that coordinate movement and cognitive function. It is the most common genetic cause of abnormal involuntary movements and cerebellar symptoms. Other features are progressive cognitive decline, speech and language delay, and psychiatric problems. Epileptic seizures
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The gene involved in HD is the resultant of an expansion of the CAG trinucleotide repeat sequence and is known as the Huntingtin gene (HTT). It is found on chromosome 4’s short arm. The HTT gene causes polyglutamine accumulation. Individuals with 27 to 35 CAG repeats in their HTT gene are at risk of developing HD. The size of the CAG trinucleotide repeat may expand into the range linked with HD when the gene is handed down from parent to child as an autosomal dominant mutation (typical 40 to 50 CAG repeats). The following generation of HD patients may have children with a juvenile form of HD with more than 60 CAG repeats and a repeat size of more than 80. The size of the repetitions grows greater in the following generation, and a higher number of repeats is frequently associated with an earlier start of signs and symptoms, a phenomenon known as genetic anticipation. Individuals with HD have higher psychiatric comorbidity than those without HD. The common psychiatric comorbidities are mood disorders, schizophrenia-like psychosis, and dementia/cognitive changes. Other than the biological factors, various psychosocial factors also play a role in the causation of depression in HD. A high rate (12.7%) of suicide has been reported in patients with HD. Suicide is the third most common cause of death in Huntington’s disease, after pneumonia and cardiovascular disease. The prevalence of schizophrenia-like psychosis is thought to be around 3–6% in patients with HD. Early age at onset of symptoms and family history of Huntington’s disease-associated psychosis are risk factors.

Case Vignette

A 40-years-old, non-diabetic, non-hypertensive male was brought for psychiatric consultation for the complaints of low mood, anxiety, lack of energy, forgetfulness, reduced appetite, hopelessness, death wishes, and disturbed sleep for the past six months. These symptoms persisted most of the time throughout the day, with worsening of the symptoms in the morning hours. There was no past history of similar or any other psychiatric illness. The patient had had abnormal involuntary choreo-atetoid movements involving limbs, trunk, and neck for the past 5 years, worsening these symptoms over the past year. The patient’s father had a history of similar abnormal movement and died at 50 years of pneumonia. Pre-morbidly, he was well adjusted to life and was working as a taxi driver. However, for the last 5 years, he could not drive taxi due to abnormal involuntary movements of his hands, neck, and trunk.

The patient was evaluated for his psychiatric disorder as well as for the abnormal movement disorder. MRI of the brain revealed diffuse cerebral atrophy. In addition, there was a signal alteration in bilateral caudate nuclei with atrophy of the caudate nuclei. He was also investigated for other systemic illnesses. All haematological parameters (blood counts, lipid profile, thyroid function test, serum B12 and folic acid, thyroid function test, serum copper and ceruloplasmin) were within normal limits. Serological tests for HIV and hepatitis B and C were negative. The genetic evaluation revealed expansion of CAG repeat sequences (50 repeats of CAG).

He was diagnosed with Huntington’s disease with Major Depressive disorder. He was prescribed antidepressant (Escitalopram 10 mg/day) and clonazepam 0.5 mg/day in divided doses. He had shown improvement in the depressive symptoms by four weeks and was advised to continue consultation from the neurology unit.

Wilson Disease

Wilson disease is an autosomal recessive condition caused by mutations in the ATP7B gene on chromosome 13, which is involved in copper transport and metabolism. Because the liver fails to transport and retain normally absorbed dietary copper, there is aberrant copper build-up in the basal ganglia, eyes, liver, and other tissues. In their second decade, approximately half of individuals with Wilson disease will develop neurological and psychiatric symptoms, while 10–25% of patients may initially report mainly mental symptoms. According to one study, in 51% of cases, psychological symptoms might have preceded neurological signals in 20% of instances. The most common psychiatric symptoms discovered were behavioural problems (irritability, aggression, noticeable changes in personality, disinhibition) or mood abnormalities (depressive characteristics),
with psychosis occurring in just 1% of patients.\textsuperscript{35} The psychiatric disorders may be present from the very start of the disease and may remain isolated for several years.

