Stem Cells (SC) therapy as an emerging therapy in neurology

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Abstract

Stem Cells (SC) therapy emerges as a potential new hope for neurological patients as it could accomplish the immunomodulatory as well as the neuroprotective functions. There is a growing body of literature that supports the potential of the SC for immunomodulation and re-myelination. Here we focus on examining the registered published and on-going clinical trials using stem cells especially the Mesenchymal Stem Cell therapy in neurological disorders such as MS, ALS, Stroke, spinal cord injuries and also some types of devastating neuropathies like POEMS. There are evidence showing that the MSC can alter the phenotype of NK cells and suppress proliferation, cytokine secretion, and cytotoxicity against HLA-class Iexpressing targets. Some of these effects require cell-to-cell contact, whereas others are mediated by soluble factors, including transforming growth factor-beta1 and prostaglandin E2, pointing to the existence of diverse mechanisms for the MSC-mediated NK-cell suppression . The MSC have been reported to block the differentiation of monocytes into dendritic cells and impair antigen presentation as well as IL-12 production. Also the human MSC alter cytokine secretion and induce more anti-inflammatory responses. Specifically, the hMSC by induction of mature dendritic cells (DC) decrease tumor necrosis factor alpha (TNF-alpha) secretion and increase IL-10 secretion . The hMSC inhibit Th1 cells, decrease interferon gamma, and affect Th2 cells by increasing secretion of IL-4. This causes an increase in the proportion of T- Regulatory cell switches the CD4+ T cell responses from a Th1 to a Th2 polarized phenotype resulting in a decrease secretion of IFN-gamma from NK cells. Generally speaking we are going to discuss the immunomodulatory effects of the mesenchymal stem cells and finally to review some interested data from our experience and other papers around the world. The positive outcomes of the transplantation of fetal neural tissue in adult rat models of a variety of neurological disorders, particularly Parkinson's disease, in the 1970s, and its translation to humans in the 1980s, raised great hopes for patients suffering from these incurable disorders. This resulted in a frantic research globally to find more suitable, reliable, and ethically acceptable alternatives. The discovery of adult stem cells, embryonic stem cells, and more recently, the induced pluripotent cells further raised our expectations. The useful functional recovery in animal models using these cell transplantation techniques coupled with the desperate needs of such patients prompted many surgeons to "jump from the rat-to-man" without scientifically establishing a proof of their utility. Each new development claimed to overcome the limitations, shortcomings, safety, and other technical problems associated with the earlier technique, yet newer difficulties prevented evidence-based acceptance of their clinical use. However, thousands of patients across the globe have received these therapies without a scientifically acceptable proof of their reliability. The present review is an attempt to summarize the current status of cell therapy for neurological disorders.

Background:

Stem cell therapy has emerged as a promising treatment for numerous neurological disorders. One such application has been recognized in stroke, a debilitating health burden that affects hundreds of thousands of individuals worldwide. Many patients would greatly benefit from the development of novel treatments for stroke with wider therapeutic windows than the current limited treatment, tPA (tissue plasminogen activator). Several key clinical trials have helped shape the field of stem cell therapy, including the intracerebral transplantation of fetal cells and neuroteratocarcinoma-derived neural progentior cells (NT2N) cells in Parkinson's disease and stroke patients, respectively. Recent studies have explored the peripheral transplantation of stem cells for acute stroke patients, paving the way for minimally invasive cell therapy clinical studies. The ten papers compiled in this special volume were selected from the recently concluded 2016 American Society for Neural Therapy and Repair (ASNTR) annual meeting, addressing various sources and profiles of stem cells and their therapeutic applications, cell death mechanisms that stand as key pathological bases underlying the stroke and therapeutic targets, and the prevailing bioethical concerns associated with cell-based treatments.

