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Neurology & Nervous System



Impact of Migraine Headache

Evaluation of Autism Diagnostic Tools

Highlights

Empty Sella Turcica and Papilloedema

Cause of Mental Illness in Adolescents

Discovering Thoughts, Inventing Future

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Microbial Induced Autoimmune Inflammation as a Cause of Mental Illness in Adolescents: A Case Series

By Daniel A. Kinderlehrer & Nancy Brown

Abstract- The incidence of mental health disorders in adolescents continues to rise. The cause of the increase in mental illness is multifactorial, including both environmental and biological causes. To investigate the latter, ten adolescents at a psychiatric residential treatment center in Colorado with the DSM-5 diagnosis of major depressive disorder (MDD), of whom seven were additionally diagnosed with generalized anxiety disorder (GAD), were chosen at random for further serologic study. Testing revealed exposure to group A *Streptococcus* (GAS) in 3 of 10 (30%); *Borrelia burgdorferi sensu lato* (*Bbsl*) in 2 of 10 (20%); and *Bartonella* spp. in 3 of 10 (30%). In addition, 9 of 10 (90%) subjects had abnormal Cunningham Panels, which measures levels of antineuronal antibodies that have been associated with psychiatric disturbances. Given the degree of psychological dysfunction in these adolescents requiring intensive residential treatment, this case series lends support to the hypothesis that exposure to infectious agents may play a role, perhaps by autoimmune mechanisms, in the significant and ongoing rise in the rate of neuropsychiatric illness in adolescents. This preliminary report adds to this premise and requires further investigation.

Keywords: *PANDAS, PANS, autoimmune, neuroinflammation, streptococcus, lyme, bartonella, cunningham panel, mental illness, adolescents.*

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MICROBIALINDUCEDAUTOIMMUNEINFLAMMATIONASACAUSEOFMENTALILLNESSINADOLESCENTSACASESERIES

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Microbial Induced Autoimmune Inflammation as a Cause of Mental Illness in Adolescents: A Case Series

Daniel A. Kinderlehrer [α] & Nancy Brown [σ]

Abstract- The incidence of mental health disorders in adolescents continues to rise. The cause of the increase in mental illness is multifactorial, including both environmental and biological causes. To investigate the latter, ten adolescents at a psychiatric residential treatment center in Colorado with the DSM-5 diagnosis of major depressive disorder (MDD), of whom seven were additionally diagnosed with generalized anxiety disorder (GAD), were chosen at random for further serologic study. Testing revealed exposure to group A *Streptococcus* (GAS) in 3 of 10 (30%); *Borrelia burgdorferi sensu lato* (*Bbsl*) in 2 of 10 (20%); and *Bartonella* spp. in 3 of 10 (30%). In addition, 9 of 10 (90%) subjects had abnormal Cunningham Panels, which measures levels of antineuronal antibodies that have been associated with psychiatric disturbances. Given the degree of psychological dysfunction in these adolescents requiring intensive residential treatment, this case series lends support to the hypothesis that exposure to infectious agents may play a role, perhaps by autoimmune mechanisms, in the significant and ongoing rise in the rate of neuropsychiatric illness in adolescents. This preliminary report adds to this premise and requires further investigation.

Keywords: PANDAS, PANS, autoimmune, neuroinflammation, streptococcus, lyme, bartonella, cunningham panel, mental illness, adolescents.

I. Introduction

Mental health problems among adolescents are increasing [1]. The most common mental health disorder in this age group is anxiety. Anxiety disorders occur in approximately 32% of adolescents 13 to 18 years of age, and 8.3% had severe impairment [2]. The number of adolescents who experienced major depressive disorder (MDD) was 21.48% in 2015 and increased by nearly a third from 2009/2010 to 2015 [1]; 13.3% of youth aged 12 to 17 report suffering from at least one major depressive episode in 2017 [3]. The suicide rate among persons aged 10 to 24 has increased 56% between 2007 and 2017; since 2014 suicide has replaced homicide as the second most common cause of death for teenagers ages 10 to 19 in the United States [4].

The cause of mental health disorders in adolescents is multifactorial, including both biological and environmental causes. Stress issues have been cited as a significant factor [5]. Common sources of stress in adolescence include social stress/peer pressure, academic pressure, isolation, dysfunctional home environment, physical or sexual abuse, bullying, low self-esteem and substance abuse. Compounding these issues, adolescents who spend more time on social media and electronic devices such as smartphones are more likely to report mental health issues, and an increase in screen time is associated with a decrease in in-person social interaction and an increase in depressive episodes [1].

It is clear that biological issues also have a significant role in mental health disorders. Neuropsychiatric symptoms can be caused by multiple organic issues including heavy metal toxicity [6], allergy to gluten [7], thyroid disorders [8], and autoimmune illness [9]. In addition, the medical literature is replete with the identification of neuropsychiatric disorders caused by infection [9,10].

Infections transmitted by ticks have been linked to a spectrum of mood and behavioral disorders. *Borrelia burgdorferi sensu lato (Bbsl),* the pathogen that causes Lyme disease, is responsible for a wide range of mental health disorders, including anxiety disorders, depression, schizoaffective disorders, bipolar disorder, eating disorders, addiction, suicide, violence, anhedonia, depersonalization and dissociative episodes [11-17].

Other tick-borne infections can also cause neuropsychiatric illness. Infections with *Bartonella* spp. have been associated with anxiety, panic disorder, depression, obsessive compulsive disorder (OCD), phobias, eating disorders, alcohol and drug abuse, psychosis and personality disorders [18-22]. *Bartonella henselae (B. henselae)* is also associated with a wide spectrum of autoimmune conditions [23-37], including pediatric acute-onset neuropsychiatric syndrome (PANS)[22].

Autoimmune mechanisms may underly the linkage between infection and neuropsychiatric disorders. In 1994, Swedo et.al. described mental health issues associated with group A *Streptococcus* (GAS) infections [38]. Based on the first fifty children who met the clinical description of neuropsychiatric disorders following streptococcal infections, Swedo outlined five diagnostic criteria for this diagnosis and coined the term pediatric autoimmune neuropsychiatric disorders

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associated with streptococcal infections (PANDAS) [39]. These criteria include OCD or tic disorder (as defined by DSM IV, American Psychiatric Association, 2000), prepubertal age of onset, an abrupt onset with relapsing or remitting course, neurological abnormalities during exacerbations (such as involuntary, choreiform movements or motor hyperactivity), and a temporal association between streptococcal infections and neuropsychiatric symptom exacerbations.

In recognition of the finding that multiple microbes in addition to GAS can trigger autoimmune encephalitis and autoimmune encephalopathies or PANDAS-like syndromes, this condition is now referred to as pediatric acute-onset neuropsychiatric syndrome (PANS), and criteria have been developed for this diagnosis. Children must have the abrupt onset of OCD or severely restricted food intake; there must be no known neurologic or medical disorder that would account for the symptoms; and include at least two of the following seven conditions: anxiety, emotional lability and/or depression; irritability, aggression, and/or severe oppositional behaviors; behavioral (developmental) regression; sudden deterioration in school performance; motor or sensory abnormalities; somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency [40]. Multiple microbes have been documented as triggering PANS including herpes simplex virus, influenza A virus, varicella zoster virus, Epstein-Barr virus, HIV, recurrent sinusitis, the common cold, *Mycoplasma pneumonia* and *B. henselae* [22,41,42].

Immune cross-reactivity between microbes and host tissues has been well documented and is attributed to molecular mimicry [43,44]. Children with PANS-like conditions exhibit elevated levels of antineuronal antibodies against dopamine receptors [45-47], lysoganglioside [48], and tubulin [49]. Antineuronal antibodies crossing the blood-brain barrier can activate calcium calmodulin-dependent protein kinase II (CaMKII), a multifunctional enzyme highly concentrated in the brain, which mediates many different learning, memory, and developmental cell pathways. CaMKII alters dopamine neurotransmission, leading to neuropsychiatric symptoms of OCD as well as tics, and youths with OCD and tics have elevations in CaMKII activity [50].The Cunningham Panel was developed to assess patients with PANS-like syndromes, and includes levels of these antibodies as well as CaMKII activity.

This exploratory study has two aims. First, to examine whether adolescents with serious mental health disorders have a higher rate of exposure to GAS, *Bbsl*, and *Bartonella* spp. than the general population. Secondly, to evaluate whether adolescents with significant mental health disorders have elevations in antineuronal antibody levels, consistent with autoimmune induced neuroinflammation as a possible cause of their disorders.

II. Methods

Subjects were randomly selected patients at a residential adolescent treatment center. The severity of their mental health issues prevented them from living at home and attending school. All were suffering from depression, and some also suffered from anxiety. Informed consent was reviewed and approved by the Western Institutional Review Board (WIRB). Consent was obtained from all subjects and their guardians.

Serum testing included Lyme ImmunoBlot IgM and IgG for evidence of exposure to *Bbsl; Bartonella* Multi-species Western Blot IgM and IgG for evidence of exposure to *Bartonella* spp.; Anti-DNase B (ADB) for evidence of exposure to GAS; and the Cunningham Panel for evidence of autoimmune neuroinflammation. The Cunningham Panel includes five assays performed on serum that measure human IgG levels by enzyme-linked immunosorbent assay (ELISA) directed against the Dopamine D1 Receptor, Dopamine D2L Receptor, Lysoganglioside-GM1, and Tubulin, as well as a cell stimulation assay which measures the ability of a person's serum IgG to stimulate CaMKII activity in human neuronal cells.

III. Results

The subjects ranged from fourteen to seventeen years of age. There were six females and four males. All ten satisfied DSM-5 criteria for MDD, and seven additionally satisfied DSM-5 criteria for GAD. Three of the subjects were diagnosed with Attention Deficit Disorder (ADD), three subjects had made serious suicide attempts, four subjects had behavior associated with non-suicidal self-injury disorder (NSSID) in the form of cutting, and one had tics. One subject had previously been diagnosed with celiac disease, but the remaining nine had no known medical disorder. See Table 1.

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Table 1: Diagnoses of Subjects

Subject	Age	Gender	MDD	GAD	Suicide attempt	Eating Disorder	NSSID (Cutting)	Tics	Medical Disorder
1	16	M	+	+	+				Celiac
2	16	F	+		+		+		
3	14	M	+	+					
4	15	F	+	+		+	+	+	
5	15	F	+	+					
6	16	F	+	+					
7	15	M	+	+					
8	17	F	+	+	+		+		
9	17	M	+						
10	15	F	+				+		

MDD, Major depressive disorder
GAD, Generalized anxiety disorder
NSSID, Non-suicidal self-injury disorder

Three of ten subjects (30%) had elevated levels of ADB. See Table 2.

Table 2: Results of Anti-DNase B testing

Subject	Anti-DNase B (RR:0-170)
1	**286**
2	125
3	<78
4	<78
5	**324**
6	113
7	<78
8	**238**
9	163
10	<78

Elevated levels are highlighted and in bold

Table 3 summarizes the results of the Lyme ImmunoBlot IgM and IgG testing. Two of ten subject (20%) had antibodies to IgG specific bands P23, P34 and P39.

Table 3: Results of Lyme ImmunoBlot testing

Subject		P93	P66	P58	P45	P41	P39	P34	P31	P30	P28	P23	P18	Results
1	IgG					++							+	NEG
	IgM													NEG
2	IgG					+							+	NEG
	IgM					-								NEG
3	IgG			+		+		+						POS
	IgM													NEG
4	IgG			+	+	+								NEG
	IgM					+								NEG
5	IgG					+				++			+	NEG
	IgM					+								NEG

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6	IgG					+	+					++		Pos
	IgM													NEG
7	IgG			+		+								NEG
	IgM													NEG
8	IgG													NEG
	IgM													NEG
9	IgG					+								NEG
	IgM													NEG
10	IgG													NEG
	IgM											+		NEG

IgG, Immunoglobulin G
IgM, Immunoglobulin M

Three of ten subjects (30%) had antibodies to either *B. henselae, Bartonella elizabethae (B. elizabethae) or Bartonella vinsonii (B. vinsonii).* See Table 4.

Table 4: Results of the Bartonella Multi-species Western Blot IgG and IgM

Subject	Bartonella Western blots	
	IgG	IgM
1	NEG	NEG
2	NEG	NEG
3	POS B. elizabethae	NEG
4	NEG	NEG
5	NEG	NEG
6	POS B. vinsonii	NEG
7	NEG	NEG
8	NEG	NEG
9	POS B. henselae	NEG
10	NEG	NEG

IgG, Immunoglobulin G
IgM, Immunoglobulin M
B. elizabethiae, Bartonella elizabethiae
B. vinsonii, Bartonella vinsonii
B. heneslae, Bartonella henselae

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Nine of ten subjects (90%) had abnormalities in the Cunningham Panel with elevations in anti-neuronal antibodies and five of ten (50%) subjects with elevations in CaMKII activity. See Table 5.

Table 5: Results of the Cunningham Panels

Subject	Anti-Dopamine D1 RR:500-2000	Anti-Dopamine D2L RR:2000-8000	Anti-Lysoganglioside RR:80-320	Anti-Tubulin RR:250-1000	CaMKII Activity RR:53-130
1	**1:8000**	1:8000	1:80	**1:2000**	125
2	**1:4000**	1:8000	1:160	**1:4000**	**137**
3	**1:4000**	1:8000	1:160	**1:4000**	**133**
4	**1:4000**	1:8000	1:160	**1:8000**	**159**
5	**1:4000**	1:8000	1:160	**1:4000**	**130**
6	1:2000	1:4000	1:80	**1:2000**	121
7	**1:4000**	1:2000	1:40	**1:2000**	123
8	**1:16000**	**1:16000**	1:320	**1:4000**	**134**
9	1:2000	1:4000	1:80	1:1000	113
10	**1:4000**	1:8000	1:80	**1:4000**	118

Abnormal results are highlighted and in bold

CaMKII, Calcium calmodulin-dependent protein kinase II

Table 6 depicts the positive results of all the assays in the ten subjects.