**Lesch-Nyhan Syndrome**

It is an X-linked recessive genetic disorder. It involves the metabolism of uric acid. This disorder is exclusively seen among males. The gene coding for the enzyme hypoxanthine-guanine phosphoribosyl transferase is abnormal in Lesch-Nyhan syndrome.\textsuperscript{37} As a result, excess production of uric acid occurs, which is responsible for the clinical manifestations. The neuropsychiatric manifestations in Lesch-Nyhan syndrome are – intellectual disability, abnormal involuntary movement of choreo-athetoid nature, and spastic cerebral palsy. Patients often present with aggressive, impulsive, and compulsive behaviour. Self-mutilating behaviour is most commonly reported in this disorder.\textsuperscript{37}

**Niemann-Pick Disease Type C**

Niemann-Pick Type C illness is an autosomal recessive neuro-visceral lipid storage condition characterized by a cellular lipid transport defect that leads to the build-up of cholesterol and glycosphingolipids in the brain and other organs.\textsuperscript{38} It is a neurodegenerative illness that progresses slowly due to mutations in the NPC1 or NPC2 genes. A considerable number of patients remain undetected or misdiagnosed due to a lack of knowledge of the condition and the generally non-specific character of early clinical symptoms.\textsuperscript{35} In addition, a significant portion of patients with this disorder have psychiatric manifestations.\textsuperscript{39} Psychiatric manifestations are frequently psychotic in character, such as paranoid delusions, delusions of reference, visual or auditory hallucinations, behavioural disorders, aggression, self-mutilation, social isolation, and so on, while depressive and bipolar disorders have also been observed.\textsuperscript{35}

Table 1 summarizes various other genetic disorders and their neuropsychiatric manifestations.

Many other congenital or genetic metabolic disorders involving the metabolism of carbohydrate, lipid, amino acid, nucleic acid, and urea cycle may have neuropsychiatric manifestations. The common neuropsychiatric manifestation is mental retardation (intellectual disability). In addition, many have behavioural problems, inattention, hyperactivity, and features of autism. A relatively small number of patients have features of mood disorder, impulsivity, and anxiety.\textsuperscript{19}

**Dysfunction of Mitochondrial Genes**

Mitochondrial functioning (synthesis of ATP, regulation of calcium, and trafficking effect) is important for neurons' survival and optimal functioning. Dysfunction of mitochondrial genes is associated with various psychiatric disorders. Disorders involving mitochondrial genes are heritable. Dysfunction (mutation) of the mitochondrial DNA may produce mood disorders in a significant proportion of patients.\textsuperscript{40} Evidence exists regarding the involvement of mitochondrial DNA in psychiatric disorders like – schizophrenia, bipolar affective disorder, neurodegenerative disorders (Parkinson's disease, Alzheimer's disease), and autism spectrum disorders.\textsuperscript{41,42} Many mitochondrial genetic disorders (DNA-G8363A, SLC25A12, A3243G), MELAS syndrome, and Lactic acidosis were associated with autistic features.\textsuperscript{19} Many Autistic children show significantly reduced levels (free and total) of carnitine and pyruvate and increased ammonia, lactate, and alanine. Mitochondrial genes play a significant role in the regulation of these ingredients. Hence, disorders of mitochondrial genes seem to be having an implication in autism spectrum disorders.

**Congenital Rubella Syndrome (CRS)**

Congenital rubella syndrome is a set of congenital defects that arise in a child as a result of a mother's rubella infection during pregnancy. CRS is characterized by a trifecta of severe birth anomalies, including sensorineural deafness, ophthalmological abnormalities, and congenital heart disease.\textsuperscript{43} CRS can also lead to many psychiatric manifestations, and up to half of all patients born with CRS have some form of psychiatric manifestations.\textsuperscript{44} Developmental delay, mental retardation, autism, impulsivity, disruptive behaviour, tantrums, self-injury, and violence are all prevalent psychiatric signs. Rubella infection is uncommon in Western nations due to widespread vaccination, although it persists in underdeveloped countries like India. Rubella was assessed as an
## Table 1: Summary of other genetic disorders with neuropsychiatric manifestations

