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Series on Childhood-onset Schizophrenia - II

Neurobiology of Childhood-Onset Schizophrenia

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ABSTRACT: In the last decade there has been an exponential increase in studies on neurobiological measures in childhood-onset schizophrenia (COS). There seems to be a consensus that structural changes in COS are more marked than in adolescence-onset (AdOS) or adult-onset schizophrenia (AOS). Atrophy of total brain volume is progressive throughout the course in COS patients unlike later-onset types where it was static. Smaller than normal amounts of regional N-acetylaspartate (NAA) is reported in the hippocampus and dorsolateral prefrontal cortex in COS. There is non-suppression of primitive reflexes (neurological soft signs) with cortical maturation in patients with COS. COS patients showed significantly greater deficits on scales of IQ, memory and perceptuomotor skills as compared to patients with AdOS and AOS. This review also discusses the various correlations between biological measures and clinical and psychopathological variables.
Key words: Childhood-onset schizophrenia (COS), Adult-onset schizophrenia, Neurobiology

INTRODUCTION

Schizophrenia has been conceptualized as a neurodevelopmental disorder, which occurs in the background of genetic vulnerability.[1,2] The absence of pathognomonic cellular phenotype in schizophrenia was seen as evidence against a neurodegenerative hypothesis of schizophrenia.[3] However, recent evidence suggests that certain clinical and neurostructural changes are progressive, a feature consistent with the neurodegenerative hypothesis.[4] Also, a few subtle histopathological, neurochemical and neurostructural deficits have been consistently reported in schizophrenia.[6] Therefore, currently the hypothesis that schizophrenia is a limited neurodegenerative disorder with neurodevelopmental antecedents is widely accepted.[5,6]

Although schizophrenia typically has its onset in the late adolescence and early adulthood, it is also seen in childhood.[7] Childhood-onset schizophrenia (COS) is defined as onset of schizophrenic illness before 12 years of age.[8,9] It is a rare condition with its prevalence being 50 times less than adult-onset schizophrenia (AOS).[10] The rarity of the disorder limits large studies and thus a definitive understanding of the etiopathogenesis of COS. However, studies on neuroimaging, molecular genetics, neurochemistry and neurobiology have helped in gradually unravelling the etiopathogenesis of COS. It seems that though a more severe form, COS is neurobiologically continuous with AOS.[11,12] Early onset of the disorder may be determined by late brain maturational processes as well as stressors unique to childhood and adolescence.

Premorbid Course

Researches on AOS suggests that the pathophysiological onset of schizophrenia predates the onset of psychosis;[4] and that its premorbid course is characterized by subtle cognitive, social and motor deficits.[13] Patients with AOS experience a deterioration in functioning during the prodromal phase, which accelerates with the onset of psychosis.[14,15] Patterns of premorbid adjustment during childhood and adolescence and subsequent "psychotic breakdown" have led to

a model that integrates neuroplasticity during childhood and adolescence, neurodevelopmental vulnerability and neurotoxicity.[16]

Studies on premorbid course of COS suggest that a majority (50%-66%) of patients show deficits in language, motor and social functioning. Motor functioning deficits were mainly in the form of delayed milestones and poor coordination.[10] Language deficits were seen in expression and comprehension;[11] whereas social deficits were expressed as social withdrawal and aloofness.[10] As with AOS, these disturbances appeared years before onset of psychosis; and probably represent vulnerability factors for COS.

A study from the United States of America concluded that premorbid impairments in COS was more severe than that seen in childhood of AOS patients though qualitatively findings were similar.[17,18] In particular, impairments in language development were more severe in COS than in AOS and adolescent-onset schizophrenia (AdOS). Therefore it seems that pathophysiology of schizophrenia involves the abnormal development of language-related brain regions, i.e. temporal and frontal lobes.[10] Another difference noted in the premorbid period was the presence of transient persistent developmental disorder (PDD) like symptoms (echolalia, hand flapping, pervasive lack of response) in COS but not in AOS. Early transient motor stereotypies indicated developmental basal ganglia abnormalities. More cytogenetic anomalies have also been reported in COS.[19,20]

NEUROBIOLOGY

An understanding of the neurobiological basis of schizophrenia is critical for establishing its diagnostic validity, predicting outcome, delineating causative mechanisms and identifying objective targets for treatment research. Over the past two decades, there have been several advances in this field; however, none of abnormalities observed till date are likely to be specific diagnostic markers for COS but they can serve as intermediate phenotypes for elucidating etiological factors. [21,22]