Table 6: Summary of Positive Results

Subject	Anti-DNase B positive	Bbsl ImmunoBlot positive	Bartonella spp. Western Blot positive	Cunningham Panel positive
1	+			+
2				+
3		+	+	+
4				+
5	+			+
6		+	+	+
7				+
8	+			+
9			+	
10				+

Bbsl, Borrelia burgdorferi sensuolato

IV. Discussion

In this case series, three of ten subjects (30%) had positive titers to ADB consistent with exposure to GAS. ADB titers become positive one week to one month after streptococcal infection and usually stay positive for months. However, in some individuals ADB titers stay positive longer than one year, including in some with streptococcal carrier states [51,52]. ADB titers are positive in the majority of patients with streptococcal induced autoimmune illnesses including rheumatic fever and post-streptococcal glomerulonephritis, as well as in patients with PANDAS [51-53]. Fujikawa et. al. found that only 8% of a non-carrier control population had elevations in ADB titers [52]. The finding that 30% of the subjects in this study had elevations in ADB levels suggests the possibility that GAS may have played a role in their mental health issues.

In this case series, 2 of 10 (20%) subjects showed evidence of exposure to or current infection with *Bbsl*. The Lyme immunoblot assay, which utilizes pure recombinant proteins as test antigens, is more sensitive and specific than the Lyme ELISA and the Lyme Western Blot [54-56]. While cross-reactivity of some *Borrelia* proteins with antigens from other bacteria and viruses is well known [40], the presence of IgG antibodies at 23-kdA (outer surface protein [Osp]C), 34-kdA (OspB) and at 39-kdA are considered specific and therefore diagnostic for *B. burgdorferi* [57-60]. Subjects 3 and 6 demonstrated IgG reactivity at Bands 23, 34 and/or 39. While these results do not meet the Centers for Disease Control and Prevention (CDC) criteria for reporting Lyme disease, the CDC criteria were established for surveillance purposes only, not for clinical diagnosis [61,62].

While neuroinflammation has been documented in both acute and persistent infection with *Bbsl* [63-65], this pathogen has not as yet been documented as a singular cause of PANS. Cross et.al. described the case of a pre-pubescent female who developed PANS with a positive Cunningham Panel, was serologically positive for *Streptococcus* but also for several tick-borne infections including *Bbsl, B. henselae,* and *Babesia*

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duncani, and responded to broad spectrum antimicrobial therapy [66]. Many of the neuropsychiatric symptoms of neuroborreliosis parallel or overlap with those of PANS, including anxiety disorders, depression, OCD and tics[11-17,67].

Some of the chronic symptoms in patients with post-treatment Lyme disease syndrome (PTLDS) are attributed to autoimmunity [68,69], and Chandra et. al. found anti-neuronal antibody levels 41 of 83 (49.4%) PTLDS patients who continued to suffer from chronic symptoms of pain, fatigue, and impaired cognition; antibodies against *Bbsl* cross-reacted with several neural proteins[63]. Likewise, Fallon et.al. found higher levels of antibodies against Lysoganglioside-GM1, Tubulin, and Dopamine D1-Receptor as well as well as elevated activity of CaMKII in patients with a prior history of Lyme borreliosis but not in those without that history[70]. Osp A has a protein sequence similar to GAS [71], and OspA is associated with autoimmune reactivity[69]. It is not unlikely that *Bbsl* is yet another microbe that can trigger PANS-like syndromes. The finding that 20% of subjects in this case series had evidence of exposure to *Bbsl* raises the possibility that this microbe is playing a role in their mental health issues.

In this case series, 3 of 10 (30%) subjects showed evidence of exposure to or current infection with *Bartonella* spp. *B. henselae,* an intracellular gram-negative pleomorphic bacillus, is the causative agent of cat scratch disease (CSD) transmitted via the cat flea. In addition to transmission via fleas, sandflies and lice, *B. henselae* can be transmitted via the Ixodes tick [72,73]. Co-occurrence of Bartonella spp. with known tick-borne pathogens such as *Bbsl* is not uncommon. A survey by Adelson et. al. of Ixodes ticks in northern New Jersey found *B. burgdorferi* present in 35% while 34% harbored Bartonella spp. [74]. Additional surveys have confirmed the high incidence of Bartonella spp. in Ixodes ticks [75,76]. The *Bartonella* bacillus is difficult to grow; therefore, culture is not recommended [77]. While polymerase chain reaction (PCR) in serum or tissue specimens is the most definitive way to diagnose infection with *Bartonella,* PCR detection lacks sensitivity (43–76%) [78]. ELISA and Indirect immunoflourescence assays (IFA) are the standard tools to diagnose bartonellosis, however increased sensitivity is associated with decreased specificity with both these antibody assays [79,80]. There is preliminary evidence that Western blot testing for *Bartonella* as performed in this case series is both more sensitive and specific than either IFA or ELISA testing [81].

B. henselae causes a wide spectrum of clinical illness in humans, including autoimmune and psychiatric illness as noted above. There is an abundance of data on infections in animals with *B. vinsonii* and *B. elizabethae,* but in humans it is limited. There are reports that both species can cause infective endocarditis [82-84], and *B. vinsonii* has additionally been reported to cause neurological abnormalities[85,86]. There are no reports of neuropsychiatric complications with these two *Bartonella* species. However, these infections need to be considered emerging illnesses at this time; few laboratories are equipped to identify these potential pathogens and correlate them with clinical syndromes. There is also the possibility of cross-reactivity among different species of *Bartonella* [87]. The relevance of positive *Bartonella* spp. IgG in three adolescents in this study is unclear.

In this case series, 9 of 10 (90%) subjects demonstrated the presence of anti-neuronal antibodies and 5 of 10 (50%) had CaMKII activation. The utility of the Cunningham Panel has been demonstrated in the assessment of PANDAS/PANS by Shimasaki et. al. They evaluated 58 patients meeting the diagnostic criteria for PANDAS/PANS who were tested pre-and post-treatment. Patients were categorized as “Improved/Resolved” (n=34) or “Not-Improved/Worsened” (n=24). The changes in assays of the Cunningham Panel paralleled changes in patient symptoms following treatment with an accuracy of 90%, a sensitivity of 88% and a specificity of 92% [88]. Chain et.al. compared 35 acute onset PANDAS patients with 28 healthy controls and found that 32 sera (91.4%) in the PANDAS group were positive for one or more of the antineuronal autoantibodies compared with 9 of 28 healthy controls (32.1%) [89]. Likewise, Connery et.al. found that the Cunningham Panel accurately predicted significant responses in aberrant behavior and social responsiveness in children with autism [90]. Multiple other studies have found an association between autoimmune neuropsychiatric disorders such as PANDAS/PANS and the biomarkers included in the Cunningham Panel [45-50, 91-96]. Antineuronal antibodies crossing the blood brain barrier and activating CaMKII may underlie the serious mental health issues in the subjects in this case series.

Hesselmark and Bejerot have challenged the utility of using the Cunningham panel to diagnose PANS [97].Their study found both low sensitivity and specificity of the Cunningham panel, and did not find a statistical difference between patients with PANS and healthy controls. But their findings have been challenged because, among other issues, they used invalid serum collection tubes—they used gold top tubes that contain both a clot activator and a serum gel separator rather than glass red top tubes that have no additives [98].

The rates of infections with GAS [99,100] and tick-borne pathogens [101] are increasing, and perhaps molecular mimicry resulting in immune cross-reactivity underlies the rise in autoimmune illnesses [102]. Non-microbial factors that underlie the development of autoimmunity are also increasing, including occupational exposures such as pesticides [103,104], dietary changes and their impact on the microbiome

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[105,106], and stress-related disorders such as post-traumatic stress disorder (PTSD) [107,108]. Indeed, all these factors can alter epigenetics [109-114], and epigenetics is crucial to the development of autoimmunity [115]. Therefore, it is possible that multiple factors are contributing to autoimmunity and are cumulative in succeeding generations.

V. Conclusion

The increasing incidence of mental health disorders in adolescents is multifactorial. Stress issues and an increase in screen time on electronic devices has appropriately received attention, but less attention has been given to the role of organic disorders. This case series documented exposure to *GAS, Bbsl* and *Bartonella* spp. in 5 of 10 (50%) subjects, raising the possibility that these microbes may be playing a causative role in the subjects' mental illness. In addition, 9 of 10 (90%) subjects had evidence of autoimmune neuroinflammation as evidenced by their positive Cunningham Panels. The high percentage incidence of antineuronal antibodies and CaMKII activation in this group of ten subjects may not necessarily be indicative of all patients in this facility due to the small sample size, but it is possible that neuroinflammation is an important contributor to the increasingly high incidence of mental health disorders in the adolescent population.

Given the serious and increasing morbidity and mortality of mental illness in the adolescent population, the implications are significant for promoting future research. Further studies in a larger cohort of patients compared with a healthy control population that would help elucidate the roles of *GAS, Bbsl* and *Bartonella* along with autoimmune neuroinflammation in the etiology of mental health issues in the adolescent population is warranted.

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Author contributions

D.A.K. conceived the premise of this research and secured IRB approval. N.B. secured approval from subjects and their guardians and implemented the collection of data. N.B. performed the analysis of the data. D.A.K. authored the manuscript.

Conflicts of interest
The authors cite no conflict of interest.

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Acronyms used:
DSM – Diagnostic and Statistical Manual of Mental Disorders
MDD – major depressive disorder
GAD – generalized anxiety disorder
GAS – group A Streptococcus
Bbsl – Borrelia burgdorferi sensu lato
OCD – obsessive compulsive disorder
B. henselae – Bartonella henselae
CSD – cat scratch disease
PANDAS – pediatric autoimmune neuropsychiatric disorders associated with streptoccal infections
PANS – pediatric autoimmune neurospsychiatric syndrome
CaMKII– calcium calmodulin-dependent protein kinase II
IgM – immunoglobulin M
IgG – immunoglobulin G
WIRB – Western Institutional Review Board
ADB – Anti-DNase B
ADD – attention deficit disorder
NSSID – non-suicidal self-injury disorder
Osp – outer surface protein
B. elizabethae – Bartonella elizabethae
B. vinsonii – B. vinsonii
CDC – Centers for Disease Control and Prevention
PTLDS – post-treatment Lyme disease syndrome
IFA – immunoflouresence antibody
ELISA – enzyme-linked immunosorbent assay
PTSD – post-traumatic stress disorder

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Empty Sella Turcica and Papilloedema: Two Cases Reports

By Dr. Eliya Shrestha, Dr. Hara Maya Gurung, Dr. Indra Man Maharjan, Dr. Babita Gurung & Dr. Hari Bikram Adhikari

Abstract- *Purpose:* To report a case of papilloedema with partial empty sellaturcica.

Methods: Retrospectively review the clinical features, magnetic resonance imaging records and treatment effects of a patient using Methylprednisoslone.

Conclusions: MRI is the preferable imaging technique for patient with papilloedema.

Keywords: *empty sella syndrome, papilledema.*

GJMR-A Classification: *NLMC Code: WL 340*



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Abstract- ***Purpose:*** **To report a case of papilloedema with partial empty sellaturcica.**

Methods: **Retrospectively review the clinical features, magnetic resonance imaging records and treatment effects of a patient using Methylprednisoslone.**

Conclusions: **MRI is the preferable imaging technique for patient with papilloedema.**

Keywords: empty sella syndrome, papilledema.

I. Introduction

Sellaturcica is a saddle shaped compartment in base of the skull which accommodates the pituitary gland. The empty sellaturcicaoccurs when there is a leakage of cerebral spinal fluid(CSF) leading to flattening and displacement of the pituitary gland. When pituitary gland is flattened and MRI cannot detect the gland it is known as Empty Sella syndrome (ESS). There are two types of ESS: Primary and secondary. Primary empty sella syndrome occurs when there is defect in diaphragmatic sella allows CSF and presses the pituitary gland. Secondary empty sella syndrome occurs when the pituitary gland is damaged by some other cause like tumor, surgery or radiation therapy (Aruna et al., 2014). The prevalence of primary sella in general population has been reported to be 8-35%(Aruna et al., 2014). The incidence has been reported more in females, the ratio being 5:1(Aruna et al., 2014).

Case 1

A young male presented to us with complaint of blurring of vision and occasional double vision since 1 week. He did not complaint of headache, vertigo nor tinnitus. On examination his visual acuity in both eyes were 6/6. His eyebrows and eyelids were in normal position. Extraocular eye movement were full in all gazes except in dextroversion. Cornea and anterior chamber were normal. Pupil in both eyes were round, regular, reacting to direct and consensual light reflex equally. Lens were clear and normal position in both eyes. Vitreous were clear in both eyes. On Fundus examination of both eyes revealed disc margin blurred and elevated. Cup were obliterated. Venous pulsation were absent. Retinal veins looked engorged and tortuous. Disc hemorrhages were also seen.

Color vision test with ishihara chart were normal in both eyes. Humphrey visual field showed enlarged blind spot and pheripheralscotoma in both eyes. Diplopia charting showed uncrossed horizontal diplopia with maximum separation at dextroversion.

Haematological test showed total count, differential count, haemoglobin, within normal limit. Biochemical test showed Random blood sugar and Serum creatinine within normal limit. Serological test for HIV, HCV AND HbsAg were negative.

With above mentioned clinical findings clinical diagnosis of both eye disc edema and right eye lateral rectus paresis were made. To rule out any intracranial pathology patient was sent to perform MRI.
MRI showed partial empty sellatursica.