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Pattern of inheritance</th>
<th>Responsible gene/chromosome/ enzyme</th>
<th>Psychiatric symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cri-du-Chat Syndrome</td>
<td>-----</td>
<td>Chromosome 5</td>
<td>Cognitive, speech, and motor delays, behavioral problems such as hyperactivity, aggression, outbursts, and repetitive movements</td>
</tr>
<tr>
<td>Klinefelter syndrome</td>
<td>X-linked</td>
<td>An extra copy of X chromosome in Males</td>
<td>Reading difficulties and problems with speech</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>X-linked</td>
<td>Missing X chromosome in Female</td>
<td>Behavioural, social and specific learning difficulties, inattention and hyperactivity.</td>
</tr>
<tr>
<td>Triple X syndrome</td>
<td>Mostly not inherited</td>
<td>An extra copy of X chromosome in Female</td>
<td>Learning disabilities, delayed development of speech, language and motor skills, behavioural and emotional difficulties.</td>
</tr>
<tr>
<td>Alport syndrome</td>
<td>Mostly X-linked</td>
<td>Mutations in COL4A3, COL4A4, and COL4A5</td>
<td>Intellectual disability</td>
</tr>
<tr>
<td>Fabry's disease</td>
<td>X-linked recessive</td>
<td>Deficiency of enzyme alpha galactosidase A</td>
<td>Psychosis, Dementia</td>
</tr>
<tr>
<td>Krabbe's disease type 3</td>
<td>Autosomal recessive</td>
<td>Deficiency of enzyme galactosylceramidase</td>
<td>Psychosis, Dementia</td>
</tr>
<tr>
<td>Sanfilippo's disease</td>
<td>Autosomal recessive</td>
<td>Deficiency of enzymes glycosidases, sulfatases and acetyltransferases</td>
<td>Psychosis, Dementia, aggression, anxiety, hyperactivity, Autism spectrum disorder</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>Autosomal recessive</td>
<td>Phenylalanine hydroxylase deficiency</td>
<td>Intellectual disability, Seizure, hyperactivity, autistic features, mood disorders and learning difficulties.</td>
</tr>
<tr>
<td>Hemocystinuria</td>
<td>Autosomal recessive</td>
<td>Cystathionine synthetase deficiency</td>
<td>Intellectual disability, Seizure, acute psychosis</td>
</tr>
<tr>
<td>Tyrosinosis</td>
<td>Autosomal recessive</td>
<td>Deficiency of enzyme Tyrosine amine transaminase</td>
<td>Intellectual disability</td>
</tr>
<tr>
<td>Maple syrup urine disease</td>
<td>Autosomal recessive</td>
<td>Branched-chain ketoacid deacarboxylase deficiency</td>
<td>Intellectual disability, Seizure</td>
</tr>
<tr>
<td>Urea cycle disorders</td>
<td>Mostly Autosomal recessive</td>
<td>Deficiency of Urea cycle enzymes</td>
<td>Intellectual disability, Self-injurious behavior, Hyperactivity</td>
</tr>
<tr>
<td>Acute intermittent porphyria</td>
<td>Autosomal dominant</td>
<td>Porphobilinogen deaminase deficiency</td>
<td>Insomnia, anxiety disorders, Behaviour changes</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>Autosomal recessive</td>
<td>deficiency of arylsulfatase A</td>
<td>Schizophrenia, Dementia, Seizure disorder</td>
</tr>
<tr>
<td>Remethylation disorders</td>
<td>Autosomal recessive</td>
<td>methylene tetrahydrofolate reductase (MTHFR) deficiency</td>
<td>Psychotic symptoms (behavioural disorders, hallucinations)</td>
</tr>
<tr>
<td>Cerebrotendinous xanthomatosis</td>
<td>Autosomal recessive</td>
<td>mutations of the gene CYP27A1</td>
<td>Psychotic manifestations, hallucinations</td>
</tr>
<tr>
<td>Creatine deficiency syndromes</td>
<td>X-linked</td>
<td>deficiencies of creatine synthesis (deficiency of AGT or GAMT) and of the creatine transporter (SLC6A8 deficiency)</td>
<td>Intellectual impairment, with severe language delay, autistic behaviors and self-mutilation, movement disorder.</td>
</tr>
</tbody>
</table>

Table continue...
etiological factor in subsets of children presenting with mental retardation/developmental delay due to probable prenatal infections/congenital abnormalities in Indian research. Cognitive impairment was observed in 7.6 to 60% of children's seropositive cases.

Other Maternal Infections During Pregnancy Attributed to Neuropsychiatric Manifestations in the Child

Maternal infection with cytomegalovirus (CMV), Varicella, Toxoplasma gondii, Treponema pallidum, Herpes simplex virus produces mental retardation.  

Fetal Alcohol Spectrum Disorders (FASDs)

Alcohol can interfere with fetal development at any point of pregnancy, even the earliest stages. FASDs are a collection of disorders that can affect a child whose mother drank alcohol while pregnant. Clinical characteristics include an atypical look, short stature, low body weight, small head size, poor coordination, low IQ, behavioural issues, and hearing or visual impairments. FASD is the leading cause of mental retardation and neurologic deficit in the western world. In addition, patients with FAS have a high rate of co-morbid psychiatric illnesses (Drug or Alcohol dependence, bipolar disorder, depression).

Epilepsy Syndromes

Pediatric epilepsy syndromes are broadly classified into two groups- idiopathic (primary) type and symptomatic (secondary) type. Many pediatric epilepsy syndromes (primary or idiopathic type) have a genetic basis. In addition, pediatric epilepsy syndromes often have neuropsychiatric manifestations. Patients with West syndrome, Tuberous sclerosis, Dravet syndrome, and Lennox-Gastaut syndrome often have cognitive deficits (intellectual disability) and features of autism. Hyperactivity is also reported in Dravet syndrome. Landau-Kleffner syndrome often has many neuropsychiatric manifestations. In addition to intellectual disability, patients present with aggression, hyperactivity, impulsivity, and features of autism.