Methods:

Stem cells may be the person's own cells or those of a donor. When the person's own stem cells are used, they are collected before chemotherapy or radiation therapy because these treatments can damage stem cells. They are

injected back into the body after the treatment. The sources of stem cells are varied such as pre-implantation embryos, children, adults, aborted fetuses, embryos, umbilical cord, menstrual blood, amniotic fluid and placenta New research shows that transplanted stem cells migrate to the damaged areas and assume the function of neurons, holding out the promise of therapies for Alzheimer's disease, Parkinson's, spinal cord injury, stroke, Cerebral palsy, Battens disease and other neurodegenerative diseases. The therapeutic use of stem cells, already promising radical new treatments for cancer, immune-related diseases, and other medical conditions, may someday be extended to repairing and replenishing the brain. In a study published in the February 19, 2002, Proceedings of the National Academy of Sciences, researchers exposed the spinal cord of a rat to injury, paralyzing the animal's hind limbs and lower body. Stem cells grown in exponential numbers in the laboratory were then injected into the site of the injury. It was seen that week after the injury, motor function improved dramatically,

Discussion:

The following diseases have been treated by various stem cell practitioners with generally positive results and the spectrum has ever since been increasing.

Conclusion:

Stem-cell-based technology offers amazing possibilities for the future. These include the ability to reproduce human tissues and potentially repair damaged organs, where, at present, we mainly provide supportive care to prevent the situation from becoming worse. This potential almost silences the sternest critics of such technology, but the fact remains that the ethical challenges are daunting. It is encouraging that, in tackling these challenges, we stand to reflect a great deal about the ethics of our profession and our relationships with patients, industry, and each other. The experimental basis of stem-cell or OEC transplantation should be sound before these techniques are applied to humans with neurological disorders. In summary, these ten selected articles from the recent ASTNR meeting highlight the potential applications for stem cell therapy in neurological disorders, detailing the laboratory evidence on the safety, efficacy, and mechanism of action of these transplantable cells, altogether forming the basis for the clinical trials. Given the prevalence of stroke, many patients would greatly benefit from novel treatments that capitalize on the promising therapeutic benefits of stem cells. Numerous studies referenced throughout the articles have indicated the potential capability of stem cell therapy in regenerating the diseased brain. We are gaining more insights into the cellular death pathways mediating stroke, and in parallel exploiting these novel disease-related mechanisms as therapeutic targets for stem cells to exert their functional benefits. Yet, these developing technologies face obstacles, such as bioethical concerns and misrepresentations, as well as exploitations by the unscrupulous media and business sector, preventing them from reaching full beneficial capacity. Accordingly, a common theme resonating throughout these papers is a push to increase translational research of cell-based therapeutics for clinical applications that will allow scientifically sound assessments of cell therapy, delineating hype from hope. Forthcoming updates on the ongoing clinical trials of cell therapy will provide valuable information on which to build the future of stem cell research and therapeutic applications.

Physical illness complicating the presentation of bipolar disorder in an elderly patient

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Abstract

It is well known that psychiatric symptoms may be caused by a wide variety of medical as well as psychiatric illnesses and it can be difficult to determine the real underlying aetiology without longitudinal observation. It is a case report of a patient with no previous psychiatric history who presented with altered mental status. The diagnosis was revised from acute psychosis to acute delirium and subsequently to bipolar affective disorder. A 62 year old Malay gentleman presented with a brief two day history of disorientation, disruptive behaviors and persecutory delusions that people were spying on him. There was no significant past psychiatric history or family history of mental illness; he had never taken any psychiatric medications before and did not abuse alcohol or illicit drugs. He had an organic workup done which was unremarkable. He was initially diagnosed with acute psychosis and treated with haloperidol l5 mg at night. Over the next 5 days, his agitation worsened and he was found to have inflammation of his left knee which was due to a flare up of gout. He was treated with colchicine and paracetamol and the inflammation subsided and the psychiatric symptoms also resolved spontaneously. As a result, the diagnosis was revised to acute delirium and haloperidol was stopped. He represented again two weeks later with full-blown symptoms of mania which included elated mood, increased energy and goal-directed thinking and activity, pressured speech and grandiose delusions. Repeated investigations were normal. The diagnosis was revised to bipolar affective disorder according to DSM-V criteria. The medication haloperidol was restarted and the dose was increased to 5 mg twice a day. The manic symptoms remitted after two weeks of treatment. This report adds to the body of evidence suggesting that physical conditions and psychiatric illness can complicate each other. Close longitudinal observation and follow-up is recommended for the proper diagnosis and management.

Introduction:

It is well known that psychiatric symptoms may be caused by a wide variety of medical as well as psychiatric illnesses and it can be difficult to determine the real underlying aetiology without longitudinal observation. It is a case report of a patient with no previous psychiatric history who presented with altered mental status. The diagnosis was revised from acute psychosis to acute delirium and subsequently to bipolar affective disorder. A 62 year old Malay gentleman presented with a brief two day history of disorientation, disruptive behaviors and persecutory delusions that people were spying on him. There was no significant past psychiatric history or family history of mental illness; he had never taken any psychiatric medications before and did not abuse alcohol or illicit drugs. He had an organic workup done which was unremarkable. He was initially diagnosed with acute psychosis and treated with haloperidol l5 mg at night. Over the next 5 days, his agitation worsened and he was found to have inflammation of his left knee which was due to a flare up of gout. He was treated with colchicine and paracetamol and the inflammation subsided and the psychiatric symptoms also resolved spontaneously. As a result, the diagnosis was revised to acute delirium and haloperidol was stopped. He represented again two weeks later with full-blown symptoms of mania which included elated mood, increased energy and goal-directed thinking and activity, pressured speech and grandiose delusions. Repeated investigations were normal. The diagnosis was revised to bipolar affective disorder according to DSM-V criteria. The medication haloperidol was restarted and the dose was increased to 5 mg twice a day. The manic symptoms

remitted after two weeks of treatment. This report adds to the body of evidence suggesting that physical conditions and psychiatric illness can complicate each other. Close longitudinal observation and follow-up is recommended for the proper diagnosis and management.

Community surveys indicate that bipolar disorder is approximately 1/3 less common in older people than in younger people, with lifetime prevalence rates estimated to be 0.5%-1% Individuals with bipolar disorder are at increased risk for early mortality, which likely accounts for its lower prevalence rate among older adults Older adults with bipolar disorder include individuals with early onset illness and those who develop the first episode of mania after age 50. While relatively rare in the community, high rates of geriatric bipolar disorder are seen in both inpatient and outpatient psychiatric treatment settings. Relapse and

readmission is common among older patients with bipolar disorder, even among those individuals who have had the illness for many years.

While there has not been consensus about how to define late-life bipolar disorder most studies have used age cutoffs between 50 and 65. Reports on symptom presentation in older and younger patients with bipolar disorder have produced some conflicting results. Studies comparing the phenomenology of bipolar disorder in younger and older patients have reported that older bipolar patients tend to have less severe manias are less likely to have psychotic symptoms and are more likely to relapse into depression after a manic episode A large 2-year prospective observational study found that elderly patients with bipolar disorder, especially early-onset bipolar disorder, were more likely to report a rapid cycling course However, a recent study of outpatients with bipolar disorder found no association between age and acute bipolar depression or mood-elevation symptom presentation

Methods:

This task force report addresses the unique aspects of OABD including epidemiology and clinical features, neuropathology and biomarkers, physical health, cognition, and care approaches.

Results:

The report describes an expert consensus summary on OABD that is intended to advance the care of patients, and shed light on issues of relevance to BD research across the lifespan. Although there is still a dearth of research and health efforts focused on older adults with BD, emerging data has brought some answers, innovative questions, and novel perspectives related to the notion of late onset, medical comorbidity, and the vexing issue of cognitive impairment and decline.

Conclusion:

Improving our understanding of the biological, clinical, and social underpinnings relevant to OABD is an indispensable step in building a complete map of BD across the lifespan. Although topics related to older-age bipolar disorder OABD have been relegated to a minor place in research and professional training, the growing elderly population means we can no longer conceptualize OABD as a 'special population' for whom understanding of the disorder and recommended management can simply be extrapolated from experience in mixed age groups. The study of OABD is a research opportunity where answers to important questions that have widespread implications for all people with bipolar disorder BD may be found e.g., the long-term effects of medications on general health, cognitive function, and brain integrity. This is the first report of the International Society for Bipolar Disorders ISBD Task Force on Older-Age Bipolar Disorder OABD. Improving understanding of the biological, clinical and social underpinnings in OABD is an indispensable step in building a complete map of BD across the life-span.

In recent years, musical stimulation, in particular the "Mozart effect" of the K448 sonata for two pianos, has been reported to decrease both interictal electroencephalographic discharges and recurrence of clinical seizures More recently, a set of Mozart's compositions was reported to be particularly beneficial in reducing seizure recurrence in children and adolescents with drug-resistant structural or genetic epileptic encephalopathies. Improved nocturnal sleep quality together with positive behavioral and mood changes were also reported. Furthermore, children appeared more compliant to a set of different music proposals than a single composition like Mozart's K448 Nevertheless, in so far available studies, there is a significant diversity with respect to protocols of music therapy as well as for kind of musical compositions, length of daily music listening, and duration of follow-up. Therefore, we conducted a prospective, randomized, open label study comparing two different protocols. Following Tomatis' method Mozart's K448 sonata or Mozart's set of compositions were compared on their effect on seizure recurrence and quality-of-life parameters, including nocturnal sleep and mood/behavioral changes, in children and adolescents with refractory epileptic encephalopathies.

Methods:

During the first study 11 outpatients, aged between 1.5 and 21 years, all suffering from drug-resistant epileptic encephalopathy associated with a severe/profound intellectual disability and cerebral palsy had to listen to a set of Mozart's compositions 2 h/day for 15 days for a total of 30 h. In the second trial, 19 patients with epileptic encephalopathies, aged between 1 and 24 years, were randomized to listen to Mozart's K448 for 2 h/day for 2 weeks or to a set of Mozart's compositions

Findings:

In the first study, 2/11 patients had a reduction of 50-75% in seizure recurrence, and 3/11 a decrease of 75-89%. Overall, 5/11 patients had a ≥50% reduction in the total number of seizures. In the second trial, 22% of the K448 group had a≥75% seizure decrease, compared with 70% of patients in the Mozart set group.

Conclusion:

The present study seems to confirm that music therapy may be an additional, non-pharmacological, effective treatment for patients with refractory epileptic seizures in childhood. The Mozart' set of different compositions can be better accepted and effective than the K448.

Socio-demographic characteristics, clinical profile and prevalence of existing mental illness among suicide attempters attending emergency services at two hospitals in Hawassa city, South Ethiopia: A cross-sectional study.

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Abstract

Suicide is a major public health problem worldwide. It contributes for more than one million deaths each year. Since previous suicidal attempt was considered as the best predictor of future suicide, identifying factors behind suicidal attempt are helpful to design suicide prevention strategies. The aim of this study was to assess socio-demographic characteristics, clinical profile and prevalence of existing mental illness among patients presenting with suicidal attempt to emergency services of general hospitals in South Ethiopia. A cross-sectional study was conducted on patients presenting with suicidal attempt to emergency departments of two general hospitals in Hawassa city from November, 2014 to August, 2015. Data was collected using semi-structured questionnaire which contained socio-demographic and clinical variables. The Mini International Neuropsychiatric Interview version 5 was used to assess the prevalence of existing mental illness among study participants. Results: A total of 96 individuals were assessed, of whom 56 were females. The mean age of study participants was 21.5 years. The majority, 75, of the study participants were aged below 25 years. Mental illness was found in only three of the study participants. Impulsivity (the time between decision to attempt suicide and the actual attempt of less than 5 minutes was reported by 30 of the study participants, of whom 18 were males. Males were found three times more likely to attempt suicide impulsively than women. Psychosocial stressors were found as immediate reasons to attempt suicide by the majority. Conclusion: The presence of stressful life events and impulsivity behind suicidal behavior of the younger generation implies that designing suicide prevention strategies for this group is crucial. Focus research is needed to systematically examine the relationship between the presence of mental illness and suicidal attempt with a larger sample size.

Introduction:

Attempted suicide is one of the major emergencies in psychiatry. Suicide attempts are considered to be the best predictors of an eventual completed suicide. Data of patients presenting with attempted suicide to the emergency settings at mental health institute settings is scanty in India. Aims: The study was carried out to assess the socio-demographic and clinical profile of the patients with suicidal attempt attending emergency services at a teaching Mental Health Institute in Northern India. Suicide is a major public health problem worldwide. It contributes for more than one million deaths each year. Since previous suicidal attempt was considered as the best predictor of future suicide, identifying factors behind suicidal attempt are helpful to design suicide prevention strategies. The aim of this study was to assess socio-demographic characteristics, clinical profile and prevalence of existing mental illness among patients presenting with suicidal attempt to emergency services of general hospitals in South Ethiopia.

Methods:

Case records of all patients with attempted suicide attending emergency services at Institute of Human Behaviour and Allied Sciences for one calendar year were reviewed. Socio-demographic and clinical details of the patients were retrieved on a Performa specifically designed for this study. A cross-sectional study was conducted on patients

presenting with suicidal attempt to emergency departments of two general hospitals in Hawassa city from November, 2014 to August, 2015. Data was collected using semi-structured questionnaire which contained socio-demographic and clinical variables. The Mini International Neuropsychiatric Interview version was used to assess the prevalence of existing mental illness among study participants.

The present study was carried out at Institute of Human Behavior and Allied Sciences , Delhi, a tertiary care teaching mental health institute in Northern India which was developed after transformation of erstwhile Hospital for Mental Diseases, Shahdara. At IHBAS, psychiatry emergency services are rendered round the clock by a qualified psychiatrist and a Junior Resident on duty with support of a consultant psychiatrist on call duty. Assessment findings are recorded on an emergency case record proforma and case record file. In routine practice, the assessment of patients involves complete and comprehensive clinical assessment for risk of suicide and risk of harm to others, assessment for evaluation of lethality and intentionality of a given attempt of suicide, in order to make an objective assessment, a scale, that is,

scale for Assessment of Risk of Suicide developed by Faculty of Psychiatry at IHBAS, is used to find out the level of suicidal risk in a given case Although majority of the patients are sent back after appropriate evaluation and management, the more serious patients having risk of harm to self or others, or severe psychopathology are either kept in short observation facility available in emergency services, or are admitted to the psychiatry wards. These patients are seen by a consultant in the same evening or next day morning when the final decision regarding the diagnosis and further management is arrived at. For this study, case records of patients who attended emergency services during a period of one calendar year were reviewed. Out of the 10913 patients who attended emergency services during this period, 56 patients were found to present with attempted suicide. Data on socio demographic details and clinical variables were retrieved from the case records of these patients and recorded in the structured proforma prepared for this study.

Results:

Of all the patients who attended emergency services during the study period, 56 patients had suicidal attempts. Majority of them were married males in the age group of 20-40 years, were from nuclear families and had urban domicile Severe Mental Illnesses were found in about 70% of the cases with duration of illness more than 24 months in 39.2%. Thirty six patients had 1 suicide attempt while 18 had 2 or more attempts in preceding one month. In 70% - 80% of the cases, the lethality and intentionality of the index episode was found to be moderate to high. Most of the cases needed inpatient treatment. Conclusion: Assessment and management of patients presenting to emergency room with suicidal behavior is a key factor in preventing suicide. There is a pressing need to identify the socio-demographic and clinical factors affecting risk of suicide in a given case. Every case presenting with suicidal ideations or attempt should be evaluated in detail.

A total of 96 individuals were assessed, of whom 56 were females. The mean age of study participants was 21.5 years. The majority, 75 of the study participants were aged below 25 years. Mental illness was found in only three of the study participants. Impulsivity the time between decision to attempt suicide and the actual attempt of less than 5 minutes was reported by 30 of the study participants, of whom 18 were males. Males were found three times more likely to attempt suicide impulsively than women Psychosocial stressors were found as immediate reasons to attempt suicide by the majority. Out of the 10913 patients who attended emergency services during the study period, 56 patients were found to have attempted suicide, indicating a prevalence of 0.51% for attempted suicide among those reporting to emergency room of a tertiary care mental health institute.

Conclusion:

The presence of stressful life events and impulsivity behind suicidal behavior of the younger generation implies that designing suicide prevention strategies for this group is crucial. Focus research is needed to systematically examine the relationship between the presence of mental illness and suicidal attempt with a larger sample size.

Executive function deficits in neurodevelopmental disorders

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Abstract

Neurodevelopmental Disorders (NDD) including autism/Asperger???s (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) has deficits described either in social communication/interaction/ imagination or in attention/concentration/ hyperactivity/impulsivity. There is significant co morbidity, from 30% to 50%. These are often associated with Executive Function Deficits (EFD). EFD is a term used to describe cognitive processes that help individual regulate, control and manage outthoughts and actions. It includes planning, working memory, attention, problem solving, verbal reasoning, inhibition, cognitive flexibility, initiation of actions and monitoring of actions. Though the EFD are not a part of diagnostic criteria, it is these deficits that cause the most morbidity in day-to-day living. The lack of behavior flexibility, emotional control and self-monitoring is the basis of presentation in people seen with the diagnosis of autism/asperger. Environment adaptations advised for ASD of routine, structure and predictability are not focused on supporting the EFDs that a person is struggling with. They do not reduce the morbidity caused in able children/adults with diagnosis of ASD. ADHD presents with difficulties in prioritizing, impulse control, being emotional with mood swings, poor time keeping, poor ability for task initialization, ability to shift attention and organization. Treatment modalities (medications like stimulants and CBT) used in ADHD does not improve EFDs and they require specific adaptations in the environment. Just focusing on core deficits in ASD or ADHD does not enhance the quality of life or the outcomes. Identifying the exact set of EFDs will allow for developing specific adaptations to enhance the quality of life for children, students and adults.

Introduction:

Executive functions are a set of cognitive abilities that are needed for regulating behavior, including inhibition, working memory, and planning. The ability to regulate behavior is important, as executive functioning has a substantial impact on short-term and long-term life outcomes such as physical and mental health, performance in school, and socioeconomic status. Executive functioning is often impaired in psychiatric disorders, including neurodevelopmental disorders, such as autism spectrum disorder and attention-deficit/hyperactivity disorder. So far, little is known about early executive functioning problems in young children with subclinical traits of ASD and ADHD.

Autism spectrum disorder is characterized by deficits in social interaction and communication, and restricted behavior and interests, whereas the main symptoms in ADHD are inattention and hyperactivity/impulsivity. The prevalence of these disorders among children under 18 years are approximately 1% and 3–5%, respectively. Children with ASD and ADHD can have lower educational achievements and poorer social outcomes, with problems often extending into adulthood. Importantly, traits of ASD and ADHD occur along a continuum of severity, ranging from sub-clinical to severely impaired. However, children with lower levels of ASD and ADHD traits, not sufficient for a diagnosis, are also suffering from daily impairments.

Executive functioning deficits associated with both ASD and ADHD are found consistently throughout the literature. The main domains in children with ASD comprise shifting, planning, and working memory, although broader executive functioning deficits across all domains have been observed as well. Conversely, children with ADHD have more pronounced difficulties in executive functioning, in the domains of inhibition, working memory, vigilance, and planning. These difficulties are not only seen among those with a clinical diagnosis, as few population-based studies suggest that children and adults with subclinical traits of ASD or ADHD also experience problems in executive functioning. These findings are important, as children with subclinical traits of disorders often remain undetected by mental health services for various reasons, including symptoms not being severe enough to warrant help seeking, stigmatization of seeking help for mental problems, and inability to pay. However, sub-clinical symptoms may be associated with other sub-clinical characteristics, such as cognition function, which may result in some impairment. Indeed, executive functioning has a substantial impact on short-term and long-term life outcomes.

Only a minority of studies in this field has focused on young children with neurodevelopmental traits. Young children with ADHD or at high risk for ADHD appear to be impaired in executive functioning, while research on young children with ASD is more inconclusive. Some studies find no differences in executive functioning between children with and without ASD, whereas others do, but depending on the different age or means of measuring executive functioning. It has been argued that performance tasks and behavioral ratings should be distinguished from each other, as they may measure different aspects of executive functioning. Performance tasks are more situational and measure abilities in a specific environment, whereas behavioral ratings focus on the ability to apply these skills in daily life, perhaps making the latter more generalizable and therefore clinically more relevant.

Conclusion:

The main aim of our study was to examine the specific neuropsychological profiles of children with a clinical diagnosis of either ADHD or SLD—with major impairment in both reading and math, or both in comorbidity (ADHD + SLD), by comparison with TD children. We were particularly interested in understanding whether the EFs profiles of four groups differed and whether the comorbid group (ADHD + SLD) showed an additive (i.e., the sum of the deficits in the isolated groups) or rather an interactive effect (i.e., a distinct deficit profile). Children in the clinical groups had been previously diagnosed at centers specialized in neurodevelopmental disorders. In the first part of the assessment, all their diagnoses had been confirmed through specific questionnaires for parents and appropriate academic achievement tests.

To test potential differences in EFs profiles, children with a clinical diagnosis of ADHD, SLD, and comorbid ADHD + SLD were compared with TD children on measures of inhibition, shifting, and updating. In our analyses, we first compared our groups considering EF measures separately. Then, we ran the same analyses considering the presence of ADHD (no/yes) and/or SLD (no/yes) as factors to see whether the comorbid group reveals an additive profile. Finally, mixed-effects models were used to analyze in detail performances at different span levels for the updating tasks.

In the group comparisons, our findings showed that all clinical groups performed worse than the TD group, and no differences emerged between any of the clinical groups on measures of inhibition and shifting. A more specific pattern emerged when the groups were compared on updating measures. Children with SLD performed less well than the other groups in the verbal task, while the groups with ADHD or ADHD + SLD performed less well than either the SLD or the TD groups in the visuospatial task. This would contradict the idea of an additive effect of the two disorders combined. The pattern was slightly different when we considered the presence or absence of symptoms of SLD or ADHD: the effects of both SLD and ADHD could be seen in the inhibition task, but only those of ADHD in the shifting task. The effect of SLD was apparent for verbal updating and that of ADHD for visuospatial updating. Notably, from a qualitative perspective, children with ADHD + SLD were not more severely impaired than those with either ADHD or SLD alone. This would contradict the interactive hypothesis that children with several problems in comorbidity exhibit a qualitatively distinct condition. Finally, by considering group performances at different span levels, a specific pattern emerged in the visuospatial updating task. Children with ADHD performed significantly worse on Span level 3 then showed a slight improvement on level 4, whereas the other groups had a more linear worsening performance with longer spans. Our results can be explained by altered motivational processes in ADHD, or the children's inability to regulate their state of activation.

The novelty of our investigation lies in that we compared these clinical groups with one another, as well as with a TD group, as previously reported. The results underlined that EFs are similarly compromised in all clinical groups, pointing to a comorbidity explanation based on a domain-general cognitive level. In particular, EF impairments, are not enough to differentiate between ADHD and SLD, shedding further light on the importance of comparisons across disorders and studies on comorbid conditions. Although ADHD is often associated with EF deficits, this association did not seem sufficient to consider EF as core-deficits of the disorder, and impairments in inhibition and shifting have also been observed in children with SLD.

Neuroinfection & neuroimmunology

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Editorial

Neuroinfection & neuroimmunology is a growing subspecialty of the nervous system. Despite remarkable diagnostic and therapeutic advancements during the past 30 years through the prevention of infectious diseases by vaccine and the development of safe, effective antimicrobial agents, neurologic infections remain to be major causes of permanent neurologic disability worldwide In this issue of Radiology of Infectious Diseases, the articles succinctly cover a range of radiologic topics of infectious or immunological diseases of the central nervous system CNS, focusing on some areas of controversy and current hot topics. The goal is to summarize the ongoing challenges in CNS infectious or immunological diseases and suggest potential areas for further exploration. Viruses may invade any part of the CNS and cause both acute and chronic neurologic diseases. Viruses constitute the most common infectious cause of encephalitis, aseptic meningitis, and myelitis. Unique disorders appear episodically in human populations and cause life-threatening systemic or neurological diseases Over 100 viral pathogens can affect the CNS, with varied clinical manifestations. Historical examples of such disorders include von Economo encephalitis, acquired immune deficiency syndrome (human immunodeficiency virus infection) and severe acute respiratory syndrome. In addition to the more commonly reviewed syndromes of meningitis, encephalitis, and myelitis, less frequent but characteristic syndromes are important to be recognized. Recently, some novel avian influenza viruses or even recently reported Zika virus for their fatal attack to CNS, have drawn great attentions all over the world Specifically, the pandemic of swine-origin H1N1 influenza that began in early 2009 had provided evidence that radiology could assist in the early diagnosis of severe cases, providing new opportunities for the development of advanced infectious disease imaging. Dr. Shi also suggested findings of high-resolution lung CT correlated with CD4+ and CD8+ lymphocyte counts and the C-reactive protein level in the peripheral blood in the initial stage of adult patients with H1N1 influenza. The sophisticated current imaging techniques enable us to study influenza at the cellular level, in animal models, and in human clinical trials to elucidate the pathogenesis of severe illness and improve clinical outcomes. Middle Eastern respiratory syndrome is a new illness caused by the Middle East respiratory syndrome coronavirus MERS-CoV infection should be suspected in patients presenting with risk factors of MERS-CoV infection, suspicious clinical, laboratory results and chest CT scans showing ground-glass opacities with a preference for the peripheral lower lobe Ebola infections in West Africa have been a major news story in the past two years. As of October, 2015, nearly 18,000 cases have been reported, with about 6500 deaths, with the infection spreading rapidly because the virus is present in all body fluids, including sweat and mucous membrane secretions. Radiology workup does not provide specific diagnosis of Ebola virus infection, however, it is indispensable to prognostic assessment in the emergency department and treatment isolation care unit The classic clinical picture of ZIKV infection is manifested by fever, headache, arthralgia, myalgia, and maculopapular rash. A major concern associated with this infection is the apparently increased incidence of microcephaly in fetuses born to mothers infected with ZIKV. Ultrasonography can reveal microcephaly with calcifications in the fetal brain and placenta Quantitative assessment of lung abnormalities based on chest radiographic and CT scores should allow clinicians to accurately monitor disease progression and provide information regarding patient prognosis. The radiologists should play a critical role in the monitoring of patients with viral infection.

Despite notable improvements in disease prevention and treatment, infectious diseases of the CNS remain an important source of morbidity and mortality, particularly in less-developed countries and in immune compromised individuals. Bacterial, fungal, and parasitic pathogens are derived from living organisms and affect the brain, spinal cord, or meninges. Infections due to these pathogens are associated with a variety of neuroimaging patterns that can be appreciated at MRI in most cases In this issue, Dr. Zhang et al. retrospectively analyzed the clinical and MRI features of cerebral paragonimiasis in 24 pediatric cases. Although the clinical manifestations of cerebral paragonimiasis were nonspecific, but MRI findings were characteristic, including irregular hemorrhage, ring-like enhancement and incommensurately larger range of edema. Therefore, MRI plays avital role in the diagnosis of cerebral paragonimiasis in children. Dr. Li et al. also retrospectively analyzed the imaging findings of 22 cases serologically and clinically confirmed as Paragonimus westermani infection during past five years. They suggested that the imaging findings of P. westermani were diverse and non-specific due to their complex life cycle and several life stages during infestation of human; however, the common features included patchy low or

mixed density lesions on brain CT and ring-enhancing lesion on brain MRI. The presences of worm cyst and migration track were considered to be the characteristic imaging features of paragonimiasis. CT is probably useful in a few patients to identify calcification and hemorrhage, typically occurred during the acute stage and in the early stages of further Paragonimus migration Routine MRI shows great advantages on the presence and degree of infections, the host response to the infection. Advanced MRI techniques such as MR spectroscopy have provided a surrogate marker of tissue chemical information, thereby could differentiate parasitic infections from other infections and also possibly monitor therapeutic response. Early detection and diagnosis of bacterial infections involving the CNS are paramount. Utilizing the clinical information in conjunction with the imaging findings is necessary to optimize treatment and ultimately improve patient care and thus reduce mortality and morbidity. Early neurosurgical intervention is advocated to prevent the ongoing risk of serious complications Therefore, pre-operative imaging workup plays a critical role in procedure planning and prognosis assessment in bacterial infection of the CNS.

Autoimmune and immune-mediated mechanisms are increasingly appreciated in many neurologic diseases. Neuromyelitis optica is an autoimmune, demyelinating disorder of the CNS with typical clinical manifestations of optic neuritis and acute transversemyelitis. The discovery of autoantibodies against aquaporin-4 changed our understanding of NMO immunopathogenesis and revolutionized the diagnostic algorithm As we have known, Wernicke encephalopathy and NMO are totally different disease entities. However, the similar lesion locations may potentially imply that there may be some correlations between them, and astrocytes may be the common target involved. The use of advanced MRI techniques may enhance our understanding of the pathogenic processes in CNS inflammatory diseases and help us identify the distinct radiologic features corresponding to specific phenotypic manifestations. Correlation between the underlying pathophysiologic mechanism of immunological diseases and imaging findings has been fully elucidated. MRI remains the imaging modality of choice in demonstrating the early signs of infection/inflammation. Furthermore, DWI and MRS also show great promise in detecting early changes than conventional MRI and provide more specific information regarding the etiology of signal abnormalities seen on conventional MRI. Chemical exchange saturation transfer (CEST) is a novel MRI technique for specifically detecting slow-to-intermediate exchange rate of protons associated with proteins and neurochemicals with water. In this issue, Dr. Wu comprehensively reviewed the interactions between activated microglia and astrocytes in the early stages of neuroinflammation and summarized the insights provided by MRS and CEST. Experimental and clinical studies were also reviewed to emphasize the contributions of MRS and CEST in investigating the pathophysiology and evolution in the early stages of neuroinflammation.