Patient was admitted and treated with Injection Methylprednisolone 1gm Intravenous for 3 days. Along with it Protonpump inhibitors was also given orally.

Case 2

An adult male aged 53 years presented to us with blurring of vision since 15 days in left eye. No history of redness, pain nor any trauma. There is no history of any systemic disease. On examination his vision in right eye was 6/6 and in left eye HM+(Hand movement). Extraocular movements were full in all gazes and painless. Anterior segment was normal. On fundus examination in right eye Disc was sharp margin pink in color, macula was normal with normal foveal reflex except myelinated nerve fiber layer in inferior temporal branch. In left eye disc was edematous with blurring and elevation of margin, cup was obliterated, vessels were tortuous. He was sent for MRI scan of head and orbit which showed isolated empty sella. He was admitted in hospital for intravenous methylprednisolone injection for 3 days followed by oral steroid for 11 days. Proton pump inhibitors were also given simultaneously.

The patient again appeared in our hospital after 6 month. On examination his vision in right eye was 6/6 and in left eye was HM. Extraocular movement were normal anterior segment was normal in both eyes except pupillary reaction. Relative afferent pupillary defect was noticed in left eye. On fundus examination right eye was normal. Left eye disc was pale in color,

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sharp margin, Vessels were attenuated, nerve fiber layer was thinned out.

II. Discussion

Empty sellaturcica is a rare disorder. We searched through Pubmed using EndNote 7 and found only 153 artcles since year 1955 till 2019. Very few article were retrived while searching for empty sellaturcica and papilloedema. Papilloedema caused by empty sellaturcica has been reported by Wang, Jianming (Wang et al., 2008). The empty sellaturcica is caused by intrasellar herniation of CSF resulting in flattening of the pituitary gland(Saindane et al., 2013). Papilloedema is a clinical diagnosis while empty sellaturcica is a radiological findings.

Papilloedema and clinical features of raised intra cranial pressure(ICP)would have lead us to suspect Idiopathic intracranial hypertension(IIH). However our patient did not have any symptoms of raised ICP like headache, vertigo, Tinnitus etc. Moreover our patient was male at age of 27 years and 53 years. IIH is more common in obese female aged 20-40 years.(Victorio and Rothner, 2013, Saindane et al., 2013). Increased fat in scalp and neck region seen in MRI has been described in cases of IIH(Saindane et al., 2013). Our patient did not showed such findings in MRI.

Papilloedema has also been reported in case of Harada syndrome (Nawasiwatte et al., 2012). Thanh-Thao Adriana Le reported a case of Vogt-Koyanagi-Harada (VKH) syndrome with bilateral papilloedema and neurological findings (Le et al., 2019).VKH is an autoimmune disease characterized by ocular (choroiditis), neurological (meningoencephalitis) and integumentary (vitiligo, inner ear) findings. VKH is more common in dark skin women of any age. However our both patients did not showed the sign and symptoms of VKH syndrome.

Shrestha et al reported a case of ocular cysticercosis with multiple disseminated subcutaneous nodules on the body with bilateral papilledema with multiple calcified cyst and scolex in brain on computed tomography (CT) scan(Shrestha and Shrestha, 2019).

III. Conclusion

These are two rare different presentation of empty sella syndrome with disc edema. The cause of disc edema was not known to us.

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By Dr. Reaz Mahmud

Abstract- *Background:* Migraine headache is one of the commonest causes of primary headache. This study aims to reveal the clinical profile & severity of migraine headache in Bangladeshi people.

Methods: Descriptive cross sectional observational study conducted in the Headache clinic Dhaka Medical college Hospital from December 2019 to March 2020. About 854 patients with headache were attended. Of that 234 patients were diagnosed as migraine according to ICHD-3 classification criteria. However, 75 patents were enrolled in this study by systematic sampling.

Results: In this study migraine burden among the headache patients found to be about 25%. The mean age of the onset of the migraine headache was found to be 25.2±11.86 years, predominantly (68%) in 15-34 years age group. 36% of the patient with migraine had positive family history which is significantly higher in patients with migraine with aura (52% vs. 30%, p value <0.5).

Keywords: *headache, migraine with aura, migraine without aura.*

GJMR-A Classification: *NLMC Code: WL 344*



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Conclusions: Clinical profile of migraine in Bangladesh differs in some trigger points like sun exposure, journey and migraine subtypes than the western world.

Keywords: headache, migraine with aura, migraine without aura.

I. Introduction

Primary headache disorders are among the commonest disorders, affecting people in all countries. Estimate is that one person in three experiences severe headache at one stage of their life. Life time prevalence of any type headache as estimated from population based studies is more than 90% for man and 95% for the women.[1] Migraine is one of the important causes of primary headaches. Migraine has a one-year period prevalence of 12 percent (17.1 percent in women and 5.6 percent in men).[1, 2] Cumulative incidence of migraine by age 85 is 18.5 percent in males and 44 percent in females.[3] Migraine is a neurovascular disease characterized by a broad spectrum of symptoms, varying from headaches that are typically unilateral and have a pulsating quality, associated with various neurological symptoms such as nausea, increased sensitivity to light and sound (photophobia and phonophobia), and aura, which may consist of visual, sensory or motor disturbances.[3] (The International Classification of Headache Disorders, 3rd edition beta version, 2013). Migraine Headache is broadly classified into migraine with aura and migraine without aura. They are diagnosed according to The International Classification of Headache Disorders, 3rd edition beta version, 2013 [3]. Migraine with aura and migraine without aura are genetically distinct. Migraine with aura (MA) is a prevalent neurological condition with strong evidence for a genetic basis[4]. The susceptibility gene loci for migraine with aura and without aura are different[5]. The clinical picture of migraine is composed of 4 different stages including the prodromal stage, aura stage, headache stage and postdrome stage. Migraine headache also has some established trigger factor[3]. Clinical profile of migraine varies person to person, country to country even in the same person. Most of the study regarding clinical profile was done in the developed countries. There is scarcity of the study revealing clinical profile in Bangladesh. This study aims to reveal the clinical profile, trigger factor, Complication functional disability, severity of migraine headache in Bangladeshi people presented in Headache clinic, Dhaka Medical College Hospital. It will give an overview of presentation of migraine and its functional consequences on the people of Bangladesh. However through this study it would be known whether the findings of other study done in abroad could be replicated or not. So it would give some light whether presentation of *migraineurs* in our country is same or different from other population. Thus the findings of this study will invoke further research as well about migraine.

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II. Methodology

A cross sectional observational study was conducted in the Headache clinic of Dhaka Medical college Hospital from December 2019 to march 2020. Institutional ethical committee approval was obtained accordingly. Patient presented in the headache clinic, was labeled as migraine by experienced Neurologist. Migraine with or without aura was defined according to International classification of headache disorders[4]. Patient of both sexes and all ages fulfilling the ICHD 3 criteria were included in the study. Migraine patient with other cause of headache like sinusitis, post traumatic headache and drug induced headache, were excluded from the study. Patients were enrolled by Systematic Sampling Method. Every 3rd patient with migraine headache attended in a headache clinic day was enrolled in this study. Measured sample size was 196. Every patient was coded by the researcher. An informed written consent was obtained from the patients. Face to face interview was conducted by using a semi structured questionnaire containing socio-demographic parameters and relevant information about Migraine. Detailed fundus examination was done in all patients. Severity of migraine was assessed using Visual Analogue scale 1-10. Migraine Disability Assessment was done using MIDAS score. Secondary causes of headache were excluded using brain imaging in suspected patients The Data was collected by Research Assistant, who is a trained doctor. Variables of the collected data were uploaded in Microsoft excel sheet. The data was analyzed by using simple descriptive statistics like mean, median and prevalence rates, standard deviation. Chi square rest was done to observe the significance.

III. Results

About 854 patients with headache were attended in the headache clinic during the study period. Of that 234 patients were diagnosed as migraine and 75 patents were enrolled in this study by systematic sampling. Most of them (72%) were female. Mean age of the study population at presentation was 31.4±12.5 Years. Most of the patient is in the age group of 19-38. Onset of Headache occurred at 25.2±11.86 years (Table 1). Onset of migraine occurs in 15-24 and 25-34 age group with significantly higher in female (Figure 1). About 36% of the study population had positive family history which is significantly common in migraine with aura patient. Most common migraine subtype was Migraine without aura (70.67%). Duration of headache was on average 17.6 hour, duration of prodrome was 2.26 hours and duration of aura was 31.34 minutes. In 47% cases patient presented with single aura and in 53% cases patient presented with multiple aura. Phobia associated in most of the cases. Quiet a large number of the patient (37.33%) had history of nocturnal arousal due to headache. About 37% of the patient had migraine complication and 42% patient presented with different co-morbidity. VAS Severity score 7.24±1.67. MIDAS severity score 7.78±5.9 (Table 1). Most of them presented with either unilateral (34.67%) or bilateral headache (50.67%). In episodic migraine most of the patient's frequency of headache was 2/week (26.67%). On the other hand 25.33% of the patient had headache in almost all the days in a week that is chronic daily headache. Visual aura (100%) was the most prevalent aura subtype followed by Brainstem aura (42%).Almost all the patient had photophobia (91.77%) (Table 2). In most of the cases patient had multiple trigger factors (53%). In most of the cases prodrome (42.67%), postdrome (49.33%) and co-morbidities (32%) were single. Trigger factors were present in 81.33 %(61) of the patient. Of that Sun exposure (37.70%), anxiety (32.79%), insomnia (37.70%) and journey (31.11%) were common (Table 4). Prodrome was present in 65.33% of the cases. Neck stiffness (67.34%) and Irritability (42.85%) were the most prevalent symptoms. Postdrome were present in 77.33 % cases (Table 3). Among them Lack of concentration and Mood change were the prevalent symptoms. About 42% of the patient presented with co-morbidity. Generalized anxiety disorder (37.5%), NUD (21.8%) and Hypertension (25%) were the most common co-morbidity. About 37% of the patient presented with migraine complication and chronic migraine with anxiety (21%) was the most prevalent complication. Complications were more prevalent among the female.

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Table 1: General characteristics of the study population

Traits	Mean ± SD or N (%)
Age	31.4±12.5 Years
age of onset of Headache	25.2±11.86 years
Sex Distribution	
Male	21(28%)
Female	54(72%)
Family History	27(36%)
Positive with Aura patient	10(52%)
Positive without Aura patient	17(30%)
	P value <0.5
Migraine subtypes	
Migraine without Aura	53(70.67%)
Migraine with Aura	18(24%)
Migraine aura sine Headache	1(1.33%)
Special form of childhood Migraine	3(4%)
Benign cyclical vertigo	1(1.33%)
Abdominal Migraine	1(1.33%)
Cyclical vomiting syndrome	1(1.33%)
Headache duration	17.6±16.12hours
Duration of aura	31.34 minutes
Number of Aura (among the aura patient)	
Single Aura	10(47%)
Multiple Aura	9(53%)
Duration of prodrome	2.26 hour
Phobia	71(96.67%)
Nocturnal Arousal due to headache	28(37.33%)
VAS Severity score	7.24±1.67
MIDAS severity score	7.78±5.9
Complications of migraine	28(37.33%)
Co-morbidity	32(42.66%)

