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Chronic Neuromuscular Illnesses

Stress in Different Periods of Ontogeny

Highlights

Screening for Cognitive Dysfunctions

Recovery in Severe Traumatic Brain Injury

Discovering Thoughts, Inventing Future

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Screening for Cognitive Dysfunctions in Patients with Combined Hashish and Tramadol Addiction

By Inara Khayretdinova, Zarifjon Ashurov & Nargiza Yadgarova

Abstract- *Relevance:* A predictor of determining the quality of treatment is the patient's cognitive abilities, which can be a useful screening tool for alerting potential problems during treatment.

Purpose: Screening of cognitive functions in patients with combined addiction to hashish and tramadol.

Materials and methods: 129 male patients divided into 3 groups: group 1 (main) -41% of patients (n=53) with combined abuse of hashish and tramadol. Group 2 (control) - 34% of patients (n=44) with tramadol dependence. Group 3 (control) - 24.8% of patients (n=32) with dependence on cannabinoids. The level of reliability P <0.05 was taken as statistically significant changes.

Results: The average score on the MOCA scale was 21.3±0.79 in patients of group 1, in group 2, 24.52±0.92 (P1-2 <0.01), in group 3, 22.8±0.8 (P1 -3> 0.05). Patients with poly addiction and hashish dependence have violations of all medical processes - fixation, retention, and reproduction. Combined abuse of hashish and tramadol results in a synergy between the two psychoactive substances, which negatively affects cognitive functioning.

Conclusion: The cannabinoid group is a major source of cognitive dysfunction. The MOSA test allows screening to the study of cognitive dysfunctions in general, regardless of individual cognitive domains, and to select the tactics of personalized drug and psychotherapeutic therapy.

Keywords: *screening, MOSA test, cognitive dysfunction, poly addiction, combined addiction, hashish, tramadol.*

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Keywords: screening, MOSA test, cognitive dysfunction, poly addiction, combined addiction, hashish, tramadol.

I. Introduction

One of the consequences under the scrutiny of researchers is cognitive dysfunction in drug addiction. Abnormal brain function in people with addiction predisposes them to make decisions with disastrous consequences for their health and well-being, and the well-being of their families and communities [1]. Many authors point out that there is an extensive literature supporting the hypothesis that long-term drug exposure leads to certain cognitive impairments [2,3,4,5]. Among drug users, the prevalence of cognitive impairment ranges from 30 to 80% [6].

Areas of the brain and processes underlying addiction overlap significantly with areas involved in basic cognitive functions [7]. Anatomically, there is an important overlap between learning and memory neural substrates and addictions. Some of the areas that show overlap include the cerebral cortex, hippocampus, amygdala, and striatum, all of which are components of the mesolimbic dopaminergic system [8]. Cognitive dysfunctions are closely associated with a strong pathological craving for the drug, with its ideational and affective components being especially pronounced. The intensity of changes in the ideational component is confirmed, along with impairments in the cognitive sphere, impaired nosognosias in most patients in the post-withdrawal period [9]. A similar reflection was found in the article by Copersino M. L. and Wiers R. W. that cognitive impairment affects addictive behavior [10,11].

Yaltonsky V.M. "The combination of legal and illegal surfactants is manifested by high neurotoxicity, which is considered as one of the main causes of neurodegenerative disorders in chemical addictions and is accompanied by neurocognitive deficits" [12].

Many authors come to the conclusion that it is the cannabinoid group that is the main source of cognitive dysfunctions in combined abuse with tramadol [13,14], which depend on the age of onset, duration, amount, and frequency of abuse [15,16,17]. Tursunkhojaeva L.A., and Rustamova J.T. in a comparative assessment of memory functions in patients with opium-hashish poly-drug addiction and opium mono-addiction, we concluded that all amnestic processes are disturbed during poly-drug addiction [18].

Cognitive impairment is a predictor of poor treatment outcome [19,20]. Cognitive dysfunction also harms treatment processes such as motivation for treatment, willingness to change, readiness for treatment, and the rehabilitation period [21]. The preservation of cognitive functions in drug addicts can reduce the risk of relapse and improve the effectiveness of rehabilitation [22]. Predictors of low treatment success and a high likelihood of relapse are memory impairments, a low level of abstraction, low psychomotor speed and impaired visual-spatial synthesis, impaired inhibition processes, and working memory [23,24]. The patient's cognitive ability is a predictor of quality of treatment outcome, which can be a useful screening tool for alerting potential problems that may arise during treatment [25,26,27]. Repeated drug use in the face of negative consequences indicates dysfunction of the cognitive mechanisms underlying decision-making. The deficit in decision making is most

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likely due to both premorbid factors and effects caused by psychoactive substances, which in the long term is associated with a high risk of relapse [28.29].

Purpose: A neuropsychological study of cognitive functions in patients with combined dependence on hashish and tramadol.

II. Materials and Research Methods

Following the goal of the study, 129 male patients were selected who underwent inpatient treatment for drug addiction in the Republican Narcological Center from 2015 to 2019. All patients are male. The patients were divided into 3 groups: group 1 (main group) - 41% of patients (n=53) with combined abuse of hashish and tramadol. For comparison, patients with opium and hashish monar addiction who were not complicated by dependence on other types of psychoactive substances were selected. 2- group (control group) -34% of patients (n=44) with dependence on opioids, abuse tramadol without a doctor's prescription to achieve euphoria, who did not use other opioids before taking tramadol. Group 3 (control group) - 24.8% of patients (n=32) with dependence on cannabinoids.

A neuropsychological study was carried out using two approaches: 1. a cognitive screening tool to distinguish between patients in the main and control groups. For the study of memory: a method of memorizing 10 words according to AR Luria, [30,31] words that are not related to each other, neutral in logic and emotional color. A set of words is presented 5 times so that the patient can fully remember them and can reproduce them in any sequence. 2. A battery of tests to determine the relationship between disease and cognitive dysfunction - Montreal Cognitive Assessment Scale (MoCA test) [32,33]. The MoCA test is sensitive to subtle cognitive impairments in a variety of populations and has a wide range of applications, including dependence on psychoactive substances [34], in contrast to MMSE (Mini-mental state examination (MMSE) MF Folstein, PR Folstein (1975), the MOSA test is more sensitive to early detection of cognitive decline. [35] The MOCA test helps to assess: executive functions, optical-spatial activity, memory, attention, speech, conceptual thinking, counting, and orientation. The sensitivity is 90%, the specificity of the method is 87%. The maximum score is 30; the cut-off point is 25/26 points [36,37]. Time for the test is approximately 10 minutes. When concluding, they were not based only on rating scales, we took into account the anamnestic information collected from the patient, as well as, if possible and the consent of the patient and his close relatives, mental status, and our observations.

The data revealed during the study were subjected to statistical processing on a Pentium-IV personal computer using the Microsoft Office Excel-2016 software package, using the built-in statistical processing functions. The level of reliability P <0.05 was taken as statistically significant changes. All patients had informed consent for examination.

III. Results and Discussion

The age of the surveyed ranged from 20 to 45 years. The average age is 30.5±6.16 years. The average age of patients at the time of examination in group 1 was 31.1±7.0 years (median 31.5; minimum age - 20 years, maximum age 45 years), in group 2 - 30.06±6.7 years (median 29.5; minimum age 20 years, maximum age 45 years), in group 3 - 31.6±7.1 (median 32.5; minimum age 22 years, maximum age 44 years.

The result of the study of the level of education, presented in Figure 1, did not reveal statistically significant intergroup differences (P 1-2, P 1-3> 0.05).

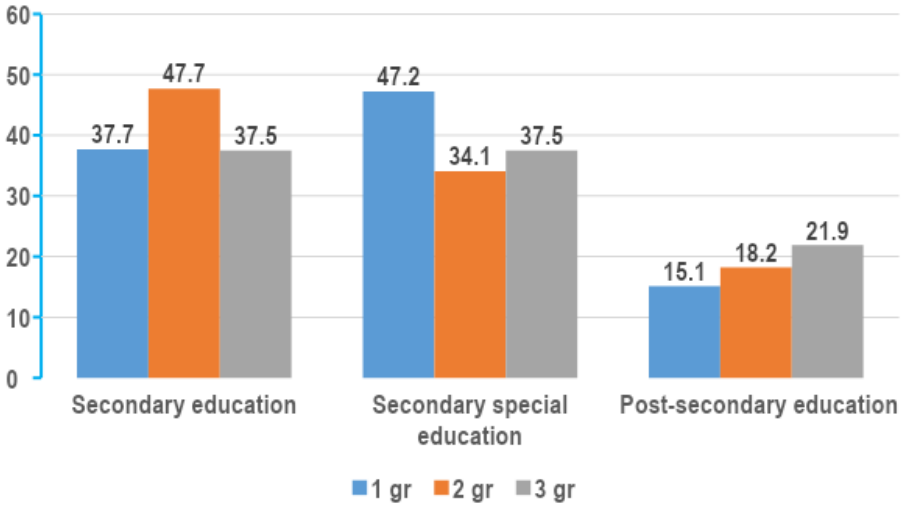

Figure 1: Distribution of respondents by education level in the study groups.

Note: differences relative to data from groups II and III are insignificant (P> 0.05)

Among the patients of the studied groups, cognitive impairments of varying severity were revealed.

The results of the study of memory by the method of memorizing 10 words showed that after the first series, which indicates the volume of auditory short-term memory, a large proportion of patients with combined addiction remembered only 2-4 words: 67.9% of patients in group 1, 11.3% patients in group 2 (P1-2 <0.001) and 53.1% of patients in group 3 (P 1-3> 0.05), in contrast, were able to reproduce 5-7 words in patients with tramadol dependence (32% of patients 1- group, 88.6% of patients in group 2 (P 1-2 <0.001) and 46.8% of patients in group 3 (P 1-3> 0.05).

When examining subjects without memory impairments, by the third repetition they reproduce, correctly, up to 9 or 10 words. Substance-dependent patients gave the following results (Table 1).

Table 1: Distribution of patients according to the results of the number of words after the third attempts

Word count	1st group (n=53)		2nd group (n=44)		3rd group (n=32)		P_{1-2}	P_{1-3}
	abc.	%	abc.	%	abc.	%		
2-4	6	11,3	0	0	3	9,3	<0,05	>0,05
5-7	31	58,4	6	13,6	13	40,6	<0,001	<0,01
8-10	16	30,1	38	86,3	16	50	<0,001	>0,05
Total	53	100	44	100	32	100		

The indicators of the volume of auditory long-term memory, taken after one hour, determined that the vast majority of patients with tramadol dependence could reproduce 8-10 words (18.8% of patients in group 1, 81.8% of patients in group 2 (P1-2 <0.001) and 37.5% of patients in group 3 (P 1-3> 0.05), while in patients with poly addiction there was a regression, the number of patients with memorization of 2-4 words increased again (20.7% of patients in group 1 (P1 -2 <0.001), and 5% of patients group 3 (P 1-3> 0.05).

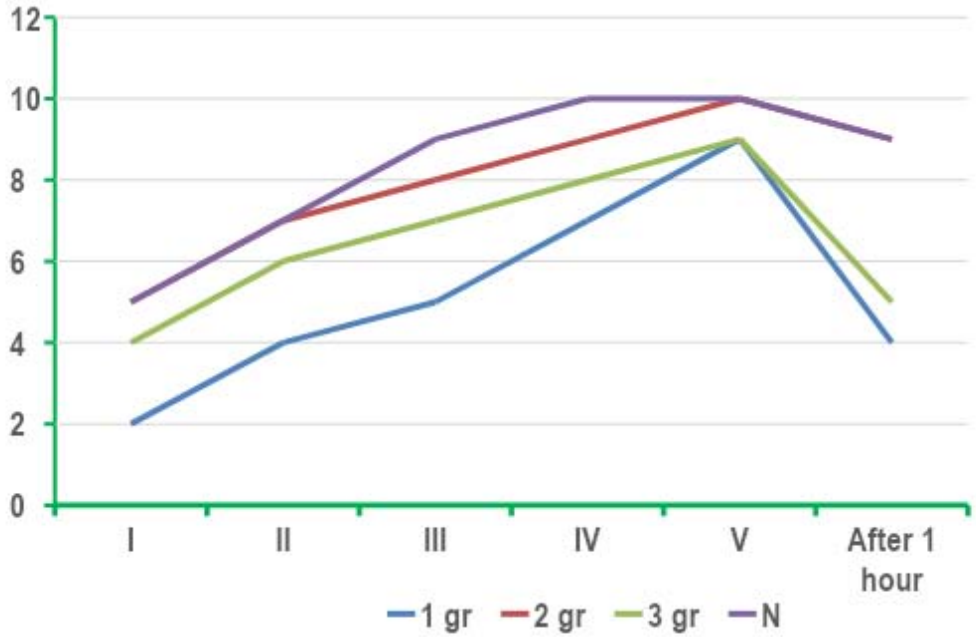

Figure 2: Shows the curves of memorization in the studied groups and in the norm.

Normally, the learning curve is steadily increasing. The curve of patients in groups 1 and 3 reflects violations of all mnestic processes - fixation, retention and reproduction. Their curve with a sharp downward slope indicates a weakening of active attention. Although the curves of patients in groups 1 and 3 are the same, the number of words in the initial and subsequent reproductions is lower with combined dependence on hashish and tramadol than with mono use of hashish. And also patients in group 1 often reproduced words in random order with the aim of not specifically highlighting previously unmentioned words. Having made a mistake, they continued to repeat it in the next tests.

Screening of cognitive function with the MOSA test also revealed intergroup differences. The average

score on the MOSA test was higher among patients in group 2 - 24.5±1.15 (P1-2 <0.01), for patients in group 1 it was 21.4±2.42 and in patients in group 3 - 22.81±1, 09 (P 1-3> 0.05). Table 2 shows the indicators of each domain of the MOCA scale in the subjects.

Table 2: Distribution of patients according to the results of the IOCA test

Indicators	1 Group (n=53)		2Group (n=44)		3 Group (n=32)		P_{1-2}	P_{1-3}
	abc.	%	abc.	abc.	%	abc.		
Draw a broken line:								
wrong	18	34,0	1	2,3	6	18,8	<0,001	>0,05
right	35	66,0	43	97,7	26	81,3	<0,001	>0,05
Optical-spatial activity (cube):								
wrong	25	47,2	14	31,8	12	37,5	>0,05	>0,05
right	28	52,8	30	68,2	20	62,5	>0,05	>0,05
Optical-spatial activity (hours):								
Контур:								
wrong	3	5,7	0	0	2	6,3	>0,05	>0,05
right	50	94,3	44	100	30	93,8	>0,05	>0,05
Numbers:								
wrong	15	28,3	4	9,1	6	18,8	<0,001	>0,05
right	38	71,7	40	90,9	26	81,3	<0,01	>0,05
Arrows								
wrong	20	37,7	9	20,5	10	31,3	>0,05	>0,05
right	33	62,3	35	79,5	22	68,8	>0,05	>0,05
Naming:								
Llion								
wrong	0	0	0	0	0	0		
right	53	100	44	100	32	100		
Rhinoceros								
wrong	16	30,2	16	36,4	16	50,0	>0,05	>0,05
right	37	69,8	28	63,6	16	50,0	>0,05	>0,05
Camel								
wrong	5	9,4	4	9,1	3	9,4	>0,05	>0,05
right	48	90,6	40	90,9	29	90,6	>0,05	>0,05
Attention:								
Direct account								
wrong	21	39,6	16	36,4	12	37,5	>0,05	>0,05
right	32	60,4	28	63,6	20	62,5	>0,05	>0,05
Reverse count								
wrong	7	13,2	8	18,2	6	18,7	>0,05	>0,05
right	46	86,8	36	81,8	26	81,2	>0,05	>0,05
Reaction (clap on the letter A)								
wrong	11	20,8	8	18,2	7	21,9	>0,05	>0,05
right	42	79,2	36	81,8	25	78,2	>0,05	>0,05
Serial account								
1 score	3	5,7	0	0	0	0	>0,05	>0,05
2 score	31	58,5	20	45,5	18	56,2	>0,05	>0,05
3 score	19	35,8	24	54,5	14	43,7	>0,05	>0,05

Repeating a sentence I								
wrong	42	81,1	31	70,5	23	71,8	>0,05	>0,05
right	11	18,9	13	29,5	9	28,1	>0,05	>0,05
Repeating a sentence II								
wrong	35	66	25	56,8	20	62,5	>0,05	>0,05
right	18	34,0	19	43,2	12	37,5	>0,05	>0,05
Fluency of speech:								
wrong	23	44,4	14	31,8	11	34,4	>0,05	>0,05
right	30	56,6	30	68,2	21	65,6	>0,05	>0,05
Abstract thinking:								
1 score	24	45,3	19	43,2	14	43,8	>0,05	>0,05
2 score	29	54,7	25	56,8	18	56,3	>0,05	>0,05
Delayed playback:								
1 score	5	9,4	0	0	0	0	<0,05	>0,05
2 score	15	28,3	0	0	3	9,4	<0,001	<0,05
3 score	25	47,2	7	15,9	11	34,4	<0,001	>0,05
4 score	8	15,1	20	45,5	18	56,3	<0,001	<0,001
5 score	0	0	17	38,6	0	0	<0,001	
Orientation:								
4 score	2	3,8	0	0	0	0	>0.05	>0.05
5 score	28	52,8	20	45,5	15	46,9	>0.05	>0.05
6 score	23	43,4	24	54,5	17	53,1	>0.05	>0.05

Among all patients with addiction to psychoactive substances, more violations were revealed in such parameters as executive skills - drawing a broken line: correct performance was 66% in group 1, 97.7% in group 2 (P1-2 <0.001), 3-group 81.3% (P1-3> 0.05). Any mistake, if corrected by the patient on his own, was counted. When assessing optical-spatial activity (cube): intergroup differences were not revealed (P1-2; P1-3> 0.05); Optical-spatial activity (hours): when drawing the correct contour and the arrangement of arrows, intergroup differences were not revealed (P1-2; P1-3> 0.05); the correct arrangement of numbers - patients in group 1 - 71.7%, group 2 - 90 , 9% (P1-2 <0.01), 3 groups 81.3% (P1-3> 0.05). Delayed reproduction (score is assigned 1 point for each named word without any prompts): 1 point was received only by patients of group 1, 9.4% (P1-2; P1-3 <0.05); 2 points - patients in group 1 - 28.3%, group 2 did not receive (P 1-2 <0.001), group 3 - 9.4% (P1-3> 0.05); 3 points - patients of group 1 - 47.2%, group 2 - 15.9% (P 1-2 <0.001), group 3 - 34.4% (P 1-3> 0.05) 4 points - patients 1 - group 15.1%, group 2 45.5% (P 1-2 <0.001), group 3 56.3% (P 1-3 <0.001); 5 points - only patients in group 2 38.6 % (P 1-2 <0.001). In the remaining domains, such as naming, attention, repetition of sentences in two approaches, fluency, abstract thinking and orientation, no statistically intergroup differences were found (P1-2; P1-3> 0.05). But draws attention, all patients of the study groups, 100% correctly named the animal "lion", while the naming of the animal "rhino" had difficulties in patients of group 3 (group 1 - 69.8% answered correctly, group 2 63.6%, group 3 - 50.0% (P1-2; P1-3> 0.05) All patients in the study of attention had difficulties in direct counting, the proportion of correct answers was low (group 1 - 60.4%; Group 2 - 63.6%; Group 3 -62.5% (P1-2; P1-3> 0.05) compared to the reverse count (Group 1 -86.8%; Group 2 -81.8%; Group 3-81.2% (P1-2; P1-3> 0.05).

Conclusion: Screening of cognitive functions in patients with the combined use of hashish and tramadol showed that there is a negative synergistic effect on cognitive function. The cannabinoid group is the main cognitive dysfunction when combined with tramadol - with combined use and mono use of hashish, violations of all mnestic processes occur: fixation, retention, and reproduction, but with deeper disorders in poly addiction.

Screening of the cognitive function of patients with poly addiction is one of the main prognostic signs and gives an idea to the clinician for a further algorithm of actions, directions for improving the specialized treatment of addiction and preventing the relapse of the disease.

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Stress in Different Periods of Ontogeny: Consequences and Peculiarities

By Viktor I. Goudochnikov

Abstract- The peculiarities and consequences of exposure to stress were described in various periods of pre- and postnatal ontogeny, in the intermediate age groups and in senescence. Principal focus was made on the actions of glucocorticoids (GC), important stress mediators and also used as pharmaceutical agents. Caution was proposed for the treatment with these drugs, especially in perinatal period.

Keywords: *glucocorticoids, ontogeny, stress.*

GJMR-A Classification: *NLMC Code: QT 162.S8*

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Keywords: glucocorticoids, ontogeny, stress.

I. Introduction

In our previous works the role of stress was characterized in the etiopathogeny of various diseases, including metabolic, neuropsychiatric and cardiovascular disorders (Goudochnikov, 2018 a, b, 2020). In addition, the importance of physiologic and cellular mediators was outlined in different mechanisms of stress and in their interactions (Goudochnikov, 2015). Finally, the contribution of stress and its mediators was described for the phenomena of programming/ imprinting and biological embedding in the framework of DOHaD – developmental origins of health and disease (Goudochnikov, 2018 c). The present study aimed at evaluation of peculiarities and consequences of stress in different periods of pre- and postnatal ontogeny, in order to elaborate the ontopathogenic model in more detailed form.

II. Stress and Related Processes

First of all, we should underline that stress is rather wide concept, what results in its overlaying with such processes as infection, malnutrition, hypoxia / ischemia, trauma (including associated with surgery), exaggerated physical activity and even drug abuse (Sullivan et al., 2006; Raff et al., 2007). Obviously, each of these processes has its own peculiarities and mediators involved. For example, the infections are characterized generally by augment of the production of pro-inflammatory cytokines (principally, interleukin-1beta, tumor necrosis factor-alfa and interleukin-6) that in turn provoke the activation of hypothalamo-pituitary-adrenal (HPA) axis. On the other hand, there exist highly complex aspects, such as socio-economic status and allostatic load characterizing more the chronic stress and its consequences.

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III. Stress and its Mediators in Gestation and in Perinatal Period

In the first place, it should be mentioned that at present the stress during pregnancy is much more frequent than previously, due to elevated number of women executing important functions and jobs (Knackstedt et al., 2005). Nevertheless, it could be thought that the fetus in humans and in animals is influenced by stress only at the end of gestation, when its HPA axis is already mature enough. However, maternal stress and related processes (infections, malnutrition, etc.) are able to influence the fetus indirectly via placenta and its hormones. One of more important aspects is the capacity of maternal cortisol to provoke the paradoxical augment of the production of corticotropin-releasing factor (CRF) by placenta, what results in the mechanism of positive feedback, with gradual elevation of cortisol levels in maternal and fetal circulation till the end of gestation (Mulder et al., 2002). If a pregnant woman suffers from exaggerated stress, then it can provoke intrauterine growth restriction or prematurity. Both of these outcomes can have adverse consequences in the long term (Hobel & Culhan, 2003; Davis & Sandman, 2006).

In physiologic situation the augment of cortisol levels at the end of pregnancy is important for causing the maturation of fetal tissues, preparing the body of newborn to live in extra-uterine environment. However, in the cases of prematurity there exists a necessity of accelerating such maturation in artificial mode, by means of administering synthetic GC (usually betamethasone or dexamethasone) to pregnant woman and / or infant. Although such treatment literally saves the lives of some newborns that otherwise cannot even breath because of pulmonary immaturity, its consequences in the long term can be quite unfavorable, affecting not only respiratory system, but also other organs and systems, including the brain (Velisek, 2005). Unfortunately, in at least one third of all the cases there occurs fetal exposure to exogenous GC in unnecessary mode (Whittle et al., 2001).

It is extremely important that both stress and exposure to GC in excess can provoke alterations of regulatory set-points in fetal HPA axis, with notable tendency to its hyperactivity in postnatal ontogeny, probably via diminution of the content of GC receptors and the consequent decrease in the efficacy of negative

feedback centrally (Maccari et al, 2003). On the other hand, such tendency, due to gradual deterioration of hippocampus in aging can result in premature appearance of age-related diseases, both cardiometabolic (hypertension, diabetes mellitus) and neuropsychiatric (depression, dementia) (Matthews et al., 2002).

It is worth to note also that infants, especially in the case of prematurity, possess low amounts of energetic and plastic reserves and moreover, must redirect a great part of them for somatic growth. Therefore, some stressors, such as surgical one, and other invasive medical procedures can have particularly adverse impact in these cases (Anand, 1990; Schmelly & Coran, 1990).

IV. Stress and Related Processes in Children

It is estimated that a half of all the children in the world suffer from exaggerated stress, as well as related processes (infections, malnutrition, etc.) (Fenoglio et al., 2006). Especially adverse is the impact of abuse or neglect in the family, with consequences in the long term (Kaufman et al., 2000). In this regard, besides CRF and GC as stress mediators, the important role in the mechanisms of such consequences belongs to glutamatergic neurotransmission and its NMDA receptors in central nervous system. The parental neglect results in the insufficient activation of such receptors, whereas physical or sexual abuse cause their hyperactivation, with the consequent predisposition to psychopathologies in posterior life (Anand & Scalzo, 2000). In addition, according to the hypothesis of "double hit", the stress in early postnatal ontogeny augments the individual vulnerability to stress in future life, already in adult state (Cirulli et al., 2009). Obviously, the children can suffer from various diseases where synthetic GCare used, but it appears that considerable adverse impact can be provoked by these drugs in the treatment of leukemias.

V. Stress and Related Processes in Advanced Age Groups

The differentiation of intermediate age groups and senescence emerged on the basis of epidemiologic analysis of morbidity and mortality rates (Goudochnikov, 2009). On the other hand, it appears that in feminine gender there occurs an acceleration of aging with the onset of menopause at the age of approximately 50 years. Probably, such acceleration is provoked by the decrease in levels of estrogens that possess neuroprotective and anti-stress actions (Goudochnikov & Prokhorov, 2012). In addition, in both genders a diminution of the levels of other anti-stress hormones, such as melatonin and neuroactive steroids, somatotropin (growth hormone) and related peptides can also contribute to greater impact of stress in advanced age groups (Goudochnikov & Prokhorov, 2014; Prokhorov & Goudochnikov, 2014).

What for synthetic GC, their use by elderly persons was studied quite scarsely in pharmacoepidemiologic and drug surveillance studies. However, it can be anticipated a priori that exaggerated GC use in advanced age groups is capable to provoke more severe forms of age-related disorders, with the impact that deserves more preoccupation in osteoporosis and the resultant bone fractures.

VI. Final Comments

Bibliographic analyses performed allow to suggest the terms of pharmacotoxicologic programming /imprinting and embedding, being applied principally to the use of GC in excess (Goudochnikov, 2018 c). On the other hand, the exaggerated stress can also cause adverse effects, with consequences in the long term. On our opinion, these aspects can be quite useful for the ontopathogenic model in DOHaD paradigm.

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Blood-based Biomarkers of Late Recovery in Severe Traumatic Brain Injury

By Vanessa C. Morales BS, Kathleen F. Weaver Ph.D.,
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Abstract- *Background:* The incidence of traumatic brain injury (TBI) in the U.S. has been estimated at 1.7 million people each year and results in $60 billion in medical and productivity costs. A TBI can result in severe and potentially chronic cognitive and physical deficits. There has been an increased focus on the use of neurologic biomarkers for both monitoring progression and predicting clinical outcomes; however, the majority of the studies are focused on the acute phase.

Objective: In this study, the goal was to longitudinally characterize biochemical correlates of neural activity up to 2 years after injury and determine if these biomarkers correlate with functional outcomes.

Methods: Participants (n=13) with severe TBI as defined by the Glasgow Coma Scale (< 8) who are less than 1 year from the time of injury were included in this study. Blood samples and functional outcomes (DRS and RBANS) were collected upon enrollment and at 3, 6, 12, 18, and 24 months following enrollment.

Keywords: *biomarker, traumatic brain injury, outcome, cognition, chronic.*

GJMR-A Classification: *NLMC Code: WE 706*

Strictly as per the compliance and regulations of:

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Results: A significant increase in NSE was observed over time, as well as a significant decrease in SBDP 145. NSE was also associated with an increase in cognitive abilities measured by the RBANS.

Conclusion: These results represent the first step in longitudinally characterizing blood-based biomarkers in chronic TBI and beginning to understand the relationship between blood-based biomarkers and functional outcomes.

Keywords: biomarker, traumatic brain injury, outcome, cognition, chronic.

I. Introduction

A traumatic brain injury (TBI) is not a one-dimensional clinical entity but rather elicits a multiplicity of cellular and molecular changes in the brain(Nortje & Menon, 2004). The result is a dynamic condition, and as such, recovery from TBI is a slow and prolonged process. Following a TBI, individuals may experience chronic physical, cognitive, emotional and social impairments with the potential for a further decline in their daily lives years after their injury (Cuthbert et al., 2015; Pretz & Dams-O'Connor, 2013; Pretz, Malec, & Hammond, 2013; Sandsmark, 2016). Consequently, it is essential to improve the prediction of a patient's prognosis specific to functional outcomes to facilitate the recovery process and improve long-term outcomes. There has been an increased focus on the use of neurologic biomarkers for both monitoring progression and predicting clinical outcomes (Agoston, Shutes-David, & Peskind, 2017).

To date, the majority of relevant information regarding the use of biomarkers to examine the progression of pathology caused by TBI is from the acute phase following injury (Yokobori et al., 2013). The most studied biomarkers of brain injury are the predominantly astrocytic-enriched proteins (i.e., S100B and glial fibrillary acidic protein, GFAP)(Agoston et al., 2017; Wang et al., 2018). Serum GFAP levels peak 20 hours after injury (Yokobori et al., 2013). GFAP has been supported as a diagnostic biomarker of acute TBI in several other large studies, including TRACK-TBI and HeadSMART in a variety of different populations. Measuring serum levels of S100B is a useful marker of brain tissue fate in TBI (Asken, Sullan, DeKosky, Jaffee, & Bauer, 2017). This biomarker is FDA approved for TBI and is already helping clinicians and researchers today, primarily in Europe. However, its lack of specificity due to its presence outside the brain has limited its use in polytrauma; thus, this biomarker has not been widely used in North America. Clinicians have successfully implemented S100B to monitor patients to evaluate the need to perform a head CT in mild TBI patients and to detect secondary injury development, like a rise in intracranial pressure in brain-injured patients (Thelin, Johannesson, Nelson, & Bellander, 2013).

In addition to the success of astrocytic markers for neuronal cell injury (neuronal-enriched marker neuronal specific enolase (NSE) and spectrin breakdown products (SBDPs) have also been shown to correlate with several outcome parameters (including age, Glasgow Coma Score, pupil reaction, or CT scan) obtained a few hours to 3 to 6 months after injury (Bohmer et al., 2011; Mondello et al., 2010; Vos et al., 2004). NSE has been shown to correlate with severe TBI in the acute phase in both human and animal models. SBDP 120 is produced during apoptosis, while SBDP 145 is produced due to necrosis following cell death in both human and animal models. The goal of this study was to longitudinally characterize biochemical correlates

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of neural activity and determine if these biomarkers correlate with functional outcomes.

II. Methods

a) Participants

Participants were eligible for the study if they were below 65 years old, had suffered a severe TBI (GCS <8) within the past year, and had a Rancho Los Amigos score greater than IV. Participants were excluded if they had a diagnosis other than TBI (i.e. spinal cord injury, other primary neurologic condition), a developmental disorder (i.e. Down syndrome), or a pre-morbid psychiatric conditions resulting in admission to a hospital. Eighteen participants meeting the above inclusion and exclusion criteria were enrolled in a consecutive sample for one year. Of the 18 participants enrolled, 13 completed the study in its entirety. They were between 16 – 61 years of age and were between 2 to 10 months post-injury at the time of enrollment (Table 1). Written informed consent was obtained for all participants. For the participant who was 16 years of age, assent was obtained directly from the participant, as well as written informed consent from the mother.

b) Study Design

Functional status and blood samples were collected upon enrollment in the study and again at approximately 3, 6, 12, 18, and 24 months following enrollment. Functional status was measured with the Disability Rating Scale (DRS) and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)(Randolph, Tierney, Mohr, & Chase, 1998; Rappaport, Hall, Hopkins, Belleza, & Cope, 1982). A quantitative sandwich enzyme immunoassay (ELISA) technique was used to analyze serum levels of NSE (R&D Systems), S100B (Millipore), SBDP145 (MyBioSource), SBDP120 (MyBioSource), and GFAP (Millipore). Samples for each participant were run in duplicate on the same plate. Protein levels were determined based on the standard curve using the average of the duplicate values. All research was done in accordance with required ethical standards for human subject's research.

c) Data Analysis

Blood-based biomarkers regressed against time since injury, RBANS, and the DRS using linear mixed-effects (LME) analyses customized for longitudinal data (Bernal-Rusiel, Greve, et al. 2012). The longitudinal LME analysis has the advantages of properly handling covariance among repeated measures as well as differences across patients in a number of repeated measures and time intervals between them. Each LME model also controlled for time since injury and severity of the injury.

III. Results

Using protein-specific sandwich ELISAs, we were able to detect levels of NSE (1.6 – 11.75 ng/ml), SBDP 145 (0.38 – 11.0 ng/ml), and S100B (0.46 – 420.0 pg/ml) in serum from chronic TBI patients over time. GFAP was only detected in 4 participants with levels from 0.12 to 6.38ng/ml. SBDP 120 was detected in 2 patients with a range from 0.33 to 7.58 ng/ml. Due to the low levels of detection of these blood-based biomarkers, they were not included in further analysis.

Initial exploration of time from injury for a sample $N = 13$ participants using a LME model found a significant increase in NSE ($F = 18.511$, $p = 0.001$; Figure 1) and a significant decrease in SBDP 145 ($F = 14.623$, $p = 0.003$; Figure 2) over time. No significant effect was observed for S100B.

When we looked at functional status and blood-based biomarkers a significant effect was observed between increasing NSE levels and higher levels on RBANS ($F = 18.088$, $p = 0.002$). We did not observe any other relationships with RBANS or the DRS and the blood-based biomarkers.

IV. Conclusion

In this study, we characterized five potential blood-based biomarkers for the chronic phase after TBI. Although the majority of research focuses the acute phase following brain injury, where potential biomarkers will return to baseline following the injury, we know that the effects of a brain injury are chronic and may persist for years after injury. Therefore, it is important to understand what neural markers are present in this phase and if they correlate with recovery. Data collection started at 2 – 10 months following a TBI and continued for two years. Of the five blood-based biomarkers that we chose to examine in chronic TBI, only three, NSE, SBDP145, and S100B, were consistently detected in our population. We observed significant changes in NSE and SBDP 145 with time since injury. Specifically, NSE increased over time, while SBDP 145 decreased with time. When we looked more closely at when this effect was taking place, we observed that the increase in NSE appeared to occur after one year following injury. NSE was also correlated with RBANS suggesting that the increase in NSE may be related to improvement in cognitive function.

Previous research has shown that GFAP and S100B, both astroglial markers, collected in the acute phase of injury correlate with injury severity, CT findings, and strongly predicted mortality and poor outcomes 3 and 6 months after injury(Metting, Wilczak, Rodiger, Schaaf, & van der Naalt, 2012; Pelinka et al., 2004; Vos et al., 2010). Astroglial activation and gliosis in response to neurodegeneration may underlie another mechanism with which GFAP could be a useful predictor in chronic

TBI. Interestingly, in this study, we were unable to detect GFAP in all participants suggesting that is may not be a reliable marker in chronic TBI. We did detect S100B; however, we did not observe any changes over time. Previous studies have suggested S100B may be most effective following mild brain injury (Metting et al., 2012; Mondello et al., 2012).

NSE, a glycolytic enzyme that is released into the extracellular space following neuronal injury and damage, has also been shown to be a good predictor of injury(Agoston et al., 2017; Bohmer et al., 2011). Our results show elevated NSE with time and a correlation with cognitive function. Thus, NSE in chronic TBI does not appear to be representing cell death as it does in the acute phase following injury. However, NSE is expressed in erythrocytes and thus lacks neuronal specificity, potentially limiting its ability as a predictive biomarker for TBI(Agoston et al., 2017). Calpain and Caspase SBDPs, which are markers for cell death, also appears to have potential prognostic and diagnostic utility(Mondello et al., 2010; Yokobori et al., 2013). In this study, we found that SBDP 145 decreased with time but did not correlate with functional outcomes. We were not able to reliably detect SBDP120.

Taken together, these results mark the first-time biomarkers have been evaluated repeatedly through a prolonged period in TBI patients. However, there are limitations with this study, such as the small sample size, severity level (only severe TBI patients were included), and variability in time from injury upon enrollment that limits the conclusions that can be made. These findings will also benefit from a control group to determine if the changes in these blood-based biomarkers are specific to TBI. Finally, there is the possibility that the sensitivity of the markers may be contributing to the results, for example, detection of noise versus real signal. However, based on the assay specifications, the protein levels we measured do fall in the middle of the detectable range and are not near the limits of detection in either direction (i.e., too high or too low).

Treatment of TBI as a chronic condition is complicated because the symptoms and clinical needs of patients vary significantly between individuals and evolve. Through future studies, we aim to establish patterns of brain activity (MRI, EEG, blood-based neural markers) that can be associated with specific characteristics such as age, gender, presence or absence of neurological injury, and level of performance on functional tasks. Examining pathological markers for neurodegeneration such as amyloid deposition and tau phosphorylation have been shown following TBI and chronic traumatic encephalopathy, this is an area we will expand our investigation for chronic TBI. Ultimately, we believe that these blood-based biomarkers can be used to predict patient prognosis, evaluate the efficacy of therapeutic interventions, and develop adaptable personalized treatment plans that can be optimized for individuals with neurological deficits.

Author Disclosure Statement

We certify that no party having a direct interest in the results of the research supporting this article has or will confer a benefit on us or on any organization with which we are associated AND, if applicable, we certify that all financial and material support for this research (eg, NIH or NHS grants) and work are identified in the title page of the manuscript.

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Author Contribution Statement

ER was the PI for this study and oversaw all aspects from design to participant recruitment to data collection, data analysis, and writing the manuscript. VM and KW completed the ELISA kits to determine protein values, provided financial support for personnel time and contributed to the statistical analysis and critical review of the manuscript. CS completed the statistical analysis and provided critical input and revision of the manuscript.

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Table 1: Demographics

Age (mean)	35.5 (± *15.2)* years
(range)	16 – 61 years
Gender	70% Male / 30% Female
Cause of Injury	31% Motor Vehicle Accident 27% Motorcycle accident 27% Bicycle accidents 15% falls / pedestrian accidents / sports injury / assaults
Time from Injury (mean)	5.5 (± *2.1)* months
(range)	2.6 – 10.4 months

Figure 1: Data show the mean of NSE levels at 6 time points (enrollment, 3, 6, 12, 18, 24 months following enrollment) following TBI. A significant increase was observed with the increase appearing greatest after 1 year (F = 18.511, p = 0.001).

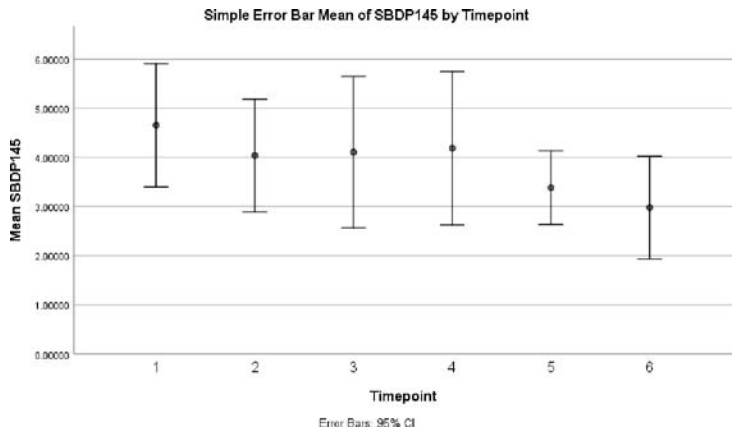

Figure 2: Data show the mean of SBDP145 levels at 6 time points (enrollment, 3, 6, 12, 18, 24 months following enrollment) following TBI. A significant decrease in SBDP 145 was observed over time (F = 14.623, p = 0.003).

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Statin Treatment May Play a Key Role in the Prevention of Dementia: A Review of the Literature

By Chiara Bandinelli, Giovanni Maria Puddu, Luca Spinardi, Giampaolo Bianchi & Marco Zoli

Introduction- Dementiais characterized by cognitive decline and deterioration of daily function, often with behavioral disturbances. Degenerative dementia includes many subgroups like Alzheimer's disease (AD), frontotemporal dementia, etc, and nondegenerative dementia mainly encompasses vascular dementia, traumatic brain dementia, and so on. Alzheimer's diseaseis the mostcommon dementia in the elderly, accounting for 60% of cases (1). There isn't specific therapy for degenerative dementia, only symptomatic treatment.

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Statin Treatment May Play a Key Role in the Prevention of Dementia: A Review of the Literature

Chiara Bandinelli [α], Giovanni Maria Puddu [σ], Luca Spinardi [ρ], Giampaolo Bianchi [ω] & Marco Zoli [¥]

I. Introduction

Dementia is characterized by cognitive decline and deterioration of daily function, often with behavioral disturbances. Degenerative dementia includes many subgroups like Alzheimer's disease (AD), frontotemporal dementia, etc, and nondegenerative dementia mainly encompasses vascular dementia, traumatic brain dementia, and so on. Alzheimer's diseaseis the mostcommon dementia in the elderly, accounting for 60% of cases (1). Thereisn't specific therapy for degenerative dementia, only symptomatic treatment.

Table 1: Causes of dementia

Causes of dementia: classification
•Alzheimer disease (60%)
•Cerebrovascular disease (20%): multi infarct dementia; subcortical vascular disease
•Neurodegenerative: Parkinson's disease; Huntington's corea; Pick's disease
•Infections: HIV; encephalitis; Creutzfeld-Jackob's disease
•Normal pressure hydrocephalus
•Nutritional: vitamine deficiencies (B12, folate, thiamine)
•Metabolic: thyroid disease, hepatic disease
•Inflammatory: chronic inflammation (vasculitis)
•Trauma
•Tumor

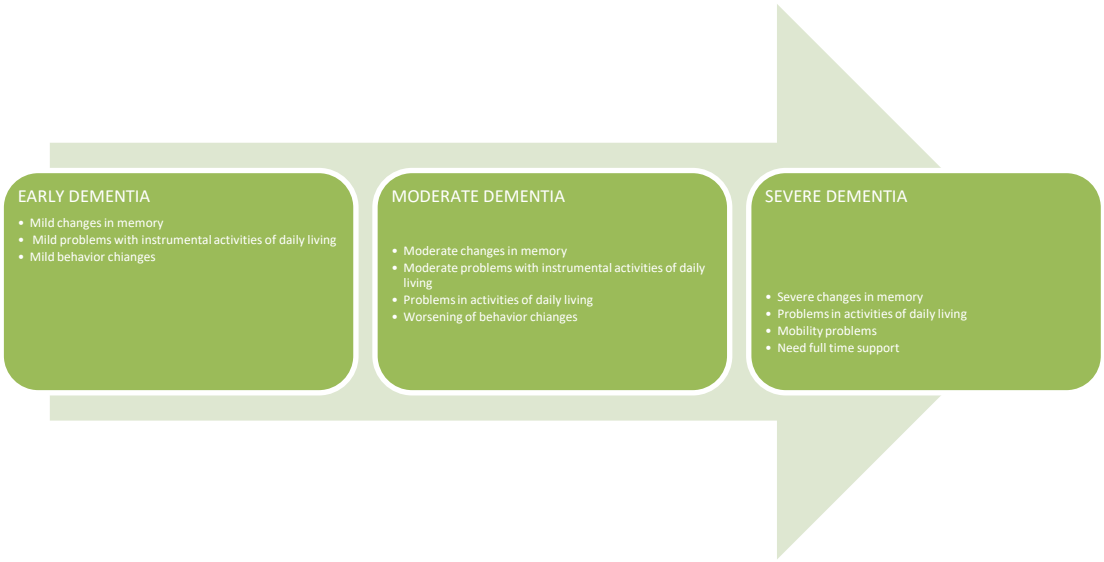

Figure 1: Dementia stages

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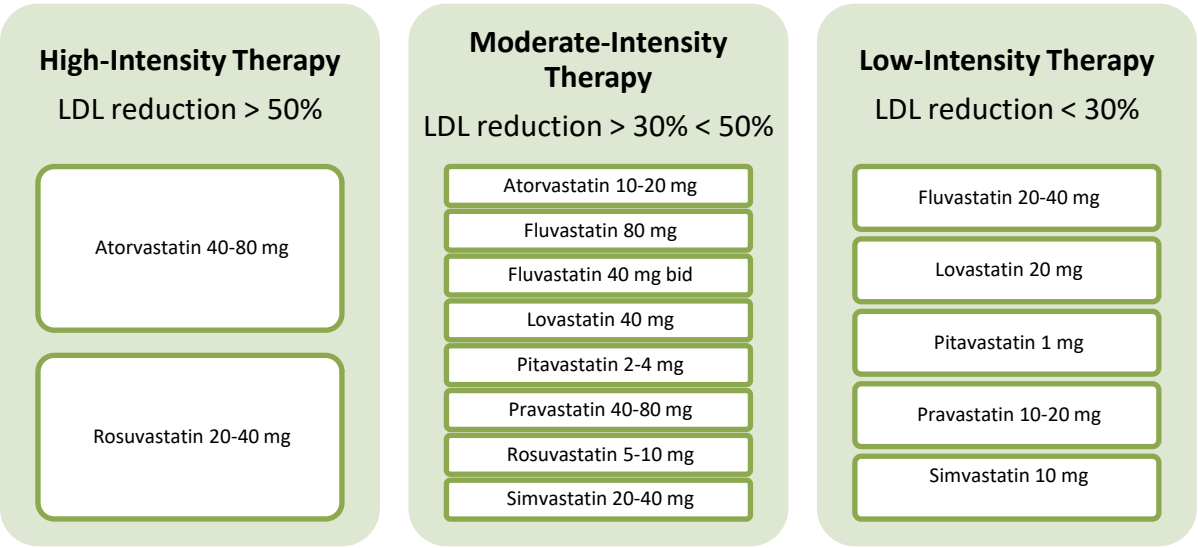
There are different mechanisms that can explain the degeneration process, including inflammation, oxidative stress, circulation of blood to the brain, increased cerebral β-amyloidpeptides, hyperinsulinemia, brain insulin resistance, andt he formation of advancedglycation end- products (2).

In literature, numerous studies havefound the implication of statinsas protectors for brain degeneration and how statins use mightlower the risk of dementia (3).

Lipidaltering agents encompass classes of drugsthatinclude hydroxymethylglutaryl-CoA (HMG) (Coenzyme A) reductase inhibitors or statins, fibric acid derivatives, bile acid sequestrants, cholesterol absorption inhibitors, and nicotinic acid. These drugs stand out for the action and type of lipid-lowering. So the indications for a particular lipid-altering agent are conditioned by the kind of lipid abnormality (4).

Statins are the most commonly prescribed class of drugs to reduce cholesterol. Their action mode is the competitive inhibition of the active site of HMG-CoA reductase, the speed-limitingenzyme in the cholesterol biosynthesis pathway. The inhibition of this active site avoids substrate access, blocking the conversion of HMG-CoA to mevalonic acid. This mechanism reduce shepatic cholesterol synthesis, increasing the production of microsomal HMG- CoA reductase and the expression of cellsurface LDL receptor, which facilitates the clearance of LDL-c from the blood and a reduction in circulating LDL-c levels. Thanks to this mechanism, statins reduce cardiovascular and cerebrovascular morbidity in primary and secondary prevention. Statinsalso have further non–lipid-related pleiotropic effects, probablydue to the inhibition of the synthesis of isoprenoid intermediates of the mevalonate pathway. These mechanisms include improvements in endothelial function, stabilization of atherosclerotic plaques, anti-inflammatory, immunomodulatory and antithrombotic effects, effects on bone metabolism, and reduced risk of dementia (5).

Table 2: Classification of statins by expected LDL reduction



As regards dementia, cholesterol can be deposited in the brain, specifically in the hippocampus, causing the degradation of the amyloid precursor protein, which causes degeneration of neurons, resulting in AD. Statins, with their lipid-lowering effect, may reduce the formation of the b-amyloid peptide in the brain. In fact, they have an impact on the homeostasis of the nervous system cholesterol, inhibit the synthesis of cholesterol, lower the cholesterol level, and thus inhibit the beta metabolism of the amyloid precursor protein. Also, apoE4, a cholesterol transporter, is a risk factor and genetic marker of familiar AD and contributes to b-amyloid deposition and the development of senile plaques. Statins inhibit apoE secretion and lower extracellular apoE levels, consequently preventing the formation of senile plaques and enhancing cognitive function. Moreover is known an age-related cognitive syndrome called cerebral small vessel disease (CSVD), which includes group of pathological processes with multiple causes that affects small cerebral vessels. Features associated with CSVD include white matter hyperintensities (WMH), lacunes, enlarged perivascular space (EPVS), and microbleeds observed through magnetic resonance imaging (MRI). CSVD can be asymptomatic; however, lesions can cause cognitive dysfunction, dementia, and mood disorders (6). Therefore measures to prevent CSVD are particularly crucial. CSVD is associated with vascular risk factors, including smoking, hypertension, hyperlipidemia, and aging. The association between

statin therapy and CSVD is well documented in the elderly: numerous evidences show that statins may decrease major vascular events and alleviate the progression of CSVD and, consequently, dementia (7).

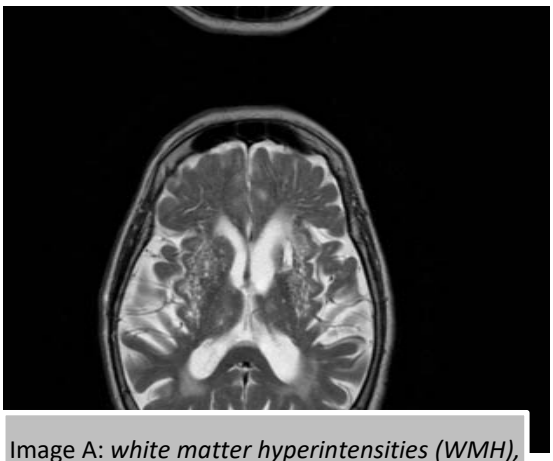


Image A: *white matter hyperintensities (WMH), lacunes, enlarged perivascular space (EPVS)*

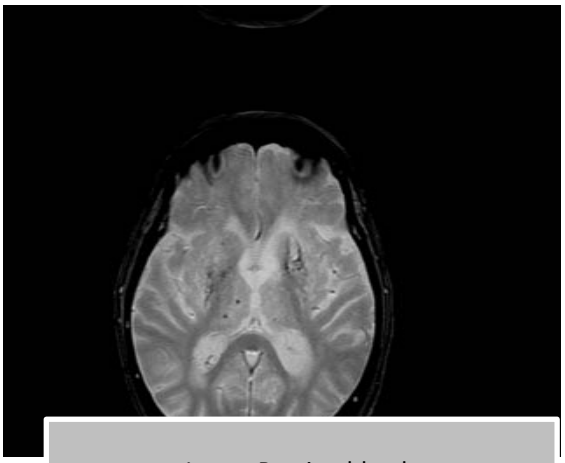


Image B: microbleeds

Figure 2: MRI brain sequences, T2 fast spin-echo(FSE) image A and T2*gradientecho (GRE)image B

II. Discussion

In the literature, there are several results about use and risk of dementia.

In November 2017, Medline, Embase, Web of Science, and the Cochrane Database identify the potential relationship between statins and dementia. Statins use was related to dementia risk decrement. Subgroup analysis demonstrates statins use was connected to Alzheimer's disease (AD) and non-AD dementia risk decrement (8).

In 2013 Chang CF, Liou YS, Lin TK et al. investigated the risk of new-onset dementia (NOD) in statin users compared to non-users. The risk of NOD was lower among statin users than non-users. The protective effect of statins for NOD seemed to be realted to high exposure to statins (9).

Cheng PY, Liu SK, Chen CL et al. found a duration-response relationship with long-term use of statin and dementia risk: one year of treatment of statins decreased by 9% the risk of dementia. The use of high dose statins for more than one year correlated with a lower risk of dementia than the use of low dose. On the contrary, fibrates or other lipid-lowering agents had no significant association with dementia risk (10). Even Hendrie HC, Hake A, Lane K, et al. found that only consistent use of statin medications during years significantly reduces the risk of incident AD (22).

For mild cognitive impairment (MCI), Bettermann K, Arnold AM, Williamson J et al. studied statin drugs and the cognitive delay decline and dementia onset in individuals with and without mild cognitive impairment (MCI) at baseline. They found that statins may slow the rate of cognitive decline and delay the onset of AD and all-cause dementia in cognitively healthy elderly individuals. On the other hand, patients with MCI may not have a comparable effect from statin use (11).

Early statin use has shown a reduction in Alzheimer's disease progression compared to late treatment, especially in AD evolution in mild-to-moderate class (12).

After stratifying by gender, the risk of incident dementia was lower in female statin users than in male statin users. It were required higher potency and longer cumulative duration of statin use for reducing the risk of incident dementia in male patients than in female patients (13).

Several studies analyzed the relationship between the subclasses of statins and the prevention of dementia. Wu CK, Yang YH, Lin TT et al. found that the more potent statins (e.g., atorvastatin and rosuvastatin) seemed to be particularly effective in the prevention of dementia (14).

On the contrary, Wolozin B, Wang SW, Li NC et al. found an association with Simvastatin and a severe reduction in the incidence of dementia and Parkinson's disease. Atorvastatin is associated with a modest decrease in incident dementia (15).

The hospitalization in people with dementia is a severe problem. In 2009 Horsdal HT, Olesen AV, Gasse C et al. examined the risk of admission with dementia related with utilization of statins in a case- control study in 4 Northern Danish counties. They found a reduced risk of hospitalization with dementia among users of statins (16).

In addiction, Reed B, Villeneuve S, Mack W et al, investigated the association between serum cholesterol levels and cerebral b-amyloid in the AD process. The elevated cerebral b-amyloid level was

associated with high cholesterol fractions suggesting a significant role for cholesterol in b-amyloid processing.

Cholesterol levels are modifiable with statin use. So, understanding the link between cholesterol levels and the b-amyloid deposition could potentially have an effect on retarding the pathologic cascade of AD (17).

Analyzing patients with ApoE4 homozygotes, the incidence of AD was significantly lower in statin users, and ApoE4/ApoE4-genotyped AD patients treated with statins showed better cognitive function throughout 10-year follow-up (18).

Regarding CSVD, a cohort study made by Guo Y, Li Y, Liu X, et al (19) analyzed MRI features associated with CSVD. They found that white matter hyperintensities (WMH) volume, WMH-to-intracranial volume (ICV) ratio, lacunes, enlarged perivascular spaces (EPVS) and microbleeds were significantly lower in the statin group than the non-statin group.

In contrast, according to the Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) trial (20), there's no evidence of benefit from statin treatment on prevention of dementia: PROSPER trial randomized patients age 70 to 82 years to pravastatin or placebo.

Patients had to perform cognitive tests at regular intervals to control memory and executive function. They have not found significant difference in cognitive function between the treatment and control groups after 42 months of follow - up (21).

III. Conclusions

Dementia is a disease that afflicts many patients, and unfortunately, there is still no class of drugs that can treat this disease. Therefore, finding medicines that can prevent or delay the progression of the disease is crucial and that's what we set out to discover when we started this review.

Statins are widely prescribed drugs in the population for their protective role in cardio and cerebrovascular events. Accumulating evidence suggests that statins may play a decisive role in the prevention of dementia.

Several studies showed that the protective effect of statins might depend on the duration (years). and the high dose of the drug. In fact, lower dosages of the drug appear appear to have less action on disease progression as well as shorter duration.

The early statin use seems to be protective for the progression of Alzheimer's disease while later use may not affect this process.

Mild cognitive impairment (MCI) is the stage between the cognitive decline of normal aging and the more severe decline of dementia. Our researches show that for MCI, there is no evidence that statins give cognitive protection for the onset of dementia. Probably their protective effect emerges more when is already expressed the mental deterioration. Concerning the subclasses of statins, there are controversial opinions on their efficacy delaying the progression of dementia (for some, atorvastatin and rosuvastatin are the most effective; for others, it is simvastatin).

Although some subclasses are more effective or faster than others, all statins still appear to delay the progression of dementia.

Stratifying by gender, the risk of dementia for statin users is lower in females than the males. In male patients is required higher potency and longer cumulative duration of statin than the females. We could explain this process by pathophysiological differences between genders and different hormone-modulated pharmacologic or metabolic mechanisms. The hormonal treatment in postmenopausal women has been associated with the decrease in cholesterol levels, even if the association between hormonal therapy and dementia is still unexplained. So considering the differences between gender is very important in the clinical practice about the use of statin.

Hospitalization is a massive problem that affects many patients with dementia. During hospitalization, the patient worsens cognitive function, becomes disoriented, and may develop behavioral disturbances. Preventing hospitalization could be crucial to limiting the cognitive and behavioral complications of dementia. We found several studies that show that the risk of hospitalization in dementia patients is lower in statins users; this finding, therefore, provides some support to the hypothesis that statins may protect against the development of dementia.

Regarding the molecular pathogenesis of dementia, especially AD, reports have indicated that there is a molecular association between the senile degeneration process in dementia and serum cholesterol levels: evidences show a correlation between elevated cerebral Aβ level and cholesterol fractions, suggesting a crucial role for cholesterol in Aβ processing. Using lipid-altering agents like statins could, therefore reduce serum cholesterol levels and thus promote less deposition of beta-amyloid in the brain.

Overall our results suggest that the utilization of statins may benefit all AD patients, especially those with an ApoE4 homozygotes genotype. In ApoE4 homozygotes, the incidence of AD is significantly lower in statin users. For future research, it would be interesting to explore the most appropriate genotypes for statin use as a preventive therapy of AD.

Traditional vascular risk factors (like diabetes, hypercholesterolaemia, hypertension, and smoking) increase the risk for CSVD, which is a significant factor in the pathogenesis of dementia. Cholesterol- lowering medications, such as statins, may have a crucial role to prevent CSVD and consequently treat and anticipate the

cognitive impairment. All in all, from the accurate review of the scientific literature, statins could have a protective role in the progression of dementia. Conversely, few studies have found no benefit from drug treatment compared to placebo. In any case, we found no aggravating effect of the statin on cognitive impairment.

We, therefore, concluded that statins might play a crucial role in the prevention of dementia. In the scientific field, their use could be an excellent resource for delaying the progression of cognitive decline. Given that dementia is the most common degenerative disease in the elderly, it is clear that its prevention can be crucial in the geriatric setting, and statins could play an essential role in this process.

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Validation of Questionnaire for Detection of Epilepsy in Guaraní

By Abente Silvia, Arbo Carlos & Cabrera Marta

Summary- In Paraguay, as a bilingual country and with a characteristic historical context, it has always been considered a challenge to reach the Guaraní-speaking population, especially those from the most vulnerable sectors, through the use of tools that bridge the gap in the language barrier in care services in general. By translating the epilepsy diagnostic questionnaire aimed at its use in primary care, the aim is to bring to the medical professional a useful element in clinical practice that also provides data of diagnostic value and treatment guide. In this work, the validation of the questionnaire, originally conceived in Spanish, was carried out, distinguishing some idiomatic aspects that add richness to the clinical history in epilepsy and define the therapeutic aspect, providing the medical professional with a material of practical use and easy to apply in clinical practice daily.

Keywords: *epilepsy, primary care, focal crises, generalized crises, guaraní.*

GJMR-A Classification: *NLMC Code: WL 385*

Validation of Questionnaire for Detection of Epilepsy in Guaraní

Abente Silvia [α], Arbo Carlos [σ] & Cabrera Marta [ρ]

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I. Introduction

Guaraní is the most widespread native language in Paraguay, considered a bilingual country, it comes from one of the majority ethnic groups in the original population of Paraguayan territory during the pre-Columbian period. For various historical and cultural reasons, it is today the second official national language, after Castilian, due to its wide range of use and socio-cultural characteristics that make it very popular, particularly in the most vulnerable economic strata.

Accompanying this linguistic peculiarity, the population that uses it is of Hispanic-Guarani mestizo origin, which is why throughout colonial history and independent life it has undergone the transformation of the linguistic evolution of the conjunction of both languages, Spanish and Guaraní, which is currently known as yopará.

We consider, therefore, very interesting to carry out an appropriate adaptation and validation of the pathology detection tools, especially in the case of Epilepsy, where the clinical manifestations can be numerous and highly variable. Through its analysis, a distinction could be made between the most appropriate terms (in the Guaraní language) to define the different symptoms of this vast pathology.

The World Health Organization estimates that there are currently around 50 million people with Epilepsy in the world. It is also estimated that approximately 70% of patients live in underdeveloped countries and there is, as if that were not enough, a treatment gap of approximately 50% in most of them. In other words, only half of the patients with epilepsy ever arrive for consultation and treatment.

The incidence of epilepsy in Latin America is around 50 per 100,000 inhabitants (new cases/year) and a prevalence of 8-10 per 1000 inhabitants (population with active epilepsy). Both figures, although estimates due to the lack of homogeneity in the statistical studies, still show much higher values than in developed countries due to various socio-cultural factors that can be intuited such as epilepsy associated with perinatal problems, in addition to that associated to head trauma (for example, in car accidents), etc. All this making the indexes considerably higher in our environment. Although there are no official statistics yet, it has been estimated that the figure at the local level is between 100,000 and 200,000 inhabitants throughout the country.

The factors identified as responsible for the treatment gap lie in the limited capacity of health systems and unequal distribution of resources, the lack of trained personnel or even a shortage of it, the lack of access to affordable medicines, in addition to the social ignorance and stigma that prevail above all in vulnerable populations and the still low priority that the majority of the countries in this region give them.

With this panorama, it goes without saying that it is our obligation as health professionals dedicated to the area of Epilepsy, to work consistently to improve and facilitate the detection of these patients in primary care, which should be the first level of care.

The objective of this work is to evaluate the usefulness of the questionnaire for the detection of epilepsy proposed by the "Manual of procedures for the early detection and treatment of epilepsy" (PAHO 2007) to establish the diagnosis and classify epilepsy seizures in primary care services for the Guaraní-speaking population.

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II. Materials and Methods

Initially, the questionnaire was translated with an expert in the popular Guarani language who proposed to adjust the best version possible for the general public to understand. Subsequently, the completion of the questionnaire was defined consecutively for all patients who come to the Neurology Service of a reference hospital in the interior of the country for the first time (Hospital Nacional de Itaugua), from August 2018 to March 2019. The questionnaire was carried out by the nursing staff who, after initial screening with the main question:

"During the past 12 months, has the patient had seizures or seizures, brief periods of loss of consciousness, involuntary shaking of the arms or legs, seemed to be disconnected from reality or unable to respond?"

in its version in Guaraní:

"Ary (year) paha jave tekovepa oguereko seizure epilepsy gua mbykymi oho chugui teko ñee, oryryi pa oipotayme, ijyva ha hetyma ndaikatuiva ombohovai mbaeve?".

Faced with an affirmative answer, the patient was at risk of presenting Epilepsy and was considered to complete the questionnaire and undergo a specialized evaluation.

Before the application of the diagnostic questionnaire, the target personnel in charge of passing the questions were trained in the management of the basic concepts of this condition, specifically in clinical diagnosis, by the neurologists of the project.

Diagnostic discrimination (validity) of the questionnaire was measured by sensitivity (ability to detect patients with epilepsy), specificity (ability not to diagnose a patient who does not suffer from epilepsy with epilepsy) and the prognostic value of a positive or negative result., considering homogeneous evaluation groups to work with a prevalence of approximately 50% among double-blind patients. The reference criterion for calculating these measures was the clinical diagnosis of epilepsy made by a neurologist and the ruling out of the diagnosis of epilepsy by the same professional.

Table of the Questionnaire in Spanish and Guaranì

ENGLISH	GUARANÍ
CENTRAL QUESTION	
Do you know a person who has epilepticseizures?	Nde eikuaa petei tekove oguerekova ataque epilepsia gua?
During the past 12 months have had this person epileptic seizures such as brief periods or loss of consciousness, involuntary shaking of the arms and legs, it was impressive to be disconnected from reality or unable to respond?	Ary (año) paha jave tekovepa oguereko achaque epilepsia gua mbykymi Oho chugui teko ñee, oryryipa oipotayme, ijyva ha hetyma Ndaikatuiva ombohovai mbaeve
SUPPLEMENTARY QUESTIONS	
1. Was the person unconscious and incapable to respond during the episode?	1. Oipa rae la tekoveakamejehe apa Ndaikatuiva ombohovai mbaeve
2. Do he/she regain consciousness after the episode?	2. Imanduapaupe ataque rire la oiko Vaekuehese?
3. How many of the indicated episodes hashe/shehad in the last 12 months?	3. Mboy ataque oguerekoumiary pahajave?
4. When was the last time and how long was it?	4. Arakae ome e chupe ipaha ha mbo y aravo hi are?
5. Has he/sheany known neurological problem?	5. Oreko pa tekove petei mba asy iñakame gua (meningitis, akambota, o u vai)
6. How long hashe/she had seizures?	6. Mbo y ochapo oguereko ha la achaque?
7. Has it gotten worse over time?	7. Oivaivepako ataque oguereko rire?
8. During the episodes was he/she with the 9. fixed gaze, blinking or did not pay attention?	8. Umi ataque jave, oma ña hata, hesapiri ndo jesarekoi mbaevere?
10. During the episodes, had he/she involuntary movements, abnormal, uncontrollable, jerks or muscle contractions?	9. Umi ataque jave oi pa je kue pota yre ndaikatuiva oñesambyhy ha oñemokuruchi?
11. Were there automatisms such as movements swallowing or savoring, purposeless repetitive hand movements?	10. Oi pa ijehegui omomyva ijehegui ijuru, Ijyva ndaikatuiva ombohova?
12. Does he/she have any warning before the crisis?	11. Oguereko mbae ohechaukava pe ataque outaha jupe?
13. Washe/she conscious after the crisis?	12. Upe ijataque rire okatu ombohovai?
14. Are these episodes related to some specific situation (fever, after crying, feeding, blow, trauma)?	13. Ko ataque ome e jupe akanundu, tase, karu, akambota rire?

III. Results and Discussion

The questionnaire was carried out on a total of 140 patients and companions, between the ages of 16 and 70, Guaraní-speaking of both sexes, of which 6 patients were excluded because they did not complete the questionnaire, leaving the groups made up of 74 patients with diagnosis of Epilepsy performed by specialists and 60 patients with discard of the day Gnostic of Epilepsy, assessed by the same team of Neurologists.

It was observed that in comparison with Sensitivity / Specificity values evaluated separately in the different clinical signs / symptoms found (Avbersek A, Sisodiya) this scale presents an exceptional level of detection (Sensitivity = 91.89%) after the first question of the questionnaire. That is, only with the analysis of response to the first question can the expected level be obtained for the detection of the condition and for an approximate prevalence of 50% in our population (since the questionnaire was carried out in 2 groups with and without the condition of similar double-blind frequency) it can be said that the sensitivity is associated with a high negative predictive value of 0.89 (NPV = 89%) in our sample, which is interpreted as a high effectiveness to rule out the condition given a negative result. Furthermore, in comparison with the reference values of another similar study carried out in the pediatric population of Ecuador (in Spanish) whose Sensitivity value was 95.10%, a fairly homogeneous result of our questionnaire in Guarani can be observed. (Carpio, Lisanti).

Diagnosis According to Questionnaire Patients with Epilepsy Patients without Epilepsy Total

Diagnosis according to questionnaire	Patients with epilepsy	Patients without epilepsy	Total
Positives	68	10	78
Negatives	6	50	56
Total	74	60	134

In the Specificity analysis, however, a drop to 83.33% was evidenced, which is to be expected since there are numerous conditions that can increase the number of false positives in the test (paroxysmal non-epileptic events). In the same way as the previous reasoning, given the equitable distribution between the participants who suffered and not the condition evaluated, this value can be associated with the positive predictive value of the test (interpreted as the possibility that the patient who tests positive actually suffers from the disease), which in our series is 0.89 (PPV = 89%). Compared with another series, a decrease in this value was observed (E = 97.06% according to Carpio et al). The difference found could be attributed to the language gap in the interpretation of the terms of the questionnaire. For example, in the Guaraní language there is no specific term for the definition of loss of consciousness due to seizures or other manifestations of focal seizures, as the term seizure used in the English language or even seizures for Spanish speech could be interpreted. although in the latter case the word used is indicative since it translates into ailment in Guaraní.

Of course, with the disaggregated analysis of the other questions it is even possible to approximate in diagnostic terms the subtype of epilepsy that the patient may be presenting or even its etiology. This evaluation has not been determined because it required a greater diagnostic detail per patient that would prolong the time required and increase costs, which was not supported for the purposes of the study.

Even so, we have found certain questions that, in the Guaraní language, have been clearly understood and have indicated with special punctuality some aspect of the clinic manifested by the patient with Epilepsy to mention: *"omaña hata" (fixed gaze) "ndo jesarekoi mbaevere "(not paying attention)" Oi pa ijehegui omomyva ijehegui ijuru, Ijyva ndaikatuiva ombohova?"* (description of automatic chewing, swallowing, etc.). Of course, the findings are not surprising considering that the main diagnostic tool in Epilepsy, even today, is still the clinic. And it is through a detailed evaluation of the patient that high levels can be reached in the diagnostic and etiological discrimination of each case. In any case, our intention through this validation is to make available to our primary care physicians a simple diagnostic detection method that also shows a high level of discrimination in seizure subtypes, when approaching a patient with suspected Epilepsy. Giving the professional a clear possibility of guidance in the initial therapy of each case.

IV. Conclusion

Epilepsy as a neurological condition, despite its significant frequency, still represents a diagnostic challenge in primary care medicine. The main factor would be the delay in the consultation by patients and relatives, because, still covered with an aura of mysticism, they resort to traditional medicine, whose representatives are healers or shamans and their interpretation and approach to epileptic seizures, is they

are closer to ancestral religious beliefs and practices than to medicine, which logically delays the diagnosis. The other side of the coin highlights the difficulty sustained by the distance that patients and their families must travel to reach a healthcare center, coupled with the lack of the necessary financial resources that displacement makes nto on a slow and painful journey. But the difficulties do not end with the arrival at a health center for primary medical care, there we run into the lack of necessary training of medical professionals in the diagnosis and therapy of epilepsy and even if that were the diagnosis, in many cases they do not have the drugs needed for treatment. Finally, it is worth mentioning that the presence of a medical professional in primary care centers may not be permanent and even in cases absent, leaving health care in the hands of nursing personnel. Everything previously exposed could be summarized in a single word, the need to Educate. At the population level, campaigns aimed at teaching how to recognize epileptic seizures prematurely and encourage their immediate consultation at a medical center. State policies that encourage the creation of a greater number of primary health care centers, with duly trained medical and nursing professionals and with the therapeutic means to deal with the cases that arise. Approach community leaders, mainly those who play roles in the health area, in such a way as to include them in the health chain without damaging their culture and beliefs. As part of our commitment and with the help of the authorities, the first steps are being taken both in the area of education and the provision of technology, as well as tools of simple and practical use such as this easy-to-apply questionnaire in the Guarani language and interpretation in health units, and any other level of the health chain. We are aware that there is still a lot of work to be done, but we will not give up the commitment made with small interventions that will generate big changes in the long run.

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Emotional & Behavioural Problems among Siblings of Children with Chronic Neuromuscular Illnesses

By Nidhi Garg & Krishna Moorthi Adhikari

Abstract- *Introduction and Objective:* To determine the prevalence of emotional and behavioral problems among siblings of children with chronic neuromuscular illnesses by using validated parent completed assessment tool.

Method: It is a cross-sectional study conducted in a tertiary care hospital from over a period of 34 months. Siblings of children with chronic neuromuscular illnesses were serially recruited while attending pediatric OPD and IPD. Parents were interviewed and requested to fill the Strength and Difficulty Questionnaire (SDQ) to assess and analyze emotional and behavioral problems among siblings.

Results: Study included 171 siblings of children with chronic neuromuscular illnesses. Of 171 siblings, 124 (72.51%) had normal scores, 25 siblings (14.62%) were in borderline range and remaining 22 (12.87%) had abnormal values. The mean ± SD of SDQ score was 12.41 ± 3.6 with median score of 11. There was no significant difference between total SDQ scores of male vs female siblings (p value= 0.229) or between birth order of the sibling or GMFCS class of the affected child to emotional and behavioural problems. Subgroup analysis was not possible because of small sample size.

Keywords: *cerebral palsy; emotional disturbances; neuromuscular diseases; sibling relations.*

GJMR-A Classification: *NLMC Code: WE 550*

Strictly as per the compliance and regulations of:

Emotional & Behavioural Problems among Siblings of Children with Chronic Neuromuscular Illnesses

Psycho-Social Difficulties in Siblings of Neurodisabled

Nidhi Garg [α] & Krishna Moorthi Adhikari [σ]

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Conclusion: This study emphasizes that identifying and treating even small proportion of siblings with behavioral problems can have a long-term impact on development and well-being of the child, family, community and nation as a whole.

Keywords: cerebral palsy; emotional disturbances; neuromuscular diseases; sibling relations.

I. Introduction

The prevalence of children living with chronic neuromuscular illnesses has risen as a result of improvement in health care facilities and change in social philosophy about their health care requirements and home-based supportive care [1]. These achievements are commendable but are accompanied by increased care giving burden being born by all members of a household with a child with disability.

Such affected children require family and community support at multiple levels for survival as well as day to day functioning. They have multiple associated comorbidities like intellectual disabilities, seizures, feeding difficulties, hearing and visual impairments and behavioural problems that impose extra financial, social and emotional burden on the family [2]. Families tend to divert all their resources in rearing such disabled child, thus exposing the well sibling to the risk of various emotional and behavioural problems as a result of parental deprivation and interplay of various other factors. The mechanism by which a particular family or a parent copes well compared to others is largely unknown. Several theories are documented which states that stress arises when the demands imposed by a patient's condition collide with a caregiver's subjective ability to respond, or when these demands obstruct the pursuit of other objectives [3].

Research exploring the impact of disability on typically developing siblings has been mixed. Vermaes et al [4] published a meta-analysis studying the psychological functioning of siblings in families with children with chronic conditions and concluded that siblings of children with disability are at increased risk of developing negative self-attributes and internalizing problems. In another study conducted to investigate behavioural adjustment among siblings of 96 children and adolescents with spinal muscular atrophy, non-affected siblings had a two to threefold higher rate of behavioural problems than the normative population [5]. There are some studies that have quoted positive effect (e.g, sibling bonding) on siblings residing in a household with a child with disability [6]. Certain studies mention interplay of four general characteristics that guides sibling adjustment to the chronic illness, namely family, parent, illness and sibling characteristics [7].

Emotional and behavioural problems among siblings of children with chronic neuromuscular illnesses have been the topic of research for many decades. A study by Williams et al mentions feelings of loneliness and isolation, anxiety, depression, vulnerability, anger, worry about the ill child, school problems, poor peer relations, withdrawal or shyness, somatic complaints,

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low self-esteem, and behaviour problems (internalizing and externalizing) among siblings with a sick child at home [7]. The Ontario Child Health Study (OCHS) found a 2-fold risk in emotional disorders, including depression, anxiety, and obsessive-compulsive disorder, and a 1.6-fold increase in poor peer relationships among siblings [8]. There are feelings of embarrassment that arise which further hamper adjusting with peers and getting involved in social activities [9].

The purpose of this study is to empirically estimate the magnitude of emotional and behavioural impairment in siblings of children with neuromuscular disability. The siblings residing in households with a child with disability are more likely to experience significant functional impairment. Functional impairment is a key indicator for the need of mental health services, and as such early assessment using easy to use tools like Strength and Difficulty Questionnaire (SDQ), CBCL etc. and interventions to check increasing severity and further adverse consequences need to be addressed.

II. Materials and Methods

A cross-sectional study was conducted in a tertiary care hospital of Maharashtra over a period of 34 months. Neurologically normal siblings (4-17 years old) of children with chronic neuromuscular illnesses (GMFCS II or more) attending paediatric out-patient department (OPD) or in-patient department (IPD) were included in the study. Siblings themselves with chronic diseases/disabilities requiring constant supervision or prolong medications or recurrent hospitalizations or dependency on others for day to day functioning were excluded. *(Figure 1)*

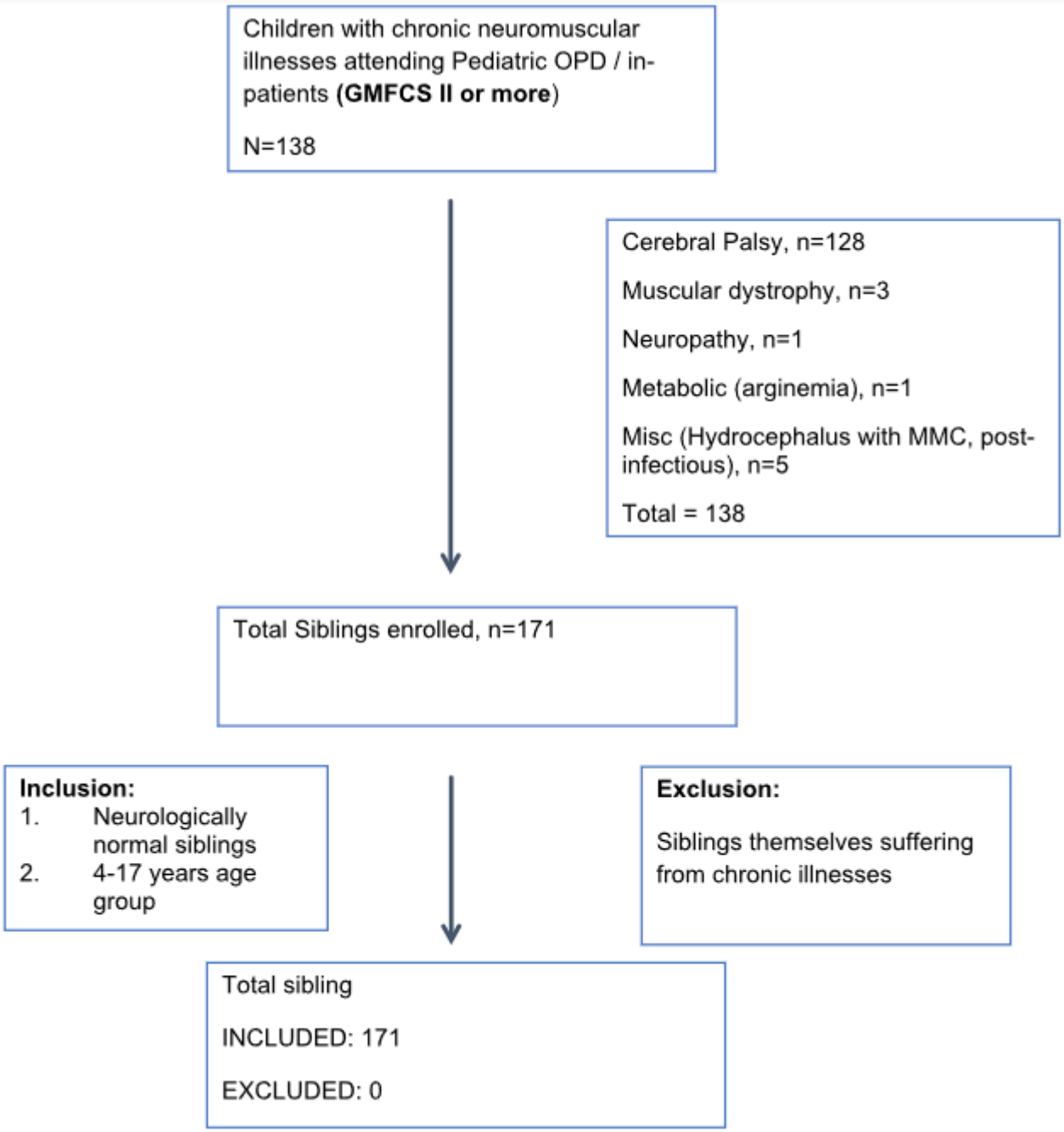

Figure 1: Flow chart showing study design

Based on few earlier studies and assuming 20% abnormal SDQ score among siblings, with 95% confidence and 5% error, the minimum sample size calculated was 171.

Data was collected by interviewing parents using pre-designed proforma to obtain the demographic data and clinical subtype, associated comorbidities and severity of functional impairment of the affected child with chronic neuromuscular illness. Also baseline demographic data was obtained for the parents and siblings using the same proforma. *(Table 1)*

Table 1: Baseline characteristics of siblings

Baseline Characteristics	Total (n=171)	
	No	%
1. Age		
a) 48-71 months	60	35.09
b) 72-119 months	62	36.28
c) 120-204	49	28.65
2. Sex		
a) Male	64	37.43
b) Female	107	62.57
3. Sibling Order		
a) I	81	47.37
b) II	74	43.27
c) III	13	7.6
d) IV	2	1.17
e) V	1	0.58
4. Goes to school		
a) Yes	170	99.42
b) No	1	0.58
5. Scholastic Performance		
a) Poor	3	1.75
b) Average	15	8.77
c) Good	153	89.47
6. Associated illnesses		
a) Yes	4	2.34
b) No	167	97.66
7. Extra-curricular activities		
a) Yes	87	50.88
b) No	84	49.12

Widely used and validated parent completed Strength and Difficulty Questionnaire (SDQ) was used for assessment of behavioral problems among siblings. Total SDQ scores and subscale scores namely emotional problems, hyperactivity issues, conduct problems, peer problems and pro-social behavior were analyzed. The cut off for normal SDQ scores was 0-13, borderline was 14-16 and abnormal was 17-40. A master sheet was tabulated in the excel format. Demographic data was tabulated and proportions and percentages were calculated. Mann-Whitney rank sum test was applied for comparison of variables with non-normally distribution data. ANOVA was used for comparison of variables with normal distribution by using Medcalc Version 9.0.1.0.

III. Results

Of 171 siblings studied, 107 cases (62.57%) were females and 64 cases (37.43%) were males. The female to male sex ratio in the entire study group was1.67:1.

In total, 171 siblings were assessed for emotional and behavioural problems based on SDQ questionnaire filled by parents. The scores ranged from 0-40. On evaluation 124 (72.51%) had normal scores, 25 siblings (14.62%) were in borderline range and remaining 22 (12.87%) had abnormal values. The mean ± SD of SDQ scores among siblings was 12.41 ± 3.6and median score was 11. *(Figure 2)*

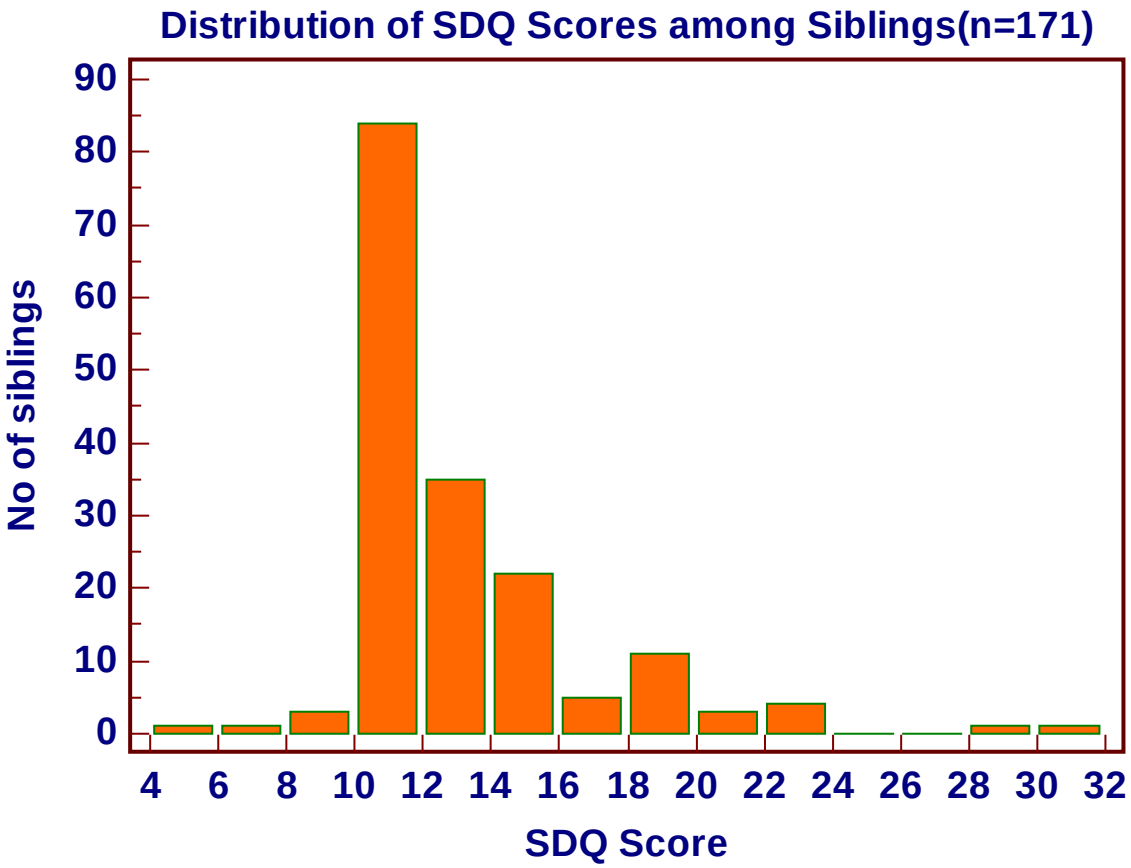

Figure 2: Distribution of Total SDQ scores among siblings

Of the total 107 female siblings 77 (71.96%) had normal, 17 (15.89%) had borderline and 13 (12.15%) females had abnormal score. Among 64 male siblings 47(73.44%) have normal, 8(12.5%) with borderline and 9 (14.06%) were with abnormal scores.

Mann Whiney rank sum test was applied to compare mean SDQ scores between male and female siblings. No significant difference was found between the two groups (p value= 0.229).

The association of sibling order with behavioural and emotional problems was analysed. Out of the total 171 siblings studied, 81(47.37%) were first order, 74(43.27%) were second order, 13(7.60%) were third order and remaining 3 were fourth and fifth order siblings. However, siblings with birth order III and beyond could not be compared because of their relatively small number available for analysis. Among 81 first order siblings 55 (67.9%) had normal, 12 (14.81%) had borderline and 14 (17.29%) siblings had abnormal score. Out of 74 second order siblings 54(72.98%) had normal, 12(16.22%) with borderline and 8 (10.8%) were with abnormal scores. SDQ scores between the first and second order siblings were compared and no significant difference was found between the two groups (p value =0.244).

Out of the total 171 siblings, 49 (28.65%) had the affected child with GMFCS III in the family, 39 (22.8%) as GMFCS IV and 77 (45.02%) were siblings of children with GMFCS V. Siblings of children with GMFCS II were not involved in this group comparison because of the relatively small number (6 cases). ANOVA was applied for comparison of mean SDQ scores among siblings of CP children with GMFCS III, IV and V. There was no significant difference in the mean SDQ scores (p=0.234) amongst siblings of cases who were grouped into three subgroups based on GMFCS class of the affected child, viz, Class III, IV and V.

Tabulation of scores under various subscales of SDQ questionnaire was carried out *(Table 2)*. It was found that majority of children had sub-scores in various domains in normal range and only few had borderline or abnormal scores. Hence separate sub-score analysis was not possible due to small number of children involved in borderline-abnormal zone.

Table 2: Table showing SDQ sub-scores of siblings

SDQ scores	Total		Female		Male	
	No	%	No	%	No	%
1. Hyperactivity Score						
Normal (0-5)	168	98.25	107	100	61	95.31
Borderline (6)	1	0.58	0	0	1	1.56
Abnormal (7-10)	2	1.17	0	0	2	3.13
2. Emotional Problems Score						
Normal (0-3)	161	94.15	101	94.4	60	93.75
Borderline (4)	6	3.51	3	2.8	3	4.69
Abnormal (5-10)	4	2.34	3	2.8	1	1.56
3. Conduct Problems Score						
Normal (0-2)	158	92.4	101	94.4	57	89.06
Borderline (3)	6	3.51	3	2.8	3	4.69
Abnormal (4-10)	7	4.09	3	2.8	4	6.25
4. Peer Problems Score						
Normal (0-2)	159	92.98	99	92.52	60	93.75
Borderline (3)	7	4.09	3	2.8	4	6.25
Abnormal (4-10)	5	2.93	5	4.68	0	0
5. Pro-social Behaviour score						
Normal (6-10)	167	97.66	104	97.2	63	98.44
Borderline (5)	0	0	0	0	0	0
Abnormal (0-4)	4	2.34	3	2.8	1	1.56

IV. Discussion

Children born with significant chronic neuromuscular problems and disabilities are living longer and achieving more due to advances in medicine and allied health services [1]. Special health care services and therapies for children with chronic neuromuscular problems can be exhaustive and expensive. Parents exhaust their financial, physical, and emotional resources to provide for their children with special health care needs [3]. In addition to the significant expenses incurred on these therapies, substantial time is spent learning to navigate the service delivery, coordinating care and augmenting therapy with practice at home [10]. The typically developing offspring fare relatively well compared with the disabled child, and parents instinctively give more time and energy to the child most in need.

There are very few Indian studies relating to this sensitive issue. In the present study an attempt was made to assess the prevalence of emotional and behavioural problems among siblings of children with chronic neuromuscular illnesses and also the factors contributing to such problems.

In our study, of the total 171 well siblings living with children with chronic neuromuscular illnesses majority (72.51%) had normal scores. Of the remaining siblings studied, 14.62% had borderline score 12.57% had abnormal total SDQ score. In similar studies, Giallo et al had reported 15-52% siblings with emotional and behavioural difficulties in at risk/abnormal range as measured on parents' completed SDQ scores [11]. In another study by Goudie et al 16-24% siblings of children with disability were reported to have some degree of functional impairment [11]. A review by Williams et al covered at least 40 studies published between 1970 and 1995 and revealed that approximately 60% of the studies reported manifestations of increased risk for negative outcomes in siblings, 30% found no increased risk while remaining 10% reported both negative and positive effects [7]. Our study revealed 12.57% children with abnormal SDQ scores which indicate lower prevalence in comparison to quoted studies. Most of the children of cerebral palsy were under regular follow up with multimodality management with ready access to all modalities of supportive therapy ensured through neurology OPD services, which had significantly reduced the stress on

the parents. This could be the plausible reason for the smaller number of children with abnormal SDQ scores.

Almost 15% of the siblings had borderline SDQs. This observation is significant as regular ambulatory clinical services with frequent assessment and counselling of parents has the potential to prevent this subgroup from transiting into abnormal score category.

Siblings were assessed separately for their behaviour on various subscales namely- emotional problems, hyperactivity, conduct issues, peer problems and pro-social behaviour. Majority of them, around 80% had subscores within the normal range. Giallo et al also found that majority of the siblings have subscores on various emotional and behavioural problems within the normal range [11]. This is an encouraging observation that siblings have emotional and behavioural functioning within the normal range on all subscales of SDQ despite the family crisis.

SDQ scores of female and male siblings were analysed separately. On comparing, no significant difference was found between the two groups (p value=0.229). In a study by S.A. Fleary et al they found significant gender difference in behavioural problems in certain domains with males having more problems in acting out and females having more issues with alienation. This difference could be attributed to different coping styles of males (externalizing) and females (internalizing) behaviour in general [12]. Hannah et al in their study in 1999 found that brothers of affected children had problem in school functioning while sisters expressed their adjustment issues through internalization [13]. However sub-scores analysis between male and female siblings was not possible in our study due to small sample size.

Sibling order could also have an impact on emotional and behavioural adjustment in children. In our study, SDQ scores of first and second order were analysed and compared to find this association. Siblings with birth order three and above could not be compared as the numbers involved was very small for analysis. On comparison no significant difference was found between the two groups (p value=.0.244). Breslau et al in their study found that neither relative birth order nor sex had a statistically significant main effect on overall level of psychological functioning in siblings but together they have significant "crossed" interaction on psychological functioning. Younger male siblings of disabled child showed greater psychological impairment, whereas among females, those younger than the disabled were better off than those older [14]. Tew et al did not find any effect of birth order on the psychological impairment of normal siblings [15].

Another probable factor that could affect the level of psychological impairment in well sibling is the level of functional impairment of the disabled child. This is because severe functional impairment poses significant and time-intensive demands on the parents. We analysed the SDQ scores of siblings based on GMFCS classification of the disabled child in the family. Majority of siblings (73.3%) scored in the normal range. On comparing the three groups no significant association was found between level of severity or functional impairment of the affected child to the degree of psychological or emotional problems in siblings (p value= 0.234). Lavigne et al in their meta-analysis found that though inter-disease variation to psychological adjustment might occur but overall, there is no significant difference on these adjustment in various sensory/neurological disorders [16].

Besides these there are certain parental and family related variables also that can affect the emotional and behavioural adjustments in siblings: absence of parental depression, good marital adjustment, high levels of community support and family resources, and effective parent-sibling communication about illness. Another important variable is maternal education and her understanding and adaptability to the circumstances [7]. Sometimes parents have to quit job, take unplanned leaves or sick leaves to take care of the affected child [7]. Though these variables were not separately analysed in our study but it was found that out of the total 129 non-working mothers interviewed, 12 (9.3%) told that they had to quit job to fulfil their responsibility as a caregiver.

As far as the limitations of the index study goes, the authors feel that similar studies, if carried out on a larger population at multiple centres involving patients of different races and ethnic origin, may give an even better insight and understanding of the psychosocial commotion caused in the siblings of the disabled children. This may help in early diagnosis of psychosocial impairment and behavioural deviation in siblings and early intervention thereafter.

V. Conclusion

To conclude, the prevalence of chronic neuromuscular illnesses among pediatric population is substantial, even with improvement in health care facilities and change in social philosophy about their health care requirements and home-based supportive care. Apart from limited mobility affected children have multiple co-morbidities which poses additional burden upon parents and other family members particularly siblings in coping with the extra responsibilities. Though majority of siblings were found to have no emotional and behavioural problems in the study but the small percentage definitely had these problems to warrant caregiver and medical attention. Using a simple, easily available and easy to administer screening tools like SDQ can help pick up these children so that necessary

interventions are applied in a timely and efficient manner. Having well-organised family-oriented neurology OPD with counselling facilities can have a long-term impact on the well-being of the siblings and the entire family who is constantly coping with a disabled child.

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Abbreviations:

ANOVA	Analysis of Variance
CBCL	Child Behaviour Check List
CP	Cerebral Palsy
e.g.	For example
GMFCS	Gross Motor Function Classification System
IPD	In Patient Department
OCHS	Ontario Child Health Study
OPD	Out Patient Department
SD	Standard Deviation
SDQ	Strength and Difficulty Questionnaire

Table of Content Summary: Identifying and treating even small proportion of siblings with behavioural problems can have a long-term impact on development and well-being of the child

What's known on this Subject: A neurologically impaired child in a family imposes immense financial, emotional and social burden. Nurturing a healthy sibling in such environment is a challenge having both positive and negative impacts on his psychological and emotional development.

What this Study Adds: A neurologically disabled child in a family can have adverse emotional-psychological effect on small percentage of normally developing siblings. Using a simple, easy to administer screening tool like SDQ can help pick up those affected and early intervention applied.

Contributor's Statement Page

Dr. Nidhi Garg and Dr Krishna Moorthi Adhikari both were fully involved in the conception, planning, intervention, data collection and interpretation, literature review, manuscript preparation and review of the write-up.

Both approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Axonal Degeneration in Guillain-Barré Syndrome: A Reappraisal

By José Berciano
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Abstract- The aim of this review was to analyse the pathophysiology of axonal degeneration in Guillain–Barré syndrome (GBS) with emphasis on early stages (≤ 10 days after onset). An overview of experimental autoimmune neuritis (EAN) models is provided. Originally GBS and acute inflammatory demyelinating polyneuropathy were equated, presence of axonal degeneration being attributed to a "bystander" effect. Afterwards, primary axonal GBS forms were reported, designated as acute motor axonal neuropathy/acute motor–sensory axonal neuropathy. Revision of the first pathological description of axonal GBS indicates the coexistence of active axonal degeneration and demyelination in spinal roots, and pure Wallerian-like degeneration in peripheral nerve trunks. Nerve conduction studies are essential for syndrome subtyping, though their sensitivity is scanty in early GBS. Serum markers of axonal degeneration include increased levels of neurofilament light chain and presence of anti-ganglioside reactivity.

Keywords: AIDP · AMAN · AMSAN · Axonal degeneration · Complement · Demyelination · Eculizumab · Electrophysiology · Endoneurial fluid pressure · Experimental autoimmune neuritis · Ganglioside · Guillain–Barré syndrome · Inflammatory oedema · Methylprednisolone · Pain · Spinal nerve · Ultrasonography.

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José Berciano

Abstract- The aim of this review was to analyse the pathophysiology of axonal degeneration in Guillain–Barré syndrome (GBS) with emphasis on early stages (≤ 10 days after onset). An overview of experimental autoimmune neuritis (EAN) models is provided. Originally GBS and acute inflammatory demyelinating polyneuropathy were equated, presence of axonal degeneration being attributed to a "bystander" effect. Afterwards, primary axonal GBS forms were reported, designated as acute motor axonal neuropathy/acute motor–sensory axonal neuropathy. Revision of the first pathological description of axonal GBS indicates the coexistence of active axonal degeneration and demyelination in spinal roots, and pure Wallerian-like degeneration in peripheral nerve trunks. Nerve conduction studies are essential for syndrome subtyping, though their sensitivity is scanty in early GBS. Serum markers of axonal degeneration include increased levels of neurofilament light chain and presence of anti-ganglioside reactivity. According to nerve ultrasonographic features and autopsy studies, ventral rami of spinal nerves are a hotspot in early GBS. In P_2-induced EAN models, the initial pathogenic change is inflammatory oedema of spinal roots and sciatic nerve, which is followed by demyelination, and Wallerian-like degeneration in nerve trunks possessing epiperineurium; a critical elevation of endoneurial fluid pressure is a pre-requisite for inducing ischemic axonal degeneration. Similar lesion topography may occur in GBS. The repairing role of adaxonal Schwann cytoplasm in axonal degeneration is analysed. A novel pathophysiological mechanism for nerve trunk pain in GBS, including pure motor forms, is provided. The potential therapeutic role of intravenous boluses of methylprednisolone for early severe GBS and intractable pain is argued.

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I. Introduction

Guillain–Barré syndrome (GBS) is an acute-onset, postinfectious and immune-mediated disorder of the peripheral nervous system, which is currently divided into several subtypes based on electrodiagnostic, pathological and immunological criteria [1, 2]. GBS includes at least four disease patterns: acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor–sensory axonal neuropathy (AMSAN) and Miller Fisher syndrome (MFS) [3]. Patients with AMAN or AMSAN frequently have serum antibodies against GM1 or GD1a, whereas reactivity against GQ1b occurs 80–95% of patients with MFS [4–6]. Conversely, in ADIP, no consistent anti-ganglioside reactivity has been found. In Europe and North America, GBS is usually caused by AIDP, whereas in Asia (China, Japan and Bangladesh), a considerable number of GBS patients have AMAN [4, 7]. In a detailed histological study of ventral spinal roots in 15 Japanese patients with GBS, 5 (33%) had predominantly axonal pathology [8]. Worthy of note is that two recent European GBS surveys, conducted in Italy and Spain, have demonstrated a substantial and unexpected proportion of axonal GBS cases, 35% and 28.5%, respectively [9, 10].

According to GBS autopsy data, axonal degeneration in GBS may be primary or secondary to inflammatory demyelination in proximal nerve trunks [11]. Delimitation between primary and secondary axonopathy is not an easy task, quite often requiring serial nerve conduction studies (NCS) [12], and in fatal cases, adequate nerve sampling with use of immunocytochemistry, fibre teasing and plastic sections [13, 14]. Imaging techniques (magnetic resonance imaging [MRI] and ultrasonography [US]) have provided valuable guidance to delimitate the topography of nerve changes [11]. Certain known biological markers, presence of anti-ganglioside reactivity and elevated serum neurofilament light chain (sNfL) concentration may point to underlying axonal pathology in GBS [4, 6, 15]. Experimental autoimmune neuritis (EAN), a widely accepted model of GBS, has provided some important information regarding the pathogenesis of any GBS subtype, and particularly the mechanisms of axonal degeneration [16].

Bearing in mind all of the above-mentioned considerations, the aim of this review was to critically analyse the pathophysiology of axonal degeneration in GBS with emphasis on initial stages of the disease, conventionally divided into two groups: early GBS (≤ 10 days after onset) and very early GBS (VEGBS; ≤ 4 days after onset). For a better pathophysiological understanding of axonal damage, an overview of EAN models will be provided.

II. Selected Electrophysiological and Imaging Considerations in GBS

In a serial electrophysiological evaluation of 70 AIDP patients, Albers and colleagues found that two of them, both with multiple serial NCS (5 and 8, respectively), showed axonal degeneration only [17]. At that time, Wallerian degeneration was a known epi-phenomenon in EAN, which may represent a "bystander" effect associated with inflammatory demyelination [18–20]. Electrophysiological criteria of GBS diagnosis have been in a state of constant flux providing an increasing accuracy for subtyping in the established disease [12, 21–23]. This is not the case of VEGBS where initial electrophysiology allows subtyping in just 20% of cases [24, 25]; so low electrodiagnostic sensitivity relies on the fact that, at early stages of the disease, its pathologic background is neither demyelination nor Wallerian-like degeneration, but inflammatory oedema causing conduction failure (see below). The pathogenic role of inaugural inflammatory nerve oedema, leading to increased endoneurial fluid pressure (EFP) as a potential cause of axonal dysfunction, has been to a large extent overlooked. Such forgetfulness makes it difficult to accurately interpret early and subsequent electrophysiological and pathological events both in GBS and EAN [11, 25].

In recent times, several advances have added accuracy for GBS diagnosis. It is well known that histopathological changes in any early GBS subtype often predominate in proximal nerve trunks [11], their detection having been improved by means of electrophysiological measurement at Erb's point [26], motor root conduction time [27], lumbar root stimulation [28] and triple stimulation technique (TST) [29]. Intriguingly in 6 AMAN patients, examined between days 1 and 6 (median, 4.5) and whose conventional NCS did not fulfil the electrophysiological criteria of GBS, TST demonstrated that all 6 patients had proximal conduction block situated between root emergences, namely ventral rami of spinal nerves and the Erb's point [29]. Therefore, these electrophysiological features correlate extremely well with pathological and US studies showing that spinal nerves are a hotspot in any early GBS subtype (see below).

Imaging techniques, including MRI and nerve US, have provided better topographic delineation of early changes in GBS [30–33]. Using post-contrast T1 sequences, MRI regularly (around 80% of scanned cases) shows cauda equina nerve root enhancement usually predominating in ventral roots [30, 32]. The MRI series by Byun and colleagues included eight GBS patients, six of them with the pure motor subtype; two enhancement patterns were noted [31]: (i) one was enhancement of both anterior and posterior spinal nerve roots, which occurred in their two patients presenting with sensorimotor neuropathy; and (ii) the other one was enhancement of the anterior spinal roots, observed in the remaining six patients presenting with pure motor GBS, which is in good correlation with the pathological background of either demyelinating or axonal pure motor syndromes [34–36].

Nerve US is a routine technique in the diagnosis of peripheral nervous system disorders [37]. In our US nerve studies, main early lesions relied on ventral rami of C5–C7 nerves, these occurring equally in patients categorized as axonal GBS or AIDP [25, 33]. Figure 1 illustrates sonograms of C5–C7 nerves (day 5 after onset) in a severe GBS patient, aged 80 years, who died on day 9 (case 1 in reference [33]). In our series, only a minority of patients showed abnormal peripheral nerve sonograms, essentially restricted to proximal median and ulnar nerves. In a previous early GBS study, there was significant enlargement in all measured nerves, except the sural nerves [38]. The obvious discrepancy calls for new US studies.

a) GBS classic pathological hallmark

Over the ensuing seven decades after its original description [39], GBS was regarded pathologically as a primary inflammatory demyelinating disease [40–44]. Autopsy studies in early GBS established that initial histological changes are characterized by endoneurial oedema, more prominent where motor and sensory roots joint to form the spinal nerve [40, 45]. It is worthy of note that Haymaker and Kernohan [45] did not identify inflammatory cells until the course was well-advanced and, therefore, then they were regarded

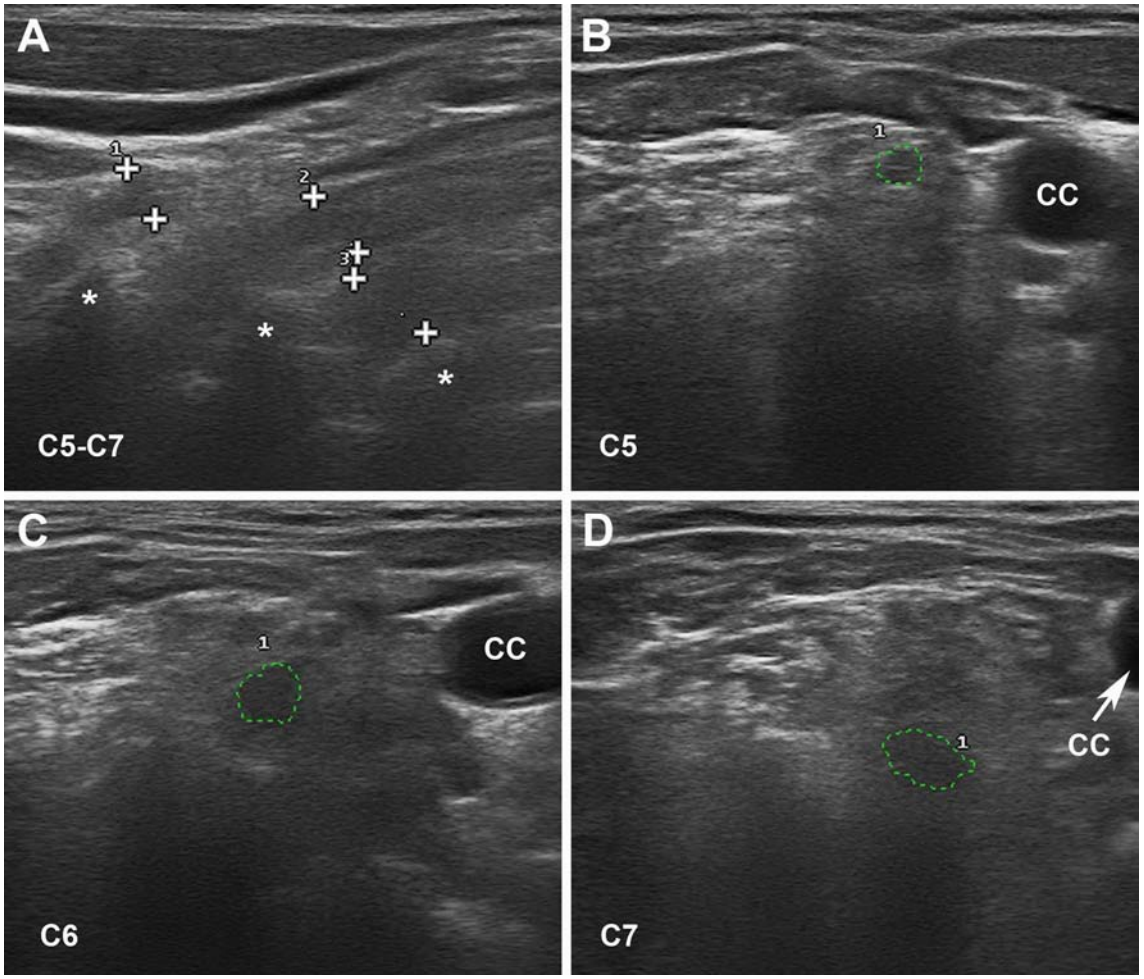

Fig. 1: US of ventral rami of C5-C7 nerves in early AIDP. Taken from reference [33]. a Sagittal sonogram showing blurred boundaries of the 3 scanned cervical nerves (callipers). Asterisks indicate transverse vertebral processes. b–d Short-axis sonograms showing the cross sectional areas of each cervical nerve(dotted green tracings), whose values are as follows: C5 = 9 mm^2 (control mean 6.22; SD 2.75), C6 = 18 mm^2 (control mean 9.63; SD 4.21) and C7 = 23 mm^2(control mean 12.29; SD 5.33). CC indicates common carotid artery

as part of a reparative process. Contrariwise, Krücke [40] recognized that endoneurial infiltrates occurred as of 24 h and were prominent as of the third day. Be that as it may, it should be noted that on traditional light microscopic study of GBS nerve biopsies, endoneurial mononuclear infiltration is visible in a minority of cases [46]; for an accurate detection of inflammatory cells, immunochemistry or thin sections are necessary [13, 14]. The outstanding lesions of ventral rami of spinal nerves are illustrated in Figs. 2 and 3.

In their seminal clinical–pathological paper comprising 19 autopsy studies, Asbury and colleagues found that the common denominator in all cases was an inflammatory demyelinative neuritis marked by focal, perivascular, lymphocytic infiltrate, affecting any level of the peripheral nervous system [41]. These authors indicated that varying amounts of Wallerian degeneration were also present, depending upon the intensity and destructiveness of lesions. They also suggested that, on the basis of the pathologic features of GBS and EAN, both disorders are a cell-mediated immunologic disorder, in which the peripheral nervous system, particularly myelin, is attacked by specifically-sensitized lymphocytes, but stating "that no oedema was observed in our series strengthens rather than weakens the homology between EAN and idiopathic polyneuritis".

b) Recognizing a distinct form of axonal GBS

Identification of an axonal form of GBS can be chronologically divided in three steps, which are analysed below.

First, a variant of GBS characterized by an acute axonal neuropathy was created by Feasby et al. [47] (for further details, see below). Not without lively debate and much controversy, the proposal of a primary axonal GBS subtype was

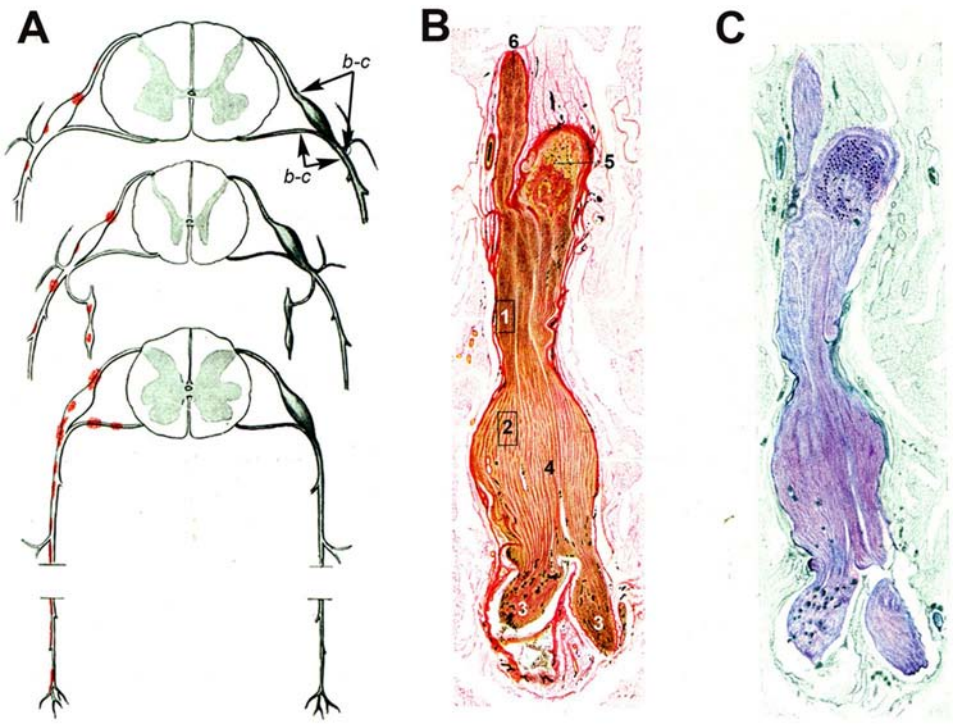

Fig. 2: Pathology of GBS. Adapted from Figs. 65 to 67 by Krücke [40] with minimal modifications. a Diagram of GBS lesions at cervical (upper row), thoracic (middle row) and sacral (lower row) levels; note that they mainly rely on proximal nerves including ventral and dorsal spinal roots, spinal root ganglia, sympathetic ganglia and ventral rami of spinal nerves (red dots). Lettering b-c indicates nerve segment illustrated in the following two images. b Longitudinal section of the nerve segment between anterior spinal root and spinal nerve from a GBS patient who died on day 18, original numbering being as follows: (1 and 2) areas illustrated by the author in other figures (specially his Fig. 68b showing abundant endoneurial inflammatory oedema, which was designated as "mucoid exudate"); (3) rami of the spinal nerve (undoubtedly, ventral and dorsal rami); (4) splinded shaped swelling of the spinal nerve; (5) spinal root ganglion; and (6) anterior spinal root (Van Gieson, magnification not specified). c The same longitudinal section showing a purplish discoloration of the spindle-shaped swelling of the spinal nerve (Cresyl violet, magnification not specified)

accepted in the literature [34, 48–54]. It is worthy of note that the earliest axonal GBS report was probably case 2 by Asbury and colleagues presenting a pure motor semeiology [41]. Three days after onset, autopsy revealed intense inflammatory lesions of ventral roots with prominent axonal retractions on silver staining; intriguingly, peripheral nerve trunks showed minimal changes. This patient, that had an influenza-like illness 10 days prior to admission, probably represents the first description of AMAN.

Second, Yuki and colleagues reported severe pure motor GBS in two adult patients, following *Campylobacter jejuni* enteritis, whose electrophysiology indicated that the predominant process was axonal degeneration of motor nerves; in both cases, there were high titres of IgG antibody against GM1 ganglioside considered pathogenic by selective motor axon involvement [55]. Soon after, Gregson and colleagues reported the case of a 52-year-old patient presenting with an acute-onset purely motor neuropathy in upper arms and thighs, though previously he had severe aching pains in the neck [56] (see below for the mechanism of neuropathic pain in pure motor GBS). There were high titres of polyclonal serum antibody to GM1, GD1b, asialo-GM1 and lacto-*N*-tetraose. Electrophysiology showed normal motor conduction velocities (MCV) and normal distal motor latencies (DML), reduced compound muscle action potentials (CMAP) without evidence of conduction block and denervation on muscle sampling. Wisely, the authors commented on "factors in favour of the pathophysiology being in part due to proximal conduction block with segmental demyelination at the root level would be the absence of F wave responses, the inflammatory cerebrospinal fluid changes and the relatively rapid recovery in the early stages of the disease. On the available evidence, it is not possible to distinguish the relative contribution of axonal versus demyelinating pathology further". As argued in this paper, such comment remains as relevant as ever.

Third, originally recognized under the rubric of Chinese paralytic syndrome, McKhann and colleagues reported 36 patients from rural areas of northern China, aged from 15 months to 37 years (median 7 years), who were admitted during a 2-week period in August 1990 with acute paralytic disease, whose electrophysiology showed CMAP amplitude

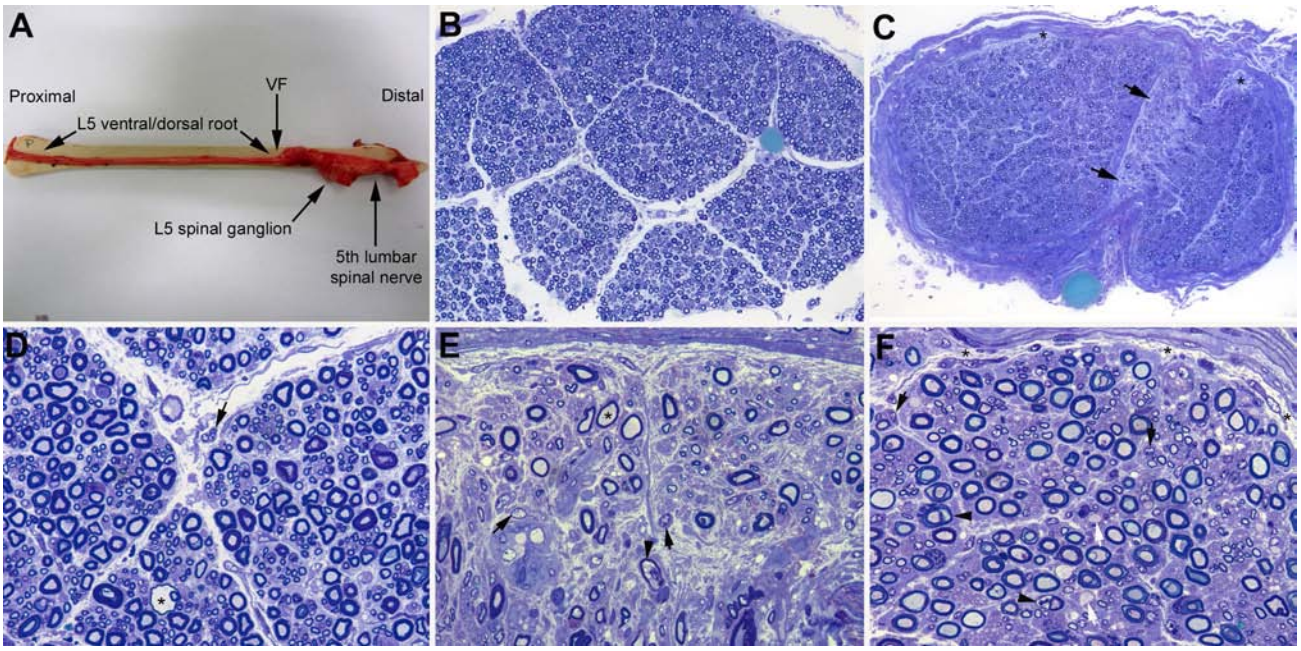

Fig. 3: Pathological features in early AIDP (adapted from case 1 by Gallardo et al. [33]). a After being dissected down, macroscopic appearance of the right L5 spinal root, L5 spinal ganglion and fifth lumbar spinal nerve. Whereas the pre-foraminal root shows normal morphology, as of the vertebral foramen (VF) note visible nerve enlargement. b Semithin cross-section of L5 ventral root, taken 1 cm above its entrance to the VF, showing that the density of myelinated fibres is preserved (Toluidine blue; original magnification × 100 before reduction). c Semithin cross-section of the ventral ramus of the fifth lumbar nerve, taken at its emergence trough intervertebral foramen, showing widespread endoneurial oedema, which is more conspicuous in septum adjacent areas (arrows) and subperineurial areas (asterisks); such oedema results in a spacing out phenomenon giving an observer the false impression of reduced density of myelinated fibres (Toluidine blue; original magnification × 65 before reduction). d High-power view of the L5 ventral root showing preservation of the density of myelinated fibres with occasional presence of mononuclear cells arrow and a fibre exhibiting myelin vacuolization (asterisk). e High-power view of the sub-septum area arrowed in C. Note the presence of florid inflammatory oedema with numerous mononuclear cells (arrows), fibres with inappropriately thin myelin sheaths (asterisk), and fibres exhibiting myelin vacuolation (arrowhead). Having in mind the spacing out phenomenon, there is reduced density of myelin fibres in comparison with L5 ventral root and sciatic nerve (previous and next images) (Toluidine blue; original magnification ×630 before reduction). f Semithin section of sciatic nerve showing some demyelinated axons (white arrows), fibres with vacuolar degeneration (arrowheads), and widespread but discreet endoneurial oedema more marked in subperineurial areas (asterisks) with presence of monuclear cells (black arrows) (Toluidine blue; original magnification × 630 before reduction)

reduction and normal MCV [57]. The disorder was considered a type of reversible distal motor nerve terminal or anterior horn lesion; intriguingly, shortly after such distal motor nerve lesion would be confirmed [58, 59]. A 4-week precedent illness occurred in 47% of patients. Worthy of note is that, despite being a pure motor syndrome, many patients had pain (see below). Two years later and under the rubric of AMAN, McKhann and colleagues reported the results of 10 autopsy studies showing non-inflammatory Wallerianlike degeneration of motor fibres in 5, demyelination in 3 and absence of lesions in 2 [35]. Afterwards, these histopathological features were reassessed in other seminal studies by the John's Hopkins Group and Chinese collaborators (reviewed in reference [60]). High IgG and IgM antibody titres to *Campylobacter jejuni* were observed. The series comprised now 12 post-mortem studies, lesions being categorized as follows: 3 AMAN, 3 AMSAN, 3 AIDP, and 3 exhibiting minimal pathology [30, 36, 59–63]. AMSAN pattern was considered similar to that originally reported in axonal GBS [47]. In AMAN, the major pathological finding was extensive Wallerian-like degeneration of the ventral roots and, usually a lesser degree, of motor fibres within the peripheral nerves; the proportion of degenerating radicular fibres increased distally toward the ventral root exit from the dura where 80% of fibres were degenerating [35], namely maximal pathology occurred in spinal nerves. A prominent feature of axonal patterns was the early presence of macrophages within the periaxonal space, surrounding or displacing the axon, and surrounded by an intact myelin sheath with the presence of IgG and the complement C3d and C5b-9 (membrane attack complex [MAC]) [64]. The authors suggested that AMAN is an antibody- and complement-mediated disorder in which relevant epitopes are present on the nodal and internodal axolemma. This notion was the starting point to create the new nosological category of nodo-paronodopathy encompassing various acute and chronic neuropathies

associated with anti-ganglioside antibodies that share a common pathogenic mechanism of dysfunction/ disruption at the node of Ranvier [65].

c) Original description of axonal GBS: only axonal pathology?

The series by Feasby and colleagues consisted of five patients, who showed severe clinical picture and electrically inexcitable motor nerves [47]. One patient (case 1) died, and 3 of the 4 survivors exhibited poor recovery. Pathological study was done in case 1. Nerve inexcitability, recorded on day 3 after onset in case 1 and on day 2 in case 4, was attributed to axonal degeneration [47, 53, 54]. However, such interpretation is questionable given that in Wallerian degeneration motor-evoked responses amplitudes are reduced by 50% at 3 to 5 days after injury, the responses being absent by day 9 [66]. Retrospectively, three alternative pathophysiological explanations could be considered here:

- First, accepting that we are confronted with a primary axonal process, so very early nerve inexcitablity could be due to distal motor conduction block induced by antiganglioside antibodies [4]; at that time, however, the pathogenic role of such antibodies in axonal GBS was unknown.
- Second, one could argue distal demyelinating conduction block [58, 67], but again this interpretation is questionable since autopsy studies in VEGBS have shown that incipient demyelination, preceded by nerve inflammatory oedema, usually appears as of day 5, florid demyelination settling down later on [11, 40, 45].
- The third pathophysiological mechanism is ischemic neuropathy to be addressed later.

Feasby and colleagues carried out a detailed autopsy study in their case 1 [47]. This patient was a 64-year-old woman presenting with ascending weakness and paresthesiae over the course of several hours. Next morning, there was are flexic tetraplegia and bulbar palsy requiring mechanical ventilation. She died on day 28. Tissue sampling included central nervous system, nerve roots and peripheral nerves, whereby conventional neuropathological examination was undertaken complemented with semithin and thin sections, and fibre teasing. Pathological features are summarized as follows: "severe axonal degeneration in nerve roots and distal nerves without inflammation or demyelination." According to the authors, macrophages containing myelin debris were common, but few scattered lymphocytes were observed; there was no perivascular cuffing with inflammatory cells, and there was minimal endoneurial oedema; it is worth noting that their Fig. 3, corresponding to a transverse semithin section of the deep peroneal nerve, shows a phenomenon of spacing out of myelinated fibres probably due to endoneurial oedema, particularly prominent in subperineurial areas (on the bottom of the image). On fibre teasing, done in deep peroneal and superficial peroneal nerves but not in lumbar roots, the main finding was axonal degeneration.

With colleagues, I reported a severe case of pure motor GBS, died on day 29 after onset, whose pathological background was macrophage-associated demyelination of ventral roots with secondary axonal degeneration [34]. At that time, we compared our pathological findings with those reported by Feasby et al. [47] concluding as follows: "We have observed, however, an apparent similarity between our pathological findings on transverse sections of ventral root and those illustrated in Feasby's work (cf our Fig. 3 and their Fig. 2). Certainly without teased fiber preparation, semithin longitudinal sections, and ultrastructural study we would have overlooked the relevance of segmental demyelination and remyelination. In fact, 24% of teased fibres from L5 ventral root exhibited de-remyelination, and this percentage might have been substantially greater at the onset of symptoms if we assume that demyelination precedes axonal degeneration." These two mentioned images are reproduced in Fig. 4; note that in Feasby's material together with active axonal degeneration, there are also signs of evident demyelination including widespread vesicular dissolution of myelin that by then had already been recognized as an elementary lesion in demyelinating GBS [42–44]; afterwards, it was demonstrated that vesicular dissolution is seen before the invasion of macrophages into myelin, and is the predominant change in the subject with symptoms for 3 days [63]. Consequently, the question arises as to whether such radicular axonal degeneration is primary or secondary to inflammatory demyelination. Although there is no exact response, what we now know is that axonal GBS may result from a proximal demyelinating process with secondary axonal degeneration [33, 68–70]. Furthermore and accepting that Feasby's case 2 might be categorized retrospectively as AMSAN (see above), the presence of demyelinating lesions could be accounted for by the fact that peripheral nerve myelin contains many glycolipids and gangliosides that are important antigens for antibody responses [71]. Concerning pathology in AMSAN, Griffin and colleagues wisely indicate that "there were rare but unequivocal examples of demyelinated internodes with intact axonal and lipid nearby filled macrophages. Definite but rare patches containing scattered lymphocytes were identified in spinal roots by immunohistochemistry and plastic sections. There was oedema in the subperineurial and endoneurial spaces in regions with numerous degenerating fibres… Strictly speaking, these cases are neither non-demyelinating nor non-inflammatory, but rather predominantly axonal and minimally inflammatory [3]." In short, separation

between AIDP and axonal GBS does not seem absolute, a fact already suggested by the heterogeneity of pathological background of the Chinese paralytic syndrome, encompassing AMAN/AMSAN, AIDP, or even minimal changes [36].

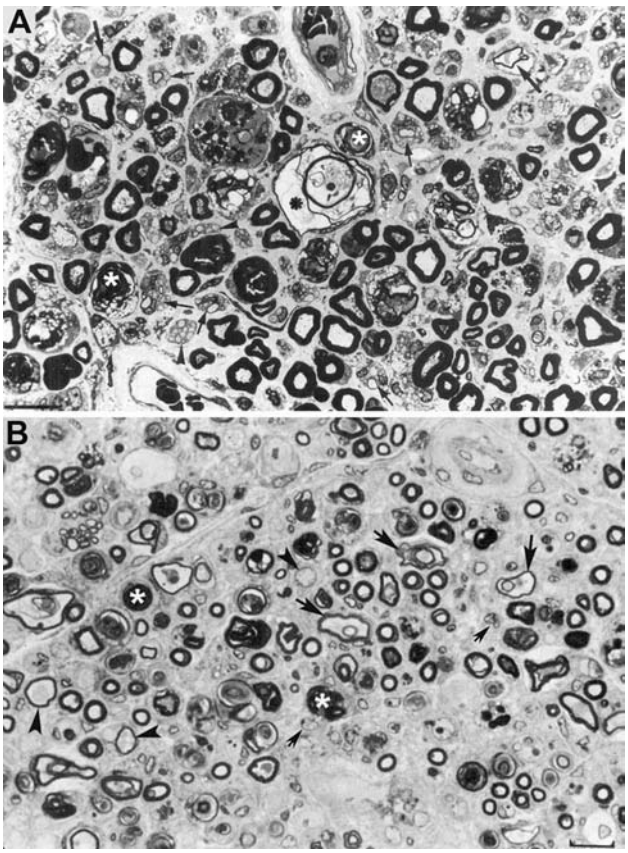

Fig. 4: Composite image to compare lesions in anterior spinal roots. Taken from Fig. 3 by Berciano et al. [34] (a) and Fig. 2 by Feasby et al. [47] (b). Both pictures correspond to transverse semithin sections of ventral lumbar roots. a Keeping up original graphic resources, note the presence of numerous endoneurial lipid-laden macrophages, sometimes encircling degenerated fibres with myelin collapse (white asterisks). There are clusters of regeneration containing either non-myelinated axons (arrowheads) or non-myelinated and thinly myelinated axons (small arrows), and also occasional demyelinated or remyelinated axons (large arrows). Black asterisk indicates a fiber exhibiting vesiculo-vacuolar dissolution of myelin (Toluidine blue; bar = 19 μm). b The original figure legend, with no graphic resources, is as follows: "Transverse section showing severe axonal degeneration". My interpretation is keeping with this criterion, as there are numerous fibers showing myelin collapse (white asterisks), which is indicative of acute axonal degeneration [13, 14]. But note also the presence of fibres with inappropriately thin myelin sheaths (arrowheads) and frequent fibres exhibiting vesiculo-vacuolar dissolution of myelin (large arrows), both features suggesting primary demyelination. In my view, there are frequent endoneurial ovoid or reniform nuclei (small arrows), which most probably correspond to macrophages (Toluidine blue; bar = 20 μm). (Reproduced with permission from Brain, Oxford University Press)

d) Axonal pathology in demyelinating models of EAN

Wallerian degeneration was already reported in the original EAN induced by the injection of peripheral nervous tissue and adjuvants [72], which were soon after correlated with a "bystander" effect (see above).

In a model of EAN passively induced in Lewis rats by intravenous injection of T line cells specific for bovine P_2 myelin protein, Izumo and colleagues reported serial animal semiology and detailed pathological changes [73]. The first signs of clinical disease, a flaccid tail and weakness of the hindlimbs started between 3.5 and 4 days postinoculation (pi), which rapidly progressed to a peak (flaccid paraplegia and forelimb paresis) between days 7 and 9. On day 4 pi, the first pathological change was marked oedema with or without cellular infiltrates in the sciatic nerve and lumbosacral nerve roots. On day 5, extensive, disseminated lesions were observed in the sciatic nerve, these being more severe and advanced proximally; they consisted of marked oedema, cellular infiltrates (granulocytes and mononuclear cells), and perivascular cuffs not only in the endoneurial space but also in the epineurium. At this time, no evidence of the characteristic changes observed in peripheral demyelination could be observed. Between days 7 and 9 pi, while inflammatory oedema declined, there appeared florid demyelination; independent of this, there were some nerve fibres showing distinct axonal

degeneration. Between days 14 and 20 pi, inflammatory oedema subsided, and the lesions were composed of advanced demyelination and axonal degeneration. An overview of their tabulated morphological findings indicates that initial inflammatory oedema predominated in sciatic/femoral nerves and lumbosacral nerve roots, late demyelination is almost widespread, and marked axonal degeneration is almost restricted to sciatic/femoral nerves. Concerning the exact mechanism of axonal degeneration in EAN, the authors commented on the possible "bystander damage", though they wisely proposed the pathogenic role of ischemia, given that in their histological material marked axonal degeneration was observed just 1 to 2 days after intense endoneurial oedema.

In the same previous P_2-EAN model, Heininger and colleagues carried electrophysiological studies after injection of graded doses of freshly activated T cells, 10^6 (lower dose) and 2×10^6 (higher dose) [74]. The severity of the electrophysiological changes correlated with severity of the clinical disease and was dependent on the number of P_2-specific T cells transferred. As might have been expected in a demyelinating disorder, injection with lower T cell dose resulted in slowing of motor and sensory nerve conduction parameters over days 4 to 7 pi. Conversely, injection of higher dose induced fulminant paraplegia on day 4 pi, and complete conduction failure in peripheral nerves and roots within 24 h, which the authors attributed to severe axonal damage at the root level. Against this proposal, it can be argued that in Wallerian degeneration, motor nerve inexcitabilty does not occur till day 9 after nerve transection [66]; an alternative pathophysiological interpretation will be addressed below.

Using residue 53–78 (SP26) of bovine P_2 myelin protein, Hahn and colleagues induced EAN in Lewis rats [75]. At low peptide dose (25 or 50 μg), scattered pathological changes (demyelination, inflammation and oedema) were observed in lumbosacral roots and sciatic nerves; there was no axonal degeneration. At higher peptide dose (75 or 100 μg), lumbosacral roots showed very active inflammatory demyelination without axonal degeneration, while sciatic nerves exhibited similar signs of inflammatory oedema and almost total axonal destruction. The authors argued that axonal degeneration occurred only with high doses of antigen and in association with very active mononuclear inflammation, but they did not address the blatant discrepancy of axonal changes between spinal roots and sciatic nerves. A few years later, in a clinical–pathological study of a fulminant GBS patient with inexcitable nerves, we also reported a different framework: almost pure demyelination in spinal roots and predominantly Wallerian-lile degeneration in peripheral nerve trunks [67]. It is worthy of note that the Canadian group had reported a centrofascicular pