Acute Demyelinating Disorders in Children

Essay submitted for partial fulfillment of the master degree of Neuropsychiatry

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2012

List of abbreviations

ACTM	Acute Complete Transverse Myelitis
ADEM	Acute Disseminated Encephalomyelitis
AIDP	Acute Inflammatory Demyelinating Polyneuropathy
AMAN	Acute Motor Axonal Neuropathy
AMSAN	Acute Motor Sensory Axonal Neuropathy
APTM	Acute Partial Transverse Myelitis
ASFSN	Acute Small Fiber Sensory Neuropathy
ATM	Acute Transverse Myelitis
ANCA	Anti Neutrophil Cytoplasm Antibodies
APCs	Antigen Presenting Cells
APS	Antiphosphlipid Syndrome
AZA	Azathioprine
BCS	Baolconcentric Sclerosis
BBE	Bickerstaff's Brainstem Encephalitis
BBB	Blood Brain Barrier
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
MTX	Chemotherapeutic Agent Mitoxantrone
CIDP	Chronic Inflammatory Demyelinating Poly-Radiculo-Neuropathy
CDMS	Clinically Definite Multiple Sclerosis
CIS	Clinically Isolated Syndrome
CMAP	Compound Muscle Action Potential
CT	Computerized Tomography
CNP	Cyclic Nucleotide Phosphodiesterase
CMV	Cytomegalo Virus
DWI	Diffusion-Weighted
DPT	Diphtheria, Pertussis and Tetanus
DMT	Disease Modifying Therapies

DEM	Disseminated Encephalomyelitis
DIS	Dissemination in Space
DNA	Double Stranded Deoxyribonucleic Acid
EEG	Electroencephalography
EMG	Electromyography
EBV	Epstein Barr Virus
EMA	European Medicines Agency
EP	Evoked Potentials
FLAIR	Fluid Attenuated Inversion Recovery
FDA	Food and Drug Administration
GA	Glatiramer Acetate
GBS	Guillain Barre Syndrome
HSV	Herpss Simplex Virus
HIV	Human Immunodeficiency Virus
HTLV-1	Human T-cell Lymphotropic Virus1
IIDDs	Idiopathic Inflammatory Demyelinating Diseases
Ig	Immunoglobulin
ICU	Intensive Care Unit
IFN-B	Interferon Beta
IPMSSG	International Pediatric Multiple Sclerosis Study Group
IM	Intramuscular
IVIg	Intravenous Immunoglobulin
LOS	Lipo-Oligosaccharides
LPS	Lipo-polysaccharides
LETM	Longitudinally Extensive Transverse Myelitis
MRI	Magnetic Resonance Imaging
MMR	Measles, Mumps and Rubella
MFS	Miller Fisher Syndrome
MIU	Million International Units
MTX	Mitoxantrone Hydrochloride
MCTD	Mixed Connective Tissue Disease

MNCV	Motor Nerve Conduction Velocity
MS	Multiple Sclerosis
MAG	Myelin Associated Glycoprotein
MBP	Myelin Basic Protein
MOG	Myelin Oligodendrocyte Glycoprotein
NCV	Nerve Conduction Velocity
NO	Neuromyelitis Optica
OCB	Oligoclonal Bands
OPCs	Oligodendrocyte Progenitor Cells
OLG	Oligodendrocytes
ON	Optic Neuritis
P2	P2 protien
PMP22	Peripheral Myelin Protein 22
PNS	Peripheral Nervous System
PCR	Polymerase Chain Reaction
PPMS	Primary Progressive Multiple Sclerosis
PRMS	Progressive Relapsing Multiple Sclerosis
P0	Protein Zero
PLP	Proteolipid Protein
RIS	Radiologically Isolated Syndrome
PRMS	Relapsing Remitting Multiple Sclerosis
MDS	Schilder Myelinoclastic Diffuse Sclerosis
SPMS	Secondary Progressive Multiple Sclerosis
SNCV	Sensory Nerve Conduction Velocity
SMEI	Sever Myoclonic Epilepsy in Infancy
SS	Sjogren's Syndrome
SMA	Spinal Muscular Atrophy
SC	SubCutenous
SAGs	SuperAntigens
SLE	Systemic Lupus Erythromatosis
TPE	Therapeutic Plasma Exchange

TMS	Transcranial Magnetic Stimulation
TM	Transverse Myelitis
US	United States
VAERS	Vaccine Adverse Event Reporting System
VZV	Varicella Zoster Virus
WBCs	White Blood Cells

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Introduction

Introduction

Normal functioning of the nervous system involves the transmission, processing and integration of information as nervous impulses. Impulse transmission along axons is greatly facilitated by the presence of myelin, the compact multilamellar extension of the plasma membrane of specialized glial cells that spirals around larger axons. In the central nervous system (CNS), oligodendroglial cells are responsible for the synthesis and maintenance of myelin, whereas schwann cells subserve this role in the peripheral nervous system (PNS) **(Harry and Toews , 1998).**

Demyelinating diseases of nervous system are characterized by lesions that are associated with loss of myelin with relative sparing of axons. Central nervous system myelin and peripheral nervous system myelin are antigenically different .Therefore, some demyelinating disorders attack the central nervous system (the prototype is multiple sclerosis), while others affect the peripheral nervous system (the prototype being Guillain-Barre syndrome) **(Reeves and Swenson , 2008).**