Neurological soft signs

Neurological soft signs may represent non-specific brain damage and dysfunction in subcortical integrative functioning.[23-24] Neurological soft signs may be intrinsic or trait-like to the schizophrenic illness as they fade away with neurological maturation in control but not in COS and AdOS groups.[25] They may reflect a neurodevelopmental abnormality that puts children at risk for schizophrenia in later life.[26,27]

There is higher presence of neurological soft signs in COS as compared to AOS and AdOS.[28] Higher frequency of neurological soft signs in COS suggests the presence of more diffuse brain damage that may explain the relative severity of COS. Severity of neurological soft signs is correlated with psychopathology and ventricular volumes. Studies suggest that COS patients have maximum dysfunction in fronto-temporal lobes.[28] An anatomical gradient may be seen in etiopathogenesis of COS wherein frontal lobe are the most affected followed by temporal and parietal lobes.

Neuropsychology

Intelligence (IQ): COS patients have lower intelligence quotient (IQ) scores than controls and later onset types of schizophrenia.[29,30] A significant deficit was seen in the premorbid and prodromal phases of the illness but the maximum decline in IQ scores was seen following the onset of psychosis.[31] It has been hypothesized that COS patients have failure to make age appropriate gains due to the illness process rather than an actual deterioration in performance. Recent evidence suggests that these cognitive deficits seen in COS may be evidence of an

ongoing or progressive pathological process as these are correlated with negative symptoms when the illness actually starts.[29,30,32]

Executive Functioning: COS patients showed more perseverative errors on measures of conceptual reasoning, set shifting (Wisconsin Card Sorting Task), attentional capacity and information processing as compared to controls.[33] However these deficits were qualitatively similar to those found in AOS patients.

Memory: COS patients had decreased performance on measures of fine motor speed, attention and short-term memory. Rote language skills and simple perceptual functions were not impaired. Deficits were seen in auditory attention, span of apprehension, verbal memory and mental flexibility. Slow reaction time was seen in visual attention and guided search. Also, COS patients have inability to distinguish important from less important stimuli (allocation of attentional resources).[33,34] COS patients had greater deficits as compared to AOS and AdOS on subtests of attention and concentration, delayed recall, verbal retention for similar pairs, dissimilar pairs, visual retention, recognition and overall memory in an Indian study.[30]

Visuospatial organization: Marked deficits in visuospatial and visuomotor organization were seen in COS patients.[12,30,33] COS patients had significantly higher error scores on Bendor Visuo-motor Gestalt test (BVMG) and Nahor Benson Test (NBT) compared to AdOS and AOS patients.[34] It has been suggested that memory deficits and executive functions deficits may reflect involvement of dorso-lateral prefrontal cortex and anterior cingulate cortex in etiopathogenesis of schizophrenia. Visuospatial deficits indicate fronto-parietal lobar involvement.

Neurophysiology

Studies on electrophysiology show general, albeit non-specific evidence of central nervous system dysfunction. More pronounced electroencephalogram (EEG) differences were noted in COS as compared to other disorders.[35] A study noted that autonomic nervous system functioning abnormality in COS was similar to AOS.[36]

Smooth pursuit eye-tracking dysfunction is a biological marker that may identify genetic risk of COS.[35] COS patients had increased smooth pursuit impairments, decreased amount of time spent engaged in tracking target, and increased rates of anticipatory saccades compared to children with attention deficit/hyperactivity disorder.[37] COS and AOS parents had higher rate of dichotomously rated eye-tracking dysfunction than their respective controls (16% vs. 1% and 22% vs. 4%, respectively). This study concluded that though genetic factors underlying eye-tracking dysfunction appeared more salient for COS, eye-tracking measures should be used with caution for endophenotypic definition due to their limited predictive power.[37]

P50 auditory evoked response and anticipatory saccades have also been studied as physiological markers for genetic risk of COS. Parents of COS had greater elevation of anticipatory saccades and diminished suppression of P50 auditory evoked responses as compared to AOS parents. The authors concluded that inheritance of both anticipatory saccades and P50 auditory evoked responses from both parents may signify increased genetic risk of COS.[35] Both responses were linked to $\alpha 7$ nicotinic receptor gene locus on chromosome 15q14.[38] Other smooth pursuit eye movement measures have been linked to chromosome 6p.[39]

Neuroimaging

Structural neuroimaging: Studies have consistently reported that COS is associated with smaller total cerebral, superior temporal gyrus and cerebellar volumes; decreased midsagittal thalamic area; and increased lateral ventricular volume and corpus callosum size.[40,41] Brain abnormality in COS correlates with symptoms both at the onset of schizophrenia and with disease progression. Decreased hippocampal volume in AdOS was related to decreased ability of patients to learn new information.[42,43] Brain morphology findings suggest more severe brain

abnormalities which could explain the earlier onset of symptoms.[44] There was greater enlargement of cavum septi pellucidi in COS than in AOS patients. Progressive gray matter losses were noted when COS patients are followed up, by adolescence there was a 10.9% decrease in frontal gray matter, 8.5% in parietal gray matter and 7% in temporal gray matter.[5] Repeated serial scans have also demonstrated differential decrease in thalamic and temporal lobe structures and increase in ventricular volume.[44,45] However, a longitudinal study found that the progressive brain changes in COS may level off when these children reach adulthood.[54] Brain volume losses were not correlated with duration of illness, suggesting that these changes plateau off after the initial few years of illness. Prefrontal and temporal grey matter losses in COS may be a familial/trait marker.[46,47] These data are similar to MRI findings in AOS suggesting a continuity of COS and later onset schizophrenia.

Functional neuroimaging: PET studies have demonstrated that COS is associated with smaller than normal amounts of regional N-acetylaspartate (NAA) in hippocampus and dorsolateral prefrontal cortex and abnormal glucose metabolism.[48,49] SPECT studies on AOS have reported hypofrontality, and altered temporal lobe and basal ganglia perfusion/metabolism.[50] A SPECT study of COS showed perfusion defects in temporal (43%), frontal (21%), and parietal (14.3%) lobes; and in right thalamus (14.3%) and caudate nucleus (7.4%).[51] These findings suggest the possibility of temporo-fronto-subcortical dysfunction in the etiopathogenesis of COS.

Neurochemistry

A Magnetic Resonance Spectroscopy study demonstrated that COS group as compared to control group have decreased levels of N-acetyl Aspartate (NAA, marker for diminished neuronal integrity); increased levels of creatine/phosphocreatine (Cr, marker for cell energy demand) in superior anterior cingulated gyrus and choline compounds (Cho, marker for phospholipid membrane disturbances which are associated with neuronal integrity) in superior anterior cingulate, frontal cortex and caudate head.[50,52] However, these changes were quantitatively as well as qualitatively similar to those found in AOS suggesting a biological continuum between COS and AOS.

Very few studies have investigated neurotransmitter systems in COS because of the rarity of the disorder; and probably because of small sample sizes they have produced inconsistent results.[53] It has been suggested that cholinergic system may be involved in syndrome pathogenesis.[54] However, treatment response studies suggest that clinical response is not correlated with changes in concentration of monoamine metabolites or monoamine ratios in the cerebrospinal fluid.[55]

Studies in AOS show decreased levels of GABA-synthesizing enzyme (glutamic acid decarboxylase [GAD67]) mRNA levels in dorsolateral prefrontal cortex (DLPFC) compared to controls. In a family-based association analysis of GAD1 gene (encodes for the protein GAD67), COS was found to be more familial and perhaps more genetically determined.[56]

GENETIC AND ENVIRONMENTAL FACTORS

Genetic factors

COS patients have higher rate (up to 45%) of schizophrenia spectrum disorders (schizoaffective, schizotypal, paranoid personality) in their first degree relatives compared to controls.[57] Many COS patients whose family members have schizophrenia spectrum disorders had prediagnosis language abnormalities that are more striking than in adult patients.

Several chromosomal abnormalities have been reported in COS, e.g. Turner's syndrome, translocation of chromosomes 1 and 7, and Velocardiofacial syndrome (deletion of 22q11).

Velocardiofacial syndrome was found in 6.4% of COS patients compared to 2.0% of AOS patients; and COS patients with the syndrome have high neurodevelopmental impairment.[58,59] At a molecular level, an association between neuregulin 1 (NRG1) and schizophrenia was reported.[60] Also, COS subjects with risk alleles have greater total gray and white matter volume loss in childhood and a steeper rate of subsequent volume loss in adolescence.[60] However, studies have not found ApoE4, HLA or trinucleotide repeats to be associated with COS.[61]

Environmental factors

A Finnish study that showed an increased incidence of COS in children with perinatal hypoxia, concluded that environment can critically influences genetic expression.[62] However, other studies have not consistently revealed significant differences between COS and AOS groups regarding obstetrical complications. Also, no association has been reported between COS and age of onset, socioeconomic status and psychological trauma.

CONCLUSIONS

The current evidence that demonstrates greater but qualitatively similar neurobiological abnormalities in COS vis-a-vis AOS, suggests a continuity between COS, AdOS and AOS. A fronto-temporo-parietal dysfunction seems central to the pathogenesis of COS. Cytogenetic anomalies suggest that COS may have a neurodevelopmental basis originating in a complex interplay of genetic and other factors. COS is likely to be a continuous or multi-event process, that is best conceptualized as a unitary progressive-deteriorating developmental disorder.

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