Teratogenic Drugs

Anticonvulsant drugs like–phenytoin produces fetal hydantoin syndrome, characterized by intrauterine growth retardation, facial dysmorphism, microcephaly, and intellectual disability. High levels of ionizing radiation in the mother during pregnancy produce a teratogenic effect and may produce congenital malformations, including mental retardation.

Congenital Endocrinopathies

Certain congenital endocrinopathies may have neuropsychiatric manifestations. Evidence suggests that patients with congenital adrenal hyperplasia
(autosomal recessive disorder) may have psychiatric manifestations due to underlying hormonal imbalance. Most patients with congenital adrenal hyperplasia present with psycho-sexual dysfunction (gender identity and orientation disorder, sexual dysfunction), adjustment disorder and even more axis I psychiatric disorders. Similarly congenital hypothyroidism presents with intellectual disability, which is preventable. Many genetic etiologies (mutation of genes synthesizing thyroxine, thyroid peroxidase and thyroglobulin) have been implicated in developing congenital hypothyroidism.

Assessment and Management of Neuropsychiatric Conditions Associated with Congenital and Genetic Disorders

Accurate assessment of congenital and genetic disorders is of utmost importance. The early manifestation may be congenital malformation (e.g. microcephaly, facial dysmorphism) or can be neuropsychiatric symptoms. When the neuropsychiatric symptoms are present in the context of a genetic or congenital disorder, it can be part of the syndrome (underlying genetic or congenital disorder); however, the symptoms may also be due to independent psychiatric comorbidity. Therefore, the individuals presenting with neuropsychiatric symptoms at a very early age need to be evaluated for congenital or genetic disorders. Figure 3 summarizes below the important information gathered from the history and physical examination in assessing congenital and genetic disorders.

When there is a great suspicion of a congenital or genetic disorder, the individual may be subjected to genetic evaluation, enzyme assay, toxicology or infection screening or evaluation of endocrinological abnormalities. The Figure 4 below summarizes the screening (first line) and specific (second line) investigations for inborn errors of metabolism, which often have neuropsychiatric manifestations. Subsequent genetic analysis can be done to look for mutation of particular genes.

Patients with a congenital or genetic disorder, when presented for psychiatric evaluation, should be evaluated systematically for their psychological well-being. All patients with congenital or genetic disorders should be considered for intellectual functioning (IQ assessment). Neuropsychological assessment may be useful in certain patients who had relatively better cognitive profiles (as administration of the test may not be possible with poor intellectual functioning). Evidence suggests that early diagnosis and treatment give a better outcome. Underlying congenital or genetic disorders may have prognostic implications; so far, the outcomes of the neuropsychiatric conditions are concerned. Suppose the neuropsychiatric conditions are part of the syndrome of congenital or genetic disorder, in that case, the prognosis often remains poor, but when the neuropsychiatric condition is independent comorbidity, the prognosis remains better.

Cognitive deficits (intellectual disability) and autistic features are common in congenital and genetic disorders and need to be dealt with as per the standard practice guidelines (behavioural intervention, speech therapy, psychosocial intervention, psychoeducation of the caregivers, skill training). The behavioural and skill training depends on the individual’s intellectual functioning level. Neuropsychiatric manifestations (anxiety, depression, psychosis, impulsive behaviour, etc.) need to be addressed with appropriate interventions (behavioural therapy, medication, etc.).
aggression, sleep disturbances) that need pharmacological intervention follow the following dictum - "Start low & go slow". The patients receiving pharmacotherapy need to be regularly monitored for side effects of the medications.

A multidisciplinary approach may be more useful in approaching neuropsychiatric disorders associated with congenital and genetic disorders. An interdisciplinary team consisting of psychiatrists, pediatricians, psychologists, and dieticians can comprehensively address the clients’ needs in a single platform. Many congenital or genetic disorders can be preventable. The strategies that may be useful in preventing many congenital and genetic disorders are –

- Pre-conception Genetic counselling
- Prompt treatment of genital and other infections during pregnancy (e.g., Toxoplasma, Rubella, CMV, Herpes, Syphilis)
- Immunisation for rubella infection
- Avoiding teratogens during pregnancy (teratogenic drugs, alcohol)

**CONCLUSION**

Neuropsychiatric disorders are commonly associated with congenital and genetic disorders. A multidisciplinary approach to patients with congenital and genetic disorders with neuropsychiatric manifestations facilitates holistic care. In the absence of an interdisciplinary team, interdepartmental liaisoning may be beneficial. As patients with congenital and genetic disorders may develop neuropsychiatric symptoms at any point in the course of the illness, hence the clinicians must be sensitized enough to diagnose these entities across the life span rather than making an impression on cross-sectional evaluation.

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