Demyelinating diseases of the CNS including acute disseminated encephalomyelitis (ADEM), acute hemorrhagic leukoencephalitis, devic's disease, multiple sclerosis (MS), transverse myelitis (TM), and clinically isolated syndromes such as optic neuritis. Demyelination of the peripheral nervous system can present acutely as the heterogeneous entity known as Guillian-Barre syndrome (GBS) **(Adamovic *et al*., 2008).**

There are multiple effectors mechanisms that operate to produce acute demyelination .Cytokines and tumor necrosis factor alpha (TNF-α) are pivotal in orchestrating immune and inflammatory cell-cell

interactions and represent potentially noxious molecules to the myelin sheath, Schwann cells, and/or oligodendrocytes. Arachidonic acid metabolites are intimately involved in the inflammatory process by enhancing vascular permeability, providing chemotactic signals and modulating inflammatory cell activities. Reactive oxygen species can damage myelin by lipid peroxidation and may be cytotoxic to myelin-producing cells. Activation of complement yields a number of inflammatory mediators and results in the assembly of the membrane attack complex that inserts into the myelin sheath-creating pores. Activated complement may contribute both to functional disturbance of neural impulse propagation, and to full-blown demyelination. Proteases, abundantly present at inflammatory foci, can degrade myelin. Vasoactive amines may play an important role in breaching of the blood-brain/blood-nerve barrier **(Hartung *et al.*, 2002).**

Demyelination is a common cause of neurological disability in young adults. Its clinical features and presentations may be highly variable, making it a diagnostic challenge **(Gupta *et al.*, 2009).**

Symptoms differ from patient to patient, and have different presentations. In CNS demyelination, manifestations can be with signs and symptoms caused by single lesion (monofocal clinically isolated syndrome) or with polyfocal features such as multiple sclerosis **(Banwell *et al.*, 2007).**Two main clinical expressions of acute demyelination of the CNS, in children, can be observed. The first is more frequently observed in young patients under 10 years old age, and the symptoms are often imprecisely described as 'acute encephalitis' **(Tardieu and Mikaeloff, 2004).** The onset is acute with headache, nausea, vomiting, fever, seizures, altered state of consciousness, motor-sensory hemisyndromes and cerebellar and brainstem dysfunction **(Gadoth, 2003).** The second

mode of expression is more frequent in teenagers and is reminiscent of observations after acute demyelination in young adults. It consists of isolated or combined symptoms, such as optic neuritis, discrete hemiparesis, brain stem-related symptoms and sensory disturbances, usually without any changes in mental state, while the latter mode is more suggestive of MS, both lead to a differential diagnosis requiring Magnetic Resonance Imaging (MRI) and biological tests to confirm the final diagnosis **(Tardieu and Mikaeloff, 2004).**

In acute demyelination of PNS such as in GBS, there is dramatic acute demyelinating neuropathy with rapid onset **(Reeves and Swenson, 2008).**

The clinical manifestations in children are often anteceded within 2 to 4 weeks by recent illness. The hallmark of GBS is an ascending weakness. Older, more verbal children and adults will present with complaints of weakness and unsteadiness. The weakness typically starts in the lower extremities and ascends into the upper extremities. This progression may extend from hours to days to weeks. In younger, less verbal children, the symptom of gait unsteadiness and ataxia is a pertinent clinical feature. Although weakness is the most common clinical feature, the most frequent initial presenting complaint in children is pain. Pain complaints consist of back pain, leg pain, and headaches and can sometimes be severe in nature **(Delanoe *et al.*, 1998).**

Sensory symptoms and parasthesia have been noted in 18% to 54% of children **(Sladky, 2004).** It should be noted that sensory symptoms are often difficult to elicit from younger, less verbal children, these sensory symptoms occur most commonly in the distal extremities **(Bradshaw and Jones, 1992).** Ataxia has been reported in almost half of the children

with GBS. Cranial neuropathies are also a common finding, seen in 15% to 50% of these children **(Hsieh, 2009).**

Acute demyelination in children can be life threatening because of profound encephalopathy, respiratory depression, and tetraplegia **(Banwell *et al*., 2007).**

Morbidity and eventual mortality in patients with the GBS are associated with cardiopulmonary instability, including blood pressure fluctuations, potentially fatal tachyarrhythmia, bradyarrhythmia, and myocarditis **(Mukerji *et al*., 2009)**. Fatigue, spasticity, ataxia, pain and bowel, bladder and sexual dysfunction are also detected as complications in cases of MS **(Kesselring, 2003).**

The diagnosis of demyelinating disorders carries important therapeutic and prognostic implications. In most cases the diagnosis is made clinically with involvement of the histopathologist and clinico-pathological correlation **(love, 2006).**

Detection of demyelinating disorders increased because of enhanced awareness and increased systematic neuroimaging and electromyography/nerve conduction studies. Laboratory data include evidence of albuminocytologic dissociation or oligoclonal bands in cerebrospinal fluid **(Adamovic *et al.,* 2008).**

The Cerebro-Spinal Fluid (CSF) profile for pediatric MS cases appears to be similar to that found in adults, with the exception of slightly higher incidence of pleocytosis in children. **Pohl *et al.*, 2004** have reported a very high sensitivity for detecting oligoclonal bands in known pediatric MS cases between ages 6 and 16 years. Other studies have suggested that a much lower rate of oligoclonal bands is found in very young patients **(Chabas *et al.,* 2006).** CSF analysis may confirm