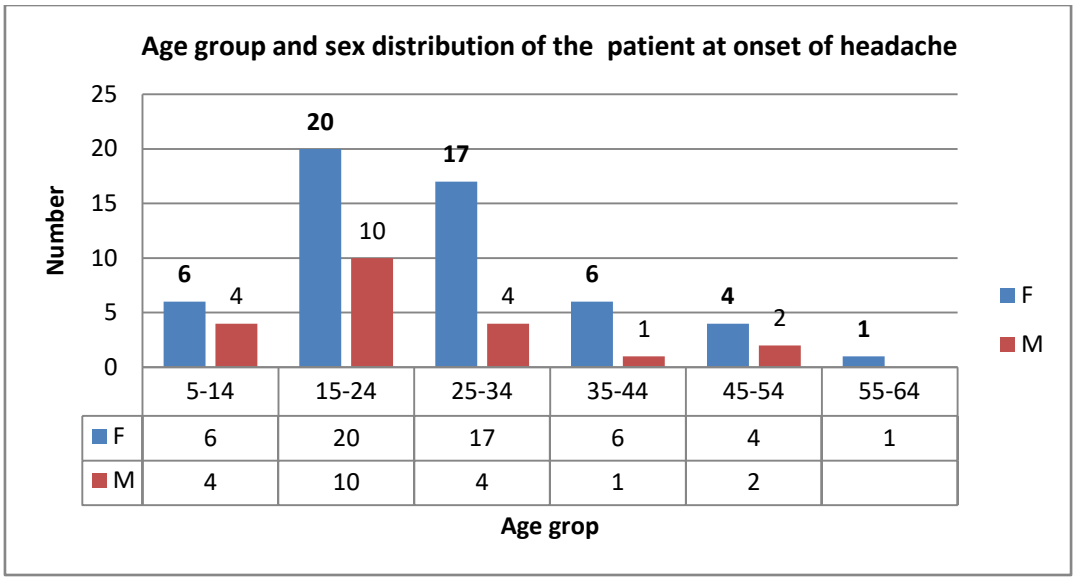


Figure 1: Age group and sex distribution of the patient of at onset of headache

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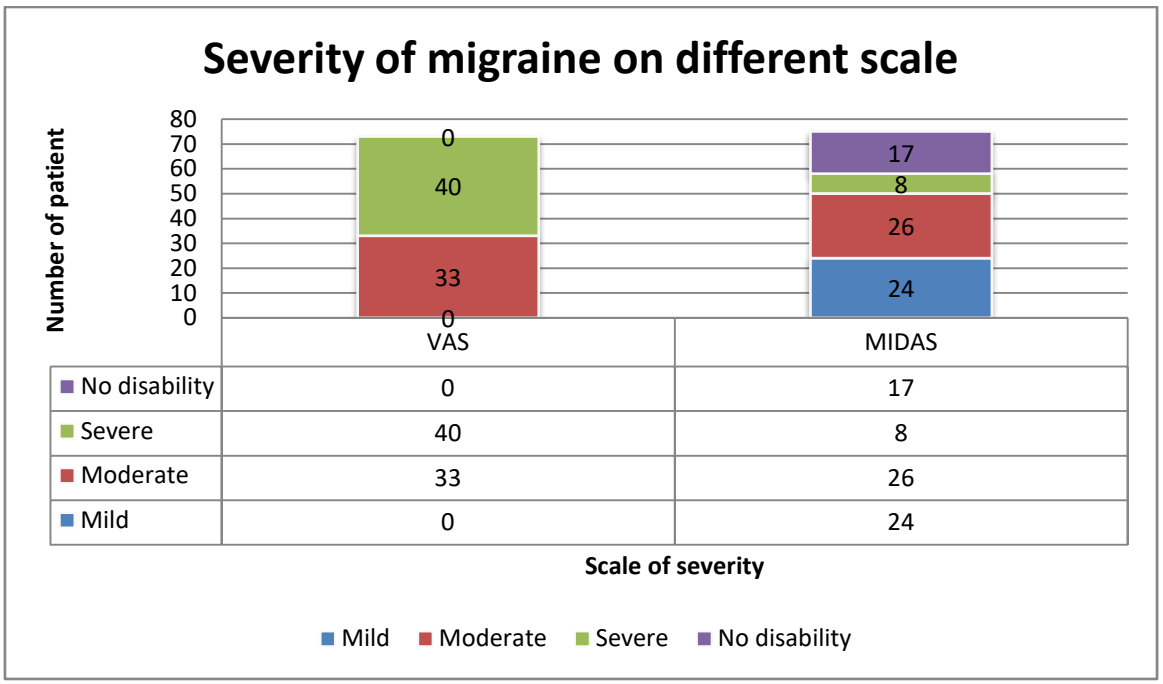


Figure 2: Severity of migraine on different scale

Table 2: Characteristics of headache

Trait	Frequency (%)
Site of headache	
Unilateral	26 (34.67)
Bilateral	38 (50.67)
Alternating	7 (9.33)
Frequency of headache(most common)	
2/week	20 (26.67)
7/week	19 (25.33)
3/week	11 (14.67)
1/week	11 (14.67)
Aura subtype(among the patient with Aura)	
Visual	
Brain stem	19 (100)
Motor	8 (42)
Sensory	1 (5)
	2 (10)
Phobia subtype	
Photophobia	69 (91.77)
Phonophobia	49 (65.17)
Osmophobia	14 (18.62)
Complication	
Absent	47 (62.67)
Present	28 (37.33)
• Chronic migraine with anxiety	16 (21.33)
• Chronic migraine with Medication overuse	8 (10.67)
• Migralepsy	
• Status Migrainosus	2 (2.67)
	2 (2.67)

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Table 3: Common trigger factors, prodrome, postdrome symptoms and Co-morbidity

Trigger factors	N (%)	Prodrome	N (%)	Postdrome	N (%)	Co-morbidity	N (%)
Sun exposure	23 (37.70%)	Neck stiffness	33 (67.34%)	Lack of concentration	24 (41.37%)	Hypertension	8 (25%)
Anxiety	20 (32.79%)	Fatigue	11 (22.44%)	Mood change	21 (36.20%)	Diabetes	4 (12.5%)
Insomnia	23 (37.70%)	Irritability	21 (42.85%)	fatigue	18 (31.03%)	Depression	4 (12.5%)
Journey	19 (31.11%)	Craving for food	2 (4%)	sleep	22 (37.93%)	Generalized anxiety disorder	12 (37.5%)
Temperature change	10 (16.39%)	Sleepiness	4 (8.1%)			Non-Ulcer dyspepsia	7 (21.8%)
Sound	11 (18.03%)	Yawing	2 (4%)			Psycogenic Dyspnoea	2 (6.2%)
Stress and exertion	8 (13.11%)					Psycogenic vertigo	4 (12.5%)
Menstruation	7 (11.47%)						
Single	28%		42.67%		49.33%		32%
Multiple	53%		22.67%		28		10.67%
Absent	!9%		34.67%		22.67%		57.33%

IV. Discussion

Migraine is one of the important primary headache disorders. Globally migraine burden among the headache patients is about 11-15%[9, 10]. In this study migraine burden among the headache patients presented in headache clinic found to be about 25%. This is a little bit higher as it was a hospital based study, mild Tension type headache in most of the cases don't appear in Hospital. The mean age of the onset of the migraine headache in this study was found to be 25.2±11.86 years, in most of the cases (~ 68%) they presented in 15-34 years age group. It is found that mostly migraine starts before the age of 40[1, 11]. Like other study[11, 12, 13] females are the worst suffer of the migraine in the present study as well (F: M 2.6:1). Migraine is largely a familial disorder. In this study 36% of the patient with migraine had positive family history which is significantly higher in patients with migraine with aura (52% vs. 30% p value <0.5). Migraine has several known trigger factors. In this study about 81% of the patient has single or multiple trigger factors. Along with other known factor sun exposure and journey was found to be the important trigger factors for Bangladeshi population. Bangladeshi female usually do not take alcohol and pure chocolate intake is less among Bangladeshi population. So these factors as a trigger were not found in this study. This study revealed that about 11% of the patient had catamenial migraines which include both cyclical and non-cyclical form. According to MacGregor[15], the prevalence of cyclical catamenial migraine is 7.2%. Migraine headache started with prodrome which persists for hours to days[1]. In this study 65% of the patient had prodrome which persisted for average 2.21 hour. A significant number of the patient had multiple prodromes (22%). Neck stiffness and irritability was the most prevalent prodrome. Migraine headache is broadly classified as migraine with aura and without aura. In this study 24% of the patient with migraine had aura. In USA 30.8 percent of female migraineurs and 32 percent of male migraineurs have aura[16]. In this study 22% of the female migraineurs and 33% of male migraineurs had aura. Four special form of migraine (Cyclical vomiting syndrome, Abdominal migraine, Benign cyclical vertigo, Episodic torticollis) are found in pediatric population[1]. In this study abdominal migraine benign cyclical vertigo and cyclical vomiting syndrome was found. Among the Patient with aura 99 percent has a visual aura. Most (60%) patients has a combination of aura symptoms, 39 percent has a visual aura exclusively. However, more than one aura symptom occurred, especially in succession in 96 percent and simultaneously in four percent of patients[17]. In this study 53% of the aura patient had combination of aura and 47% patient had exclusive visual aura. In the present study 100% of the patient had visual aura, 42% had brainstem aura and 10% had sensory aura. Aura symptoms usually persist for 5-60 minutes. In this study Average duration of aura was 31 minutes. Migraine pain is unilateral in 60 percent of cases and bilateral in 40 percent. However, 15 percent of the patient migraine always occurring on the same side[18]. In this study about 50% patient had bilateral headache, 35% patient had unilateral headache and 10% cases had alternating headache (ie. Stared unilaterally and then become bilateral). Migraine headache usually persisted for 4-72 hours. In this study average duration of headache was about 18 hours. Migraine headache is by definition moderate to severe headache. In this study 44% had moderate headache and 56% had severe headache according to VAS score.

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Frequency of migraine attack varies in different study. In a study among the neurologist it was found that, 25 percent, four or more severe attacks a month; 35 percent, one to four severe attacks per month; 38 percent, one or less severe attacks per month; and 37 percent, five or more headache days per month.[19]. In this study 25% patient had chronic daily headache, 26% patient had >5 attack/ month and 15% patient had < 4 attack per month. In almost all cases migraine is associated with phobia. In this study 92% patient had photophobia and 62% had phonophobia. Postdrome is the fourth and final phase of a migraine attack. For those having a severe migraine episode, the shift from headache to postdrome can be difficult to identify. Postdrome usually persist < 24 hour. In one study it is found that 90% patient had postdrome, 67% patient had loss of concentration and 75% has tiredness[20]. In this study 77% patient had postdrome symptoms, of which lack of concentration is found in 41%, fatigue in 36% and mood change in 36% of cases. Co-morbidity makes migraine management challenging. In this study bout 42% of the patient presented with co-morbidity. Functional co-morbidity (Generalized anxiety disorder, Depression, Non-ulcer dyspepsia, Rage attack) is the most prevalent in this study. Migraine poses a significant impact in the daily life of the migraineurs due to its complications and functional disability. Chronic migraine with anxiety, medication overuse, migralepsy & status migrainosus were found as a complication of migraine in this study. In this study a significant number of the patient was found with medication overuse (10%). Functional disability in this study was assessed with MIDAS score. As patient had to recall the previous 3months events the findings might not be representative. According to MIDAS score Patient largely had Mild (32%) to Moderate (34.67%) disability, 8% patient severe disability.

This study characterizes patients with headache disorders who sought medical treatment with a headache neurology specialist. Therefore, it is inappropriate to generalize the results of this study to headache disorders in the community. In this study sample size was limited. In some cases patient had to recall previous events. There was possibility of recall bias in this study.

V. Conclusion

Proper diagnosis, assessment of the severity, detection of the trigger factors, counseling would be the cornerstone of migraine management. To make a plan and guideline of management, clinical profile of the disease of the respective population is the paramount importance. This study was the attempt to know the profile and impact of migraine in Bangladeshi population. Migraine with brainstem aura occurs in significant number of the patient having moderate disability. So, further study is needed to evaluate brain stem migraine to characterize it and better management.

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Appendix

MIDAS score: [8](Migraine Disability Assessment score (MIDAS)

MIDAS score – Migraine Disability Assessment Questionnaire	
On how many days in the last 3 months did you miss work or school because your headaches?	(days)
How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.)	(days)
On how many days in the last 3 months did you not do household work because of your headaches?	(days)
How many days in the last three months was your productivity in household work reduced by half of more because of your headaches? (Do not include days you counted in question 3 where you did not do household work.)	(days)
On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches	(days)
MIDAS Score	**(points)**
Score Interpretation:	

Score	Grade
0-5	Little or no disability
6-10	Mild disability
11-20	Moderate disability
>20	Severe Disability

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Pre-Hospital and In-Hospital Delay of Acute Ischemic Stroke Patients in India

By S. Lakshmi Sabapathi, Pharm.D & M. R. Vijaya Kumar M.pharm., ph.D.

Abstract- Diseases that take place in developing countries could owing to poverty, lack of healthcare infrastructure, restricted access to the hospital. Many developing countries like India growing well economically and extending urbanization in recent years despite this large Indian population lives in poverty. However, risk factors for stroke in urban populations are like other developed nations. Stroke is the third common cause of death due to disease in India. The acute ischemic stroke has to be treated within few hours after the beginning of symptoms; if time goes beyond >4.5 after the onset of symptoms, thrombolytic drugs ineffective not only time, other contraindications also equally contribute to thrombolytic therapy. The use of thrombolytic in contraindication patients would further exaggerate the stroke. The various factors could cause a delay the management of acute ischemic stroke from pre-hospital delay to delay in diagnosis and treatment. An effective strategy is needed to meet the challenges in India.

Keywords: *acute ischemic stroke, delay, thrombolytic, contraindication.*

GJMR-A Classification: *NLMC Code: WL 356*



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Pre-Hospital and In-Hospital Delay of Acute Ischemic Stroke Patients in India

S. Lakshmi Sabapathi, Pharm.D [α] & M. R. Vijaya Kumar M.pharm., ph.D. [σ]

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Keywords: acute ischemic stroke, delay, thrombolytic, contraindication.

I. Introduction

Stroke is the most complicated global public health complication. Report of the Global Burden of Diseases study conducted in 1990. In developing countries like India, both communicable and non-communicable diseases are a double burden. Globally, stroke is the third general cause of death after CHD and cancer. In recent times the incidence of stroke in India mounts higher than in western countries in India, the actual incidence rate of stroke is between 145-154/1,00,000 persons in a year. The major reason for increasing stroke incidence in India due to poor medical facilities in rural most populations are living. Few factors are certainly associated with a delay in the management of acute ischemic stroke-like pre-hospital delay due to late arrival, long-distance, rural living, poor knowledge, and Community awareness, along with other factors like delay in a hospital due to lack of CT scan facilities in rural and remote areas, inadequate infrastructure, delays often seen in the treatment of patients with acute ischemic stroke. Thrombolytic therapy for acute ischemic stroke was being approved in 1996 However, only 1% to 2% of patients with ischemic stroke have estimated to be eligible for it because of the time window. The beneficial effect of thrombolytic in acute ischemic stroke up to 4.5 hours of stroke symptom onset; previous guidelines were suggested 3 hours of thrombolytic also have some contraindication so, checking inclusion and exclusion is vital before starting therapy.

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a) Pre-delay into the hospital

The pre-hospital delay not declined since 2006 in India, with the many patients unsuccessful to arrive before 3 hours. Most population in developing countries like India living in rural areas where the health system is poor. one of the reason for emergency department arrival beyond 3 hours is a delay in transportation, transportation delay in urban areas due to excess of traffic, in the rural area due to shortage of ambulance service and distance from the hospital. Knowledge of stroke is relatively poor among people in India, especially in rural areas. A Study in Northwest India revealed both patients and their relatives did not have enough knowledge about the stroke and its symptoms, ignoring, personally thinking the symptoms would resolve quickly. Living or being alone during the onset of stroke, Stroke while sleeping, especially at mid-night, also contributes to factors in the pre-hospital delay.

b) Delay in hospital

Stroke units in the hospital provide a multi-regulated approach by neurologists, stroke physicians, stroke nurses, physiotherapists, speech therapists, and occupational therapists involve in cohesive and organized care of the patients. The number of strokes–care hospitals and those with obligated stroke units is not many in India. Insufficiency of imaging facilities and extremely high cost of thrombolytic agents and mechanical thrombectomy are the major hindrances in the proper management of acute ischemic stroke.

c) Delay in diagnosis

Indian government hospitals divided into PHC, CHC, SDH, and DH among these; only DH have a CT scan facility. Patients should be transported into DH or medical college hospital or multi-specialty hospital because other categories of hospitals do not have CT scan facility. It is certainly a timely process if patients reach into non-CT scan hospital. CT scan in-hospital admission also the factor causing the in-hospital delays; it is strongly impacted by factors such as patient admission process delay, shortness of staff, the distance between hospital stroke unit or causality, and CT room.

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d) Delay in management

The decision-making process for thrombolytic selection should be a factor affecting in-hospital delay. The study revealed that the process of decision-making for intravenous thrombolytic contributed to a prominent factor in-hospital delay. Acute ischemic patients firstly examined by an emergency unit followed by being informed to the neurologist. Once a definite diagnosis made, medical professionals should communicate with their family members, informing the risk of intravenous thrombolytic and collecting information about the present and the previous history of patients to determine inclusion or exclusion criteria are necessary. If a patient contraindication to the thrombolytic agents; a mechanical thrombectomy is an alternative option. It takes more time because it is a surgical procedure. The high cost of thrombolytic therapy and mechanical thrombectomy makes it inaccessible to economically backward patients.

e) Management of acute ischemic stroke

The only pharmacological agent approved for the management of acute ischemic stroke is IV- (rt-PA).A reperfusion therapy that should be administered well inside a time 4.5 hrs right after symptom onset. It officially approved for management in acute ischemic stroke in 1996. The limitation on IV-rt-PA treatment beyond 4.5 hrs rules out most stroke patients admitted beyond this time-window as a result, dramatically restrain the eligible population. Tissue plasminogen activator within 4.5 hrs of the onset of symptoms remarkably boosts clinical outcomes in patients with acute ischemic stroke. Thrombolytic dissolve thrombi in the vascular bed by converting plasminogen to form plasmin. Plasmin is a proteolytic enzyme that burst the cross-links across fibrin molecules to break the structure of clots. The most important thrombolytic drugs used in ischemic stroke to stimulate plasminogen are urokinase/streptokinase and tissue plasminogen activators. The major pharmacological agent in tissue plasminogen activators is alteplase, which is converts plasminogen to the proteolytic enzyme plasmin, which is ruptures fibrin to dissolve. Apart from the pharmacological agents, mechanical thrombectomy also an indication in the management of acute stroke if time limits cross 4.5 hrs. In recent times reperfusion therapies also have been performed in mechanical embolus disruption or removal of a fibrin clot. Mechanical thrombectomy devices resolve the ischemic but not fully occluded clot. It is regaining perfusion through the earlier occulted artery. The application of retrievable stents into the ischemic part of blood vessels promptly relieves the block and improves the blood circulation. Now the day's most neurologists prefer mechanical thrombectomy to bring off reliable results similar to those seen by cardiologists in the treatment of myocardial infarction by angioplasty(stent).

Less than 3 hrs

If within 3 hrs use intravenous alteplase therapy, well-defined manifestations are observed.

3 to 4.5 hrs

Intravenous alteplase therapies shold be provided that treatment initiated within 3 to 4.5 hrs of well-defined manifestations will be observed. Patients in this period will also determine if they are candidates to mechanical thrombectomy.

4.5 to 6 hrs

Patients within 4.5 to 6 hrs from stroke manifestation onset must not receive intravenous alteplase because of contraindication, but patients might be eligible for mechanical thrombectomy.

6 to 24 hours

Patients beyond 6 hrs from ischemic stroke symptom onset could not entitle for treatment with intravenous alteplase. Nevertheless, mechanical thrombectomy might be eligible if the hospital using an imaging-based selection of patients.

Beyond 24 hrs

Patients beyond 24 hrs from ischemic stroke symptom onset could entitle neither alteplase nor mechanical thrombectomy.

So timing is more important in the application of alteplase or mechanical thrombectomy in acute ischemic stroke.

II. Inclusion and Exclusion Criteria for Thrombolytics

a) Inclusion Criteria

Within 3 hrs of stroke symptom onset:

Ischemic stroke diagnosis with mild to severe but impairs stroke symptoms, the onset of symptoms <3 hrs before proceeding treatment, age > 18 years.

Between 3-4.5 hrs after stroke symptom onset:

Age < 80 years, without any previous history of diabetes mellitus and prior stroke, NIHSS score < 25, presently not taking any oral anticoagulants, CT scan Imaging does not establish the involvement of > ⅓ of middle cerebral artery territory.

If otherwise eligible:

Blood pressure range below < 185/110 mm Hg, patients taking an anti-platelet drug-like (aspirin or clopidogrel or aspirin and clopidogrel) if the benefit outweighs the small risk of symptomatic intracerebral hemorrhage.

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Exclusion Criteria (Table 1)

Table 1

Absolute contraindication

- Present condition of acute Intracranial Haemorrhage
- Past History of any Intracranial Haemorrhage
- Brain tumour, arteriovenous malformation, or aneurysm
- Just recent intracranial or intra-spinal surgery
- Severe to very Hypertension (systolic >185 mmHg or diastolic >110 mmHg)
- Arterial puncture at incompressible part in past 7 days
- Thrombocytopenia and Coagulopathy
- Severe Hypoglycaemia or Hyperglycaemia<50 or >400 mg/dL
- Advanced Age>80
- Severe Stroke and Coma
- Recent Major Surgery
- Central Nervous System Structural Lesions
- Dementia
- Platelet count <100000/mm3
- Heparin received within 48 h resulting in abnormally elevated aPTT above the upper limit of normal
- Currently or recently application of anticoagulant with INR >1.7 or PT >15 s
- Currently or recently application of direct thrombin inhibitors or direct factor Xa inhibitors
- CT scan established multi-lobar infarction (hypodensity>1/3 cerebral hemisphere)

Relative contraindication

Current proof proposes that under some situation, with caution consideration and measuring of the risk to benefit, patients might receive thrombolytic therapy despite≥1 relative contraindications.

- Just minor or rapidly improving stroke symptoms (clearing automatically)
- Pregnancy at all trimesters
- Onset of seizure with neurological destruction
- Major surgical operations or serious injuries (within past 14 day)
- Recent GIT tract or urinary tract bleeding (within past 21 days)
- Recent acute coronary infarction (within past 3 months)

III. Meeting the Challenges of Stroke in India

Improving stroke knowledge and education, Improving awareness about risk factors and warning symptoms to the general population, sharing of knowledge as well as technical between research institutions, Increasing more number of stroke units and trained professionals to tackle the high Indian population, enhanced quality of care for stroke patients in India by improving guidelines and designated hospitals infrastructure, train research facilities for basic and clinical research regarding stroke.

IV. Conclusion

The management of acute ischemic stroke has a time window due to delay by factors like pre-hospital delay and delay in-hospital have contributed patients into ineligible candidates for the thrombolytic therapy. The factors contributing to delay could not easily minimize because of greater challenges in developing countries like India. The challenges should be meeting by-improving stroke education, infrastructure, and guidelines.

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Conflict of Interest

The author declares that there are no conflicts of interest.

Abbreviations

CHD: Coronary heart disease; CT: Computed tomography; PHC: Primary health centre; CHC: Community Health Centre; SDH: Sub-District Hospitals; DH: District Hospitals; IV: Intravenous; (rt-PA): Recombinant tissue plasminogen activator; NIHSS: The national institutes of health stroke scale; PTT: partial thromboplastin time; INT: International normalized ration; PT: Prothrombin time

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PSI Hypothesis

By Cengiz Mordeniz

Abstract- Throughout history, human beings have experienced supernatural events that created new religions, mythologies, etc. to frighten people into forcing them to obey the authority. Due to the progress in science and technology, life style, and the way of scientific thinking, superstitions, and empty beliefs are not anymore means to convince people. Human beings are looking for more concrete manifestations to believe. The belief would be replaced by the scientific mind. Belief is a cover over the questions or suspicions in mind. The reality is to clear the mind by reasonable thinking and explain all the parapsychological events scientifically so that abstracting without any concrete base would not be accepted. Instead, scientific based mind will be the true evidence to think on the parapsychological events.

Keywords: belief, cognitive bias, magic, psi, extrasensory perception, poltergeist, psychokinesis.

GJMR-A Classification: NLMC Code: WL 340

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I. Introduction

Psi is the term for the experiences that cannot be explained by the existing science, such as extrasensory-perception (ESP), psychokinesis (PK), poltergeist, near-death, out-of-the-body, apparitional, and reincarnation experiences (Irwin, 2007).

ESP is a general term used for information acquisition other than conventional sensory processes of sight, sound, taste, touch, and hearing.PK is an ability to influence the environment by intention or other mental activity alone without motoric intervention. Poltergeist experiences refer to movements of objects, noises, fires, water inundations, bites, scratches, pinches, or demonic persecution caused by a deceased person.

Another category of sensorial capacity of the mind is the detection of near-death (NDEs) and religious and mystic (RMEs) experiences, such as clinically proved cessation of the brain and heart activities, besides other extra-sensorial phenomena like a premonition, generated by the mind power. This relation shows that each individual is a distinct entity, not only as the matter structure is concerned, but also from an informational point of view, according to the personal features inherited from the parents and the habits acquired during the life.

The "out-of-the-body experience" (OBE) refers to experiences in which one's visuo-spatial perspective and one's self are experienced to have departed from their habitual position within one's body. Evidence from neurology, cognitive neuroscience, and neuroimaging suggests that OBEs are related to a failure to integrate multisensory information from one's own body at the temporo-parietal junction (TPJ). This multisensory disintegration at the TPJ leads to the disruption of several phenomenological and cognitive aspects of self-processing, causing illusory reduplication, self-location, perspective, and agency that are experienced as an OBE.

The term apparition, derived from the Latin word apparere (meaning "to show oneself"), is used for the presence of a living or dead person or animal, that is not actually there. This term is a bit broader than the more popular term ghost (from the German word geist for "mind" or "spirit"), which refers to the apparition of a deceased person, usually in connection with a haunting. Experiences with apparitions are of interest to parapsychologists for three main reasons:

First, the process of witnessing an apparition involves the use of extrasensory perception or ESP: this is why some people (particularly psychics and mediums) are able to see or otherwise "sense" apparitions, while others are not.

Second, physical phenomena associated with apparitions, such as odd sounds and object movements, involve the use of psychokinesis (PK), or "mind over matter." The apparition can be formed through a PK-related process.

Third, apparitions can be interesting in investigating their relation to alleged hauntings.

There are several types of apparitions that have been documented by psychical researchers and parapsychologists since the late 19th century such as deathbed visions, haunting, crisis, and post-mortem apparitions, or of the bystander-type.

Crisis: a crisis apparition appears to a witness at a time when the person experiences a state of crisis, whether an accident, illness, or even the threat of death.

Post-mortem: a post-mortem apparition appears after a person's death, anywhere from several hours to several years after.

Deathbed Vision: Near the moment of death, some terminally ill and dying patients have described seeing images of people and places and images.

Haunting: Most of the apparitions seen at haunted sites appear as shadowy forms, floating lights, and hazy mist-like clouds. In most cases, these kinds of apparitions have a geophysical and psychological explanation (Roll, 2004).

Bystander-Type: Rather than being seen in the place where they once lived or worked, some apparitions have

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been witnessed near people who once knew them in life.

Reincarnation (past life memories): In areas of the world where reincarnation is accepted, one can identify three forms: pre-natal and post-mortem identity, the continuing or dissolving the self and family identity. The word reincarnation derives from the Latin, literally meaning "entering the flesh again."

Rebirth is found in major Indian religions and ancient Sanskrit texts of Buddhism, Hinduism, and Jainism. In the Buddhist approach, life and death are seen as one whole, where death is the beginning of another life. Via hypnotic age-regression techniques, many patients can recall past-life memories. Personal projections, expectations, and desires appear as mind-related projections, creating an imbalance that makes it difficult to differentiate from real inner emotional remembrance. Reincarnation, also called transmigration or metempsychosis, is the concept of being reborn into new lives. Some religions adopt the reincarnation in life cycle, as a path to purity and salvation.

Seven factors that have a possible link with Psi performance are aging, relaxation, emotional response, experimenter effects, magnetic field, personality, and belief. The psychological experiences and behaviors of a person can be mapped to the portions of the brain that are metabolically the most active during the experience. These active regions can be visualized by such technologies as positron emission tomogprahy (PET), single positron emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI). Apparitional experiences may be termed as "conscious dissociation of self-identity" to distinguish it from pathological unconscious dissociative identity disorders. (Caputo, 2019)

French expression for the phrase 'already seen' is a 'deja vu' regarded as some sort of precognition and has been revealed as an anomaly related to the memory, with many similar occurrences; déjà entendu (already heard), déjà eprouve (already experienced, felt, attempted or tried), deja fait (already done), déjà pense (already thought), déjà raconte (already recounted, told), déjà senti (already felt emotionally smelt), déjà su (already known intellectually), déjà trouve(already found, met), déjà vecu (already lived through, fully experienced or recollected in its entirety) and deja voulu (already desired, already wanted.) (Neppe, 2015).

The sensation of deja vu arises from two streams of cognition: the phenomenological experience of recognizing a current situation and the awareness that this feeling of recognition is inappropriate. (O'Connor, 2010).

Deja vu experience has also been described in many novels and poems and formulated in dreams, organic factors, and unconscious memories. It seems that the temporal region is the origin of the deja vu phenomena. Three structures are clearly associated with deja vu experiences as a part of neurological conditions (hippocampus, parahippocampal gyrus, and temporal neocortex). The pathophysiological hypothesis of deja vu in epilepsy involves either the limbic regions of the temporal lobe or the temporal neocortex or both of them. A new hypothesis of corticolimbic network suggests that deja vu results from an abnormal synchronization between rhinal cortices and hippocampus. (Moulin, 2017).

Regarding structural anatomy and the brain morphology, there is significantly less grey matter in subjects reporting deja vu accompanied with an inverse correlation between the frequency of deja vu experiences and the grey matter volume in the regions including bilateral mesiotemporal regions (with maximal effect within hippocampi and parahippocampal gyri), insular cortices, superior temporal sulci, basal ganglia, and thalamus. (Brazdil et al. 2012).

It is already known from neurophysiological studies that epileptic illusions of déjà vu are ictal manifestations arising from discharge in the temporal cortex of patients with TLE (temporal lobe epilepsy). In 1998 the existence of a common but often unrecognized clinical entity called benign TLE. It is characterized by seizure onset in adulthood, frequent familial history, and epileptic déjà vu that often represents the only predominant ictal symptom. Déjà vu is an ictal phenomenon in apparently normal individuals and represents the mildest manifestation of the TLE phenotype. (Labate, 2013).

The connection between false memories formation and deja vu in healthy individuals have been shown by using hypnosis, fMRI (Chadwick, 2016), and EEG (Sederberg, 2007).

In false memory creation, certain areas of the brain (hippocampus, temporal, and prefrontal cortex) play a significant role. False memories emerge from a similarity-based neural code in the temporal pole, called the semantic hub of the brain. Each individual has a partially unique semantic code within the temporal pole, that can predict idiosyncratic patterns of memory errors. EEG is used to distinguish true from false memories by increased gamma oscillations immediately preceding a bilateral response in the hippocampus and temporal and prefrontal cortices (primarily in the left hemisphere. Deja vu experiences are not a sign of a pathological state of the brain, but rather a normal occurrence in everyday life. Familiarity based memory error is the cause of the formation of deja vu experience in healthy individuals. Deja vu occurring in simple partial seizures does not form the same in healthy individuals. Hippocampus and parahippocampal gyrus are structures directly connected in the formation of new memories which play a vital role in the process of recognition of scenes and places. Deja vu can be divided into two forms: the first one occurs in healthy

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people and the second is linked to various psychiatric and neurological conditions and they differ in the frequency and length of the experience, where longer deja vu suggests illness. Deja vu defines erroneous familiarity and deja vecu refers to erroneous recollection (Ilman et al, 2016).

Deja vu experience is a product of false activation of connections between mesiotemporal memory structures and neocortical areas directly involved in the perception of the environment by a mechanism responsible for memory consolidation at its peak during sleep (Spatt 2002).

With the help of intracranial EEG monitoring, three theories for dysfunctions have been proposed: dysfunction in the medial temporal lobe of the non-dominant hemisphere, the superior lateral temporal cortex, and neuronal network that engages both medial and lateral parts of the temporal lobe. (Panayiotopoulos, 2012).

Deja vu can be a part of a secondarily generalized seizure or equivalent to a simple partial seizure followed by feelings of fear. (Vlasov, 2013).

Cortical spreading depression (CSD), defined as a wave of electrophysiological activity that originates strictly in the occipital region, has shown deja vu symptoms in the sufferers of chronic migraines. (Petrusic 2014) and in patients that suffer from a vestibular disease in correlation with depersonalization and derealisation symptoms. (Jauregui-Renaud, 2008).

Deja vu can indicate many pathophysiological states of the brain, such as temporal lobe epilepsy and migraine. Paranormal beliefs (PB) in telepathy, witchcraft, and precognition are common in the general population (Schetsche, 2018).

The biopsychosocial approach considers individuals as active subjects comprised of material, cognitive, emotional, and relational resources. It has already been shown that irrational beliefs about health were significant predictors of adherence to rehabilitative care in persons affected by cardiovascular diseases and diabetes (Anderson, 2014). It is important to understand the role of illusory beliefs about health even in the diagnostic and therapeutic process, and their eventual impact on the outcome, such as adherence to medical prescriptions and the duration and the result of the treatment (Capone, 2016).

Persons who believe in the paranormal have a higher tendency for an external locus of control (Newby, 2004).

In contrast, according to the Cognitive Adaptation Theory, the tendency to develop illusory beliefs is found just in those persons who, in a way, give up on seeking an explanation for threatening circumstances or experiences that are otherwise difficult for them to explain—such as being afflicted by an illness—in terms of, for example, the conviction of being able to personally control the course of the illness, or the treatment. Persons having high levels of illusory beliefs present low levels of self-efficacy. Absence of a sense of self-efficacy makes paranormal beliefs very comforting to deal with triggered anxiety. The relationship between the paranormal and health has been accepted in terms of self-serving illusions or illusory beliefs that are certainly false but allow a fundamental function for mental health. Some types of beliefs, such as religious and fatalistic, may inhibit health care utilization and health care behaviors, leading to poor health outcomes (Franklin, 2007).

Paranormal Health Beliefs Scale (PHBS) has been developed to investigate adolescents' adherence to the system of paranormal beliefs about health. The scale consists of 31 items that are distributed in five related dimensions: Religious Beliefs (RB) ($\alpha = .90$), Superstitious Beliefs (SB) ($\alpha = .83$), Extraordinary Events Beliefs (EEB) ($\alpha = .79$), Parapsychological Beliefs (PsiB) ($\alpha = .73$), and Pseudo-scientific Beliefs of a biomedical nature (MedB) ($\alpha = .67$). (Utinans, 2015).

Cognitive-perceptual characteristics connected to positive schizotypy (i.e., magical ideation, odd beliefs, unusual experiences, and referential thinking) incline individuals toward unusual beliefs. Studies report a link between referential thinking, the tendency to find self-relevant meaning within random events, and belief in the paranormal. Belief in the paranormal arises from an individual's attempts to structure the world in person-centered and magical causality. Anomalous beliefs are associated with intuitive-experiential thinking (processing style) and the failure to appraise evidence, experiences, and thoughts to critical analytical-rational processing. Thinking style varies as a function of belief type. (King, 2009).

Lucid dreaming is a dissociated state, which combines aspects of waking and dreaming. Specifically, it denotes conscious awareness of the lucid state of the dream periods using pre-agreed eye-movement signals. Concomitantly, lucid dreaming possesses consciousness-related features such as access to waking memories, increased insight and control, positive affect, body dissociation, and logical thought. Other criteria used to distinguish lucid dreams are the memory of the waking state, sentence of freedom of decision, and full intellectual abilities. (Baird, 2019).

The development of physiological measurement and enhanced understanding of rapid eye movement (REM) sleep enabled researchers to produce empirical evidence for lucid dreaming to develop an objective measurement technique. Noting individual differences in prevalence and frequency, much research has focused on identifying the psychological variables that facilitate lucid dreaming. The Big Five personality factors (openness to experience, conscientiousness, neuroticism, extraversion, and agreeableness) explain a small but substantial portion of the variation.

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Specifically, openness to experience positively predicted lucid dreaming frequency, whereas agreeableness correlated negatively. Furthermore, controlling for nightmare frequency eliminated the relationship between neuroticism and lucid dreaming frequency. The openness findings reported small significant relationships between lucid dreaming frequency, openness to experience, associated dimensions (thin boundaries, absorption, imagination), and openness facets of fantasy, aesthetics, and feelings. (Hess, 2017).

Spontaneous paranormal experiences are associated with openness and exploration of psychological space. Internal sensitivity predicts propensity to psi experiences. These factors explain the relationship between paranormal experience and lucid dreaming. ESP phenomena are a more "modern" form of paranormal belief in line with the current worldviews, compared to more traditional forms of superstitious beliefs or religious beliefs. Irrational beliefs are often used as an umbrella term that comprises a variety of psychological constructs: from specific cognitive biases to a wider class of epistemologically suspect beliefs (superstitions, paranormal and pseudoscientific beliefs, conspiracy theories, etc.) or cognitive styles (analytical versus intuitive thinking), but also unsubstantiated self-related beliefs. Experimental parapsychology uses accepted scientific methods to study alleged anomalous phenomena such as telepathy, clairvoyance, precognition, and psychokinesis. (Alcock, 2017)

Precognition, which is the ability to obtain information about a future event before the event actually occurs, brings into question the notion of free will alongside with notion of cause and effect. Exceptional experiences (EE) are experiences that deviate from ordinary experiences, for example, precognition, supernatural appearances, or déjà vues. Most people have EE at least once in their life like hearing the voices of dead loved ones, precognition, supernatural appearances, or déjà vues. Despite the high frequency of EE in the general population (prevalence of EE is estimated to be 30%-75%), little is known about their effect on mental health and about the way people cope with EE, which causes subjective suffering with a high negative valence, and magical ideation (MI) conceptually close to psychosis. Successfully coped EE adds improves psychological health. (Schetsche, 2005).

Much of parapsychology research is concerned with proving that psi is real *Precognition* is defined as a perception or behavior (not a physiological measure) that is influenced by future events. Non-ordinary mental expressions called *psi*. are associated with altered states of consciousness and potential specific interactions between mind and reality that are currently not explained by known physical or biological mechanisms the *psi hypothesis*, states that anomalous experiences are simply forms of interactions falling outside currently known biological and physical mechanisms if psi-related processes are present in the brain, even unconsciously, they should be observable using functional neuroimaging.

Three general categories of factors that could oppose or suppress psi effects are:

1. Human motivations: Inconsistent psi effects are attributed to unconscious processes. The most frequently discussed motivation that could inhibit psi is fear of psi. The strongest opposition to psi may derive from genetically-based personality characteristics.
2. A mechanistic property of nature
3. Higher consciousness

Extrasensory perception (ESP) refers to information that is perceived outside of the five senses.

This includes phenomena such as telepathy, clairvoyance, and knowledge of future events.

Telepathy refers to communication outside of the known senses.

Brain-to-brain communication via the Internet is possible.

Animal "telepathy":

The biological predisposition to transfer thoughts is not limited to human beings.

When flocks of birds turn seemingly automatically or wheel together, this quick inference from all birds at the same time is thought to be similar to telepathy.

Telepathy has two abilities of categories:

1. Telepathic communication: ability to transmit information from one mind to another
2. Telepathic perception: the ability to receive information from another mind knowing an opponent's moves and attacks.

Telepathy is an umbrella term for any ability that involves projecting, reading, and manipulating thoughts.

Basic level:

Mind Reading/thought detection: ability to read /sense the thoughts of others,

Visual Mind reading: to see the thoughts of others

Memory reading: read the target's memories

Psychic communication: open up secret conversations and relay covert information

Empathy: interpret the emotions of others

Telepathy: communicate through emotions.

Telepathic speaking: speak using only the mind

Advanced Level

Binding: Restrict the Movements of Others Via the Mind

Download: Quickly process, store or download information through another's mind

Dream walking: enter in people's dream

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Emotion manipulation: make one pleased, happy, pained, or any other emotion
Knowledge Projection: project knowledge into another mind

Telepathic Language Instruction: teach languages telepathically

Knowledge replication: replicate the learned knowledge and skills of others

Mental hallucination: cause mental hallucinations

Telepathic Invisibility: become invisible via telepathy

Mental Inducement: temporarily push the target's mind into the wanted state.
Mind control. manipulate the minds of others via the thought process

Mind Image: project one's image to the mind of other
Mind link: develop a permanent mental bond with any person, also called imprinting

Mind Melding: fuse one's consciousness with another

Mind walking: enter the mind of other

Omnilingualism: intuitively understand all languages

Telepathic translation: translate all languages

Psionic inundation: launch psi-bolts to cause mental damage

Neurocognitive deficit: shut down an opponent's higher brain function

Telepathic Static: project telepathic static

Psychic İnhibitors: place inhibitors in mind to limit the target's capabilities

Psychic Navigation: create a mental map of the area

Psychic shadow: mask psychic presence, hiding from other psychics

Psychic shield: erect a psychic shield to protect the minds of oneself and/or others

Psychic torture: torture victims mentally

Pushing: implant memories, thoughts, and emotions into others

Sensory Scrying: perceive through the senses of other beings

Speaking inducement: make others say whatever one wants

Telepathic aura: project telepathic field

Telepathic Hijacking: hijack telepathic communication

Telepathic language Instruction: project language information to others to communicate

Telepathic prediction: know an opponent's moves and attacks by reading the brain waves

Telepathic relay: act as a mental relay station for a group of minds, allowing minds to speak to one another through the user

Thought Manifestation: make one's thoughts visible to all

Thought Manipulation: control the thoughts of others

Master Level

Clairtelepathy detect mental resonances from other locations and times

Consciousness transferal: transfer one's mind to a new body

Darkside view: communicate with and bring out the dark side of a person's personality

Lightside view: communicate with and bring out the good side of a person's personality

Memory manipulation: erase, restore and alter the target's memory

Mental manipulation: manipulate the functions of the mind.

Mind exchange: transfer one's mind into another's body, taking control of that body

Possession: project one's mind into the body of a living being to inhabit and control them

Projective Omnilingualism: emit a field that translates every spoken language

Psychic Energy Manipulation. produce and manipulate mental energy

Psychic constructs: generate constructs out of mental energy

Psychic wave manipulation generate and manipulate thought waves

Psychosomatic Illusion: create powerful illusions that may cause severe physical damage

Remote telepathy: use telepathy from a long-range

Subconscious manipulation: manipulate the subconscious

Subliminal messaging: implant thoughts/ideas into the subconscious

Telepathic surgery: Perform neuropsychic surgery, healing and/or damaging the mind

Telepathic dilation: the power of water down the abilities of others by blocking neurological signals.

Ultimate Level

Cosmic empathy: interpret the emotions of billions or more subjects at once

Cosmic telepathy: read the thoughts of billions or more subjects at once

Mental projection: project thoughts into reality

Neural jumpstart: the power to augment another's abilities by accelerating neuronal activity

Mindscape transportation: transport physical matter into one's conscious or subconscious thoughts

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Absolute Level

Mindscape Materialization: the ability to will one's thoughts and their inner world into reality

Omni-empathy: the ability to sense and feel an infinite number of emotions across all universes, planes, and dimensions

Omni-telepathy: ability to read, sense, communicate with, and control an infinite number of minds across all universes, planes, and dimensions

Unmind: ability to be connected with all things and their essences

Techniques

Telepathic combat: use telepathy in physical combat

Telepathic intelligence. ability to heighten ones intelligence using telepathy (Telepathy)

Hypotheses: Based on the preliminary research, the following hypotheses would be fair:

1. Our brains are wired to pick up subtle social cues;
2. Our brains are wired and automatically reflect intentions and emotions in the presence of others;
3. For our brains to connect across large distances, we have to be dialed into such frequency that is comparable to that of an Internet connection;
4. If people have the capacity for telepathy, some people may be more capable than others, and
5. The hippocampal and parahippocampal brain regions may be involved in telepathic communication since they are involved in integrating memories and subtle aspects of language communication (sarcasm);
6. ESP could depend on fast inference, which requires more openness to another, as implied by the oxytocin study.

One of the earliest records of a witch is in the Bible in the book of 1 Samuel, thought to be written between 931 B.C. and 721 B.C. It tells the story of King Saul seeking the Witch of Endor to summon the dead prophet Samuel's spirit to defeat the Philistine army. The witch roused Samuel, who then prophesied the death of Saul and his sons. The next day, Saul's sons died in battle, and Saul committed suicide. Other Old Testament verses condemn witches, such as the oft-cited Exodus 22:18, which says, "thou shalt not suffer a witch to live." Additional Biblical passages caution against divination, chanting, or using witches to contact the dead.

Witch hysteria really took hold in Europe during the mid-1400s, when many witches confessed, often under torture, to a variety of wicked behaviors and executed by burning at the stake or hanging. Single women, widows, and other women on the margins of society were especially targeted. Between the years 1500 and 1660, up to 80,000 suspected witches were put to death in Europe. Around 80 percent of them were women thought to be in cahoots with the Devil and filled with lust. Germany had the highest witchcraft execution rate, while Ireland had the lowest.

When witchcraft is practiced as a religion, it is called by the Old English term for witch, Wicca. This term is used to counter all the negative stereotypes that society assigned to witchcraft. Wicca is primarily a religion that worships nature and sees all creation as sacred. In fact, all Wiccan holy days follow the cycles of nature and the changes in the seasons. Wicca also worships both a male and female deity, a female Goddess and a male God, who created the world and everything in it. In addition to spells, series of rituals and prayers were conducted by Wiccans in witchcraft to ask for divine help in a certain aspect of life. All spells must adhere to the Wiccan Rede, the witchcraft code of conduct, meaning that any spells used to manipulate, dominate, or control another person is forbidden. In witchcraft, spells may also be changed or adapted to suit a Wiccan's personality or specific wishes in casting the spell. On this site, there is a range of free spells to practice at home. The Wiccan Rede is the rule of conduct that all witches must follow while practicing witchcraft. It rules that a witch may engage in any action, as long as it is carefully considered, and her actions harm nobody, including themselves. Witchcraft is ruled by the Threefold Law, which is the belief that any action taken by any witch that affects another person, will come back to the witch threefold, whether it be harmful or good.

Clairvoyance: The term clairvoyance (from French " Clair" meaning "clear" and " voyance" meaning "vision") refers to the ability to gain direct visual telepathic information about an object, person, location or physical event through non-physical sense other than the known human senses... Is clairvoyance innate, or can it be developed through various psychic development exercises, meditation, or yoga? Clairvoyance today falls under the heading of pseudoscience or Paranormal Psychology. There have been anecdotal reports of clairvoyance and 'clear' abilities throughout history in different cultures and clairvoyance has been associated with religious or shamanic figures, offices, and practices. For example, ancient Hindu religious texts list clairvoyance amongst other forms of 'clear' experiencing, as siddhis, or 'perfections', skills that are yielded through appropriate meditation and personal discipline.

The earliest record of somnambulistic clairvoyance is credited to the Marquis de Puysegur, a follower of Franz Mesmer, who in 1784 was treating a local dull-witted peasant named Victor Race. During treatment, Race reportedly would go into trance and undergo a personality change, becoming fluent and articulate, and giving diagnosis and prescription for his own disease as well as those of others. When he came

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out of the trance state he would be unaware of anything he had said or done. It is reported that although Puysegur used the term 'clairvoyance', he did not think of these phenomena as "paranormal", since he accepted mesmerism as one of the natural sciences.

Clairvoyance has been reported as the ability of some mediums during the spiritualist period of the late 19th and early 20th centuries, and psychics of many descriptions have claimed clairvoyant ability up to the present day. Early researchers of clairvoyance included William Gregory (chemist), Gustav Pagenstecher, and Rudolf Tischner. These were largely qualitative experiments in which selected participants sought to identify a concealed target image or to provide accurate information about the history of a target object.

A significant development in clairvoyance research came when J. B. Rhine, a psychologist at Duke University, introduced a standard methodology, with a standard statistical approach to analyze the data, as part of his research into extrasensory perception. (Clairvoyance)

Paranormal beliefs are associated with mental disorders such as schizophrenia and personality traits such as neuroticism and schizotypy, which refers to a set of tendencies to have psychotic-like experiences. Paranormal beliefs are associated with developmental instability, and therefore with mutation load. Those who have fearful attitudes to the paranormal tend to find anomalous experiences emotionally disturbing. Certain psychotic symptoms such as hallucinations and thought insertion can occur in non-disturbed individuals, so having odd beliefs and experiences is not in itself an indicator of mental illness. What seems to differentiate clinically disturbed by healthy individuals is that the former have more negative responses to anomalous experiences. When disturbed individuals have what appear to be “psychic” experiences (regardless of whether these are real), they tend to respond with negative emotions such as fear, whereas well-adapted individuals tend to regard these experiences more positively. There is evidence that both schizotypy and paranormal beliefs are associated with artistic creativity and mystical experience. It is more likely to to be a mixture of adaptive and maladaptive traits rather than a pure aberration, as it is highly socially valued. (Schofield, 2007).

People with paranormal beliefs who interpret unusual experiences in a positive and meaningful way may have better mental health than those with similar beliefs but a more negative attitude to them. Hence, the presence of paranormal beliefs is not necessarily either adaptive or maladaptive, and therefore not necessarily evidence of harmful mutations.

Certain psychotic symptoms such as hallucinations and thought insertion can occur in non-disturbed individuals, so having odd beliefs and experiences is not in itself an indicator of mental illness. What seems to differentiate clinically disturbed by healthy individuals is that the former have more negative responses to anomalous experiences. When disturbed individuals have what appear to be “psychic” experiences (regardless of whether these are real), they tend to respond with negative emotions such as fear, whereas well-adapted individuals tend to regard these experiences more positively.

The linkage of brain structure with transformational experience has been via four important brain areas:

1. the limbic system, which generates and modulates emotions,
2. the sensory areas (e.g., hearing and vision)
3. the orientation association area in the posterior superior parietal lobe, where the self-world and self-other identity distinction is made,
4. the attention association area in the prefrontal cortex is important in intention, will, and modulation of emotion.

Visual imagery occurs when perceptual information is accessed from memory. Endogenous DMT (N, N-dimethyltryptamine) is described as the source of visionary Light in transpersonal experiences. Its primary source, the pineal, has traditionally been referred to as the Third Eye. DMT production is particularly stimulated, in the extraordinary conditions of birth, sexual ecstasy, childbirth, extreme physical stress, near-death, and death, as well as meditation. Pineal DMT also plays a significant role in dream consciousness. (Gallimore, 2016)

Psi is defined as a means by which information can be obtained from a distance without the use of the ordinary senses, and encompasses a broad range of experiences including putative telepathy (mind–mind connections), clairvoyance (perceiving distant objects or events), and precognition (perceiving future events). Psi also includes mind-matter interactions (psychokinesis), which is the ability to influence external matter without the use of any known physical mechanism. Neuroanatomical regions postulated to have a role in mediating psi include the reticular formation, right parieto-occipital areas, and occipital region, primarily on the right. The frontal lobes act as a filter to inhibit psi and that the neuro-psychological mechanisms mediating this inhibition include self-awareness. The concept of self-awareness being involved in the mechanisms mediating the brain’s inhibition of psi may explain the mind-matter interaction effects. (Freedman, 2018)

Much research has focused on the role of a magnetic field in affecting human performance as well as Psi performance. Some further investigations have discovered that geomagnetic activity also affects people’s memory retrieval and complex perception, such as presences, fears, and odd smells. (Booth, 2005).

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A group of monkeys, who lived on a Japanese island, had acquired the ability to wash sweet potatoes before eating them. It was discovered earlier, that another group of monkeys living on another island had acquired the same technique. The two groups were obviously not in physical contact but the information, according to the theory of morphic fields, had traveled non-locally and synchronously reaching other members of the same species. (More likely, it is just parallel evolution).

In the quantum realm, Wolfgang Pauli discovered that the ultimate laws of nature are not subject to the principle of causality - they are nothing more than a mandala of shapes that synchronize matter and interconnect it in all its parts – in the psychological and cognitive realm. The synchronism between the mental state of an individual and an event in the world of the matter showed that in addition to the known laws of physics, others are still not known well. In light of the discoveries of modern physics, everything really seems connected.

The neurosurgeon Karl Pribram has endorsed the Bohmian theory of the holographic nature of reality by numerous studies with rats. Despite several subsequent removals of parts of their brain, the rats continued to preserve memories. Following the results of these experiments, it was impossible to admit a localized existence. The same human ability to draw instantly on any memory, between billions and billions of pieces of information confirms the non-localization of memories, and therefore the non-classifiable nature of time. The process of life is intimately connected with the process of the observer who looks at reality. A bio-systems' proper psyche can interact as an «observer» with the observed in a fully conscious way. (Giuliodori, 2014).

The human being has potential for some parapsychological faculties that are still not explained scientifically. Therefore they are considered magic or miracles realized by selected and special people. In reality, every human being may manifest some supernatural powers by some rituals. Performing a miracle or psi experience should not raise anyone to a divine status. A saint is no different from a sincere and unhypocritical human being, regardless of gender, who is full of love. With scientific progress, more and more events considered miracles will be explained by logical shreds of evidence.

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Evaluation of Autism Diagnostic Tools among Young Children: A Systematic Review

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Abstract- Autism is a physical and mental condition that cause significant social, communication, and behavioral challenges. There is often nothing about how people with Autism Spectrum Disorder (ASD) look that sets them apart from other people. Still, people with ASD may communicate, interact, behave, and learn in ways that are different from most other people. The learning, thinking, and problem-solving abilities of people with ASD can range from gifted to severely challenged. Early diagnostic of ASD is very essential because delay detection may cause an increase in severity level. Autism diagnostic tools can play a significant role in the early detection of ASD. There are several diagnostics tools for ASD detection. The main objective of this study was to evaluate autism diagnostic tools among the children and find out the diagnostic outcome of early detection of ASD by systematic review. Some authentic databases like PUBMED, Google Scholar, Scopus were searched using keywords of relevant topics, and a protocol was developed with defined inclusion and exclusion criteria.

Keywords: *Autism Spectrum Disorder (ASD), ADI-R, CARS, GARS-2, ASD diagnostic tools.*

GJMR-A Classification: *NLMC Code: QS 681*



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Evaluation of Autism Diagnostic Tools among Young Children: A Systematic Review

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Abstract- Autism is a physical and mental condition that cause significant social, communication, and behavioral challenges. There is often nothing about how people with Autism Spectrum Disorder (ASD) look that sets them apart from other people. Still, people with ASD may communicate, interact, behave, and learn in ways that are different from most other people. The learning, thinking, and problem-solving abilities of people with ASD can range from gifted to severely challenged. Early diagnostic of ASD is very essential because delay detection may cause an increase in severity level. Autism diagnostic tools can play a significant role in the early detection of ASD. There are several diagnostics tools for ASD detection. The main objective of this study was to evaluate autism diagnostic tools among the children and find out the diagnostic outcome of early detection of ASD by systematic review. Some authentic databases like PUBMED, Google Scholar, Scopus were searched using keywords of relevant topics, and a protocol was developed with defined inclusion and exclusion criteria. The published study article abstracts were downloaded and screened according to PRISMA criteria. After checking the homogeneity of data, the relevant sources and contents were included, and irrelevant contents were excluded for the study. We have finally considered 40 published article for our study.

After an in-depth study, we found all three diagnostics tools have significantly able to detect ASD. ADI-Ris used in maximum case but effectiveness is slightly low compare to CARS and GARS-2. Geographical and ethnographic socio-cultural differences may cause different impacts on the performance of the ASD diagnostic tools. There is also a scope of improvement of ASD diagnostic tools as per geographical ethnographic, and genetic differences of children.

Keywords: Autism Spectrum Disorder (ASD), ADI-R, CARS, GARS-2, ASD diagnostic tools.

I. Introduction

Autism is a complex condition that affects normal speech and functional behavior. It usually presents with a wide variety of experiences and skills. Autism or Autism Spectrum Disorder (ASD) can be a mild to a moderate issue that doesn't necessarily need the full-time treatment of a special facility. Learning, thinking, and problem-solving can vary greatly from one person with autism to another. Some people with ASD need more assistance than others, depending on the severity of their needs (CDC, 2020).

Diagnosing autism is daunting because there is no medical examination, including a blood test, to detect ASD. Doctors evaluate a child's history and behavior to make a diagnosis. The early diagnosis of children with ASD allows for the initiation of therapies that can enhance social and everyday life skills, resulting in a higher quality of life (Jennifer Harrison Elder, 2017). The American Academy of Pediatrics (AAP) recommends that children be tested for developmental delays at any health checkup. Screening detects developmental delays as early as 18 months of age (Sarabeth Broder-Fingert, 141).

Despite the agreement that ASD diagnoses occur more often today, researchers continue to question if the explanation is because of the rise in cases or a more precise diagnosis, or perhaps both. Regardless, one cannot ignore the fact that ASD is a prevalent disorder, with 1 in 68 children being diagnosed with some sort of ASD (Centers for Disease Control and Prevention, 2020).

Therefore, the clinician's appraisals of the symptoms of ASD remains the current norm for

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diagnosis. In 2013 the Diagnostic and Statistical Manual of Mental Disorders was updated to include two main ASD symptoms: chronic social and communication difficulties and an unusual preoccupation with certain habits and interests (American Psychiatric Association, 2013). Additionally, ASD severity has now become part of the diagnostic process, which shows the severity of the patient's symptoms. Research into ASD rejects conventional conceptualizations of ASD as a discrete entity and thus promotes ASD as a spectrum. The validity of objective tests of ASD has been shown across many cultures (Constantino, 2011). The study is now being conducted to promote the use of standardized, percentile-based definitions of ASD symptom manifestation. These percentile-based approaches have proven useful in characterizing other observable health disorders, such as anorexia nervosa and hypertension. At present, specialist professional judgment is needed to signal that someone has severe deficiency to the key symptom areas of ASD.

There are several methods to diagnose autism in a child, but none is to be used specifically. Diagnostic systems use sources from both the parents and guardians of the children, and a professional's evaluation of the children's conduct. Under certain cases, the primary care provider might offer further examination or therapy for a child and family if appropriate. Such advanced medicine encompasses pediatric neurologists, geneticists, developmental-behavioral pediatricians, and early intervention programs that offer assessment services (CDC, 2020).

CDC suggested four Diagnosis tools of Autism Spectrum Disorder for Healthcare Providers:

- Autism Diagnosis Interview-Revised(ADI-R)
- Childhood Autism Rating Scale (CARS)
- Gilliam Autism Rating Scale– Second Edition (GARS-2)
- Autism Diagnostic Observation Schedule–Genericexternal icon (ADOS-G)

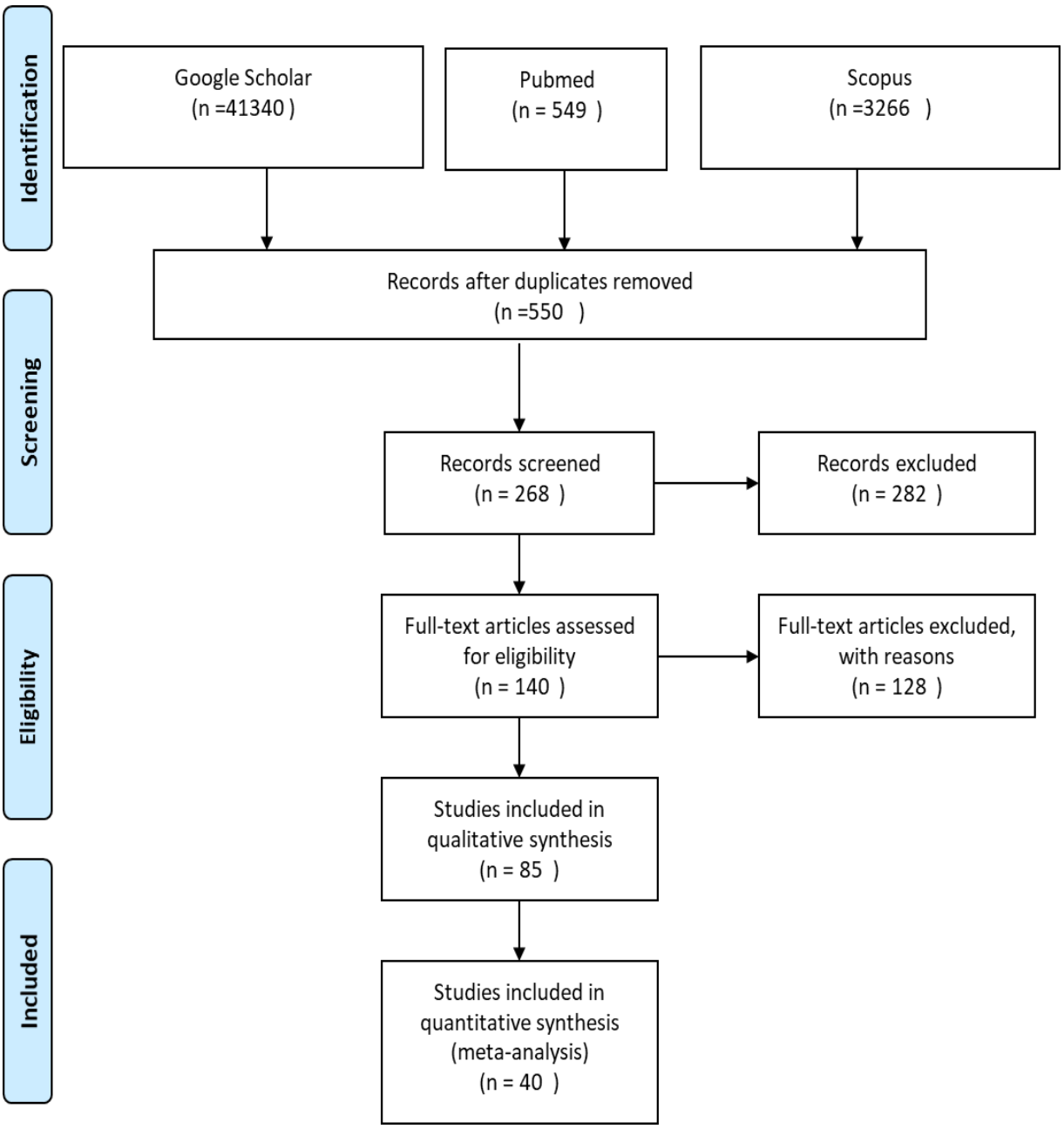
II. Objective of the Study

The main objective of this study was to evaluate autism diagnostic tools among the children and assess the diagnostic performance of early detection of ASD by systematic review.

III. Methodology

A state-of-the-art science review was performed, as stated by Grant and Booth, to provide broad and up-to-date information related to the early diagnosis and treatment of ASD. Population, intervention, comparisons, outcome study strategy was used focusing on the evaluation of autism diagnostic tools. A reliable searching database like PUBMED, Google Scholar, Scopus was performed using keywords of a relevant topic. A protocol was developed with defined inclusion and exclusion criteria. The abstracts of publications identified will be screened according to PRISMA criteria. After checking the homogeneity of data, the relevant contents were included, and irrelevant contents were excluded for the study. After screening, all studies finally included 40 studies for our study. The PRISMA model is showing below:

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IV. Results

The table 1 and 2 shows some of the relevant results of three ASD diagnostic tools of selective study:

Table-1: Comparative analysis of autism diagnostic tools

Study	Study Type	Method of study	No of ASD Child	Age range (in Year)	P Value	95% Confidence Interval	
						lower	upper
Autism Diagnosis Interview – Revised (ADI-R)							
(Catherine Lord, 2006)	Original Article	Prospective	67	2-9	0.001	1.6	7.3
(Annelies de Bildt, 2015)	Original Article	Prospective observational	1104	1.75-4	0.002	2.1	8.3
(Eric Zander, 2017)	Original Article	Cross sectional	10	2-17	0.001	0.93	5.8

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Childhood Autism Rating Scale (CARS)							
(Colby Chlebowski, 2010)	Original Article	Retro prospective study	606	3.5-5.5	0.001	0.88	4.6
(Alessandra Pereira, 2008)	Original Article	Cross sectional study	60	3-17	0.05	-0.84	0.61
(Tamara Dawkins, 2016)	Original Article	Cross sectional study	183	1-62	0.03	1.2	2.3
Gilliam Autism Rating Scale – Second Edition (GARS-2)							
(Mahboubeh Ghayour, 2018)	Original Article	Case control study	26	2-7	0.001	0.345	1.71
(Martin A. Volker, 2016)	Original Article	Cross Sectional Study	240	3-21	0.001	0.65	1.28
(Linda Sue Jacksona, 2013)	Original Article	Prospective Study	100	4-21	0.02	0.861	1.38

Table-2: Effectiveness of autism diagnostic tools.

Name of diagnostic tools	Number of study review	Effectiveness rate of the tools	Average effectiveness
Autism Diagnosis Interview – Revised (ADI-R)	13	96.5%	97.166%
Childhood Autism Rating Scale (CARS)	14	98%	
Gilliam Autism Rating Scale – Second Edition (GARS-2)	13	97%	
Total Study	40		

Note: We just evaluating top three of the ASD diagnostic tools.

V. Discussion

We considered the four ASD diagnostic tools for discussion here:

a) Autism Diagnosis Interview-Revised (ADI-R)

The ADI-R is a formal interview with the parents of children referred for the diagnosis of potential autism or autism spectrum disorders. An interview with someone with a mental age of at least 24 months and assessing actions in the fields of mutual social interaction, communication and language may be used for diagnostic purposes. A method for diagnosing autism in adults and infants. The instrument assesses actions in three categories: social interaction; communication, and language; and thoughts and desires that are limited and repetitive. One study stated, early childhood ASD and lower language capacity were in the mild-to-moderate range of the ADI-R. Almost half of the older and phrase expression ASD-group fell into the little-to-no concern range (Annelies de Bildt S. S., 2004).

b) Childhood Autism Rating Scale (CARS)

A quick and simple evaluation can be used on any child from 2 years old. The CARS assessment assesses five classification systems for autism and lists the symptoms, skills, and behaviors covered. One frequently used scale for measuring gains achieved in the treatment of autism is the Childhood Autism Assessment Scale (Eric Schopler, 1980). To evaluate symptoms consistent with autism, the CARS evaluates 14 domains, while the 15th domain rates general experiences of autism. Each domain is rated on a scale of one to four; higher scores suggest more difficulty. Scores will vary from 15 and 60; scores below 30 mean that the child is in the non-autistic range, scores between 30 and 36.5 indicate mild to moderate autism, and scores from 37 to 60 indicate extreme autism. The CARS highlights good alignment between DSM-IV criteria and signs of Asperger Syndrome. In a survey of 274 children at preschool (Adrienne Perry, 2005). a strong concordance rate of 88 percent was found between classifications made using the CARS and DSM-IV criteria. An analysis of 54 children diagnosed with autism disability found that the CARS-A and DSM-IV criteria were strongly comparable.

c) Gilliam Autism Rating Scale – Second Edition (GARS-2)

The guide supports students, caregivers, and physicians in recognizing autism in children aged three to twenty-two. It is useful in estimating how bad a child's condition is. The Gilliam Autism Assessment Scale-Second Edition is a diagnostic test for autism spectrum disorders between 3 and 22 years. It was developed to assist diagnosis for people with a type of autism and help discern those with extreme developmental problems from those usually developing. The GARS-2 was developed as a complementary instrument to

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facilitate the diagnosis of autism, and it is meant to be used in conjunction with other screening approaches.

d) *Autism Diagnostic Observation Schedule – Generic (ADOS-G)*

A diagnostic technique for people accused of developing autism that measures social, communication, play, and creative use of materials. The observational plan includes four 30-minute modules that are structured to be delivered in various ways to different people as appropriate. The Autism Diagnostic Observation Schedule, the new version (ADOS-R) contains revised diagnostic algorithms and standardized severity ratings for tests used to test children under ten. This form of autism is characterized by impairments in social-communication and the occurrence of limited, repeated, and stereotyped activities and interests (Association, 2013). Autism used to be conceived of as a disease that affects children. However, reports of young adults with this type of ASD (autism spectrum disorder) show varying results. One study stated, the observational schedule consists of four 30-minute modules, each designed to be administered to different individuals according to their level of expressive language. Psychometric data are presented for 223 children and adults with Autistic Disorder (autism), Pervasive Developmental Disorder Not Otherwise Specified (PDDNOS), or non-spectrum diagnoses. With each particular module, the groups struggle with the same degree of language expression. These test results show significant interrater and test-retest reliability for individual products, excellent interpreter reliability within the medical situations, and excellent internal consistency among the domains.

VI. Conclusion

In this study, we found that several studies used different types of diagnostic tools. All the tools have significantly able to determine ASD. ADI-R is used in maximum cases, but effectiveness is slightly low compare to CARS and GARS-2. Geographical and ethnographic socio-cultural differences may cause different impacts on the performance of the ASD diagnostic tools. There is also a scope of improvement of ASD diagnostic tools as per geographical ethnographic, and genetic differences of children. Further study is needed worldwide to assess the effectiveness of ASD diagnostic tools.

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Author contribution

I designed, searched literature, and prepared the manuscript for submission. All co-author contributes for searching.

Potential Competing interest

No potential competing interest.

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9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.



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Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.



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Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

The Administration Rules

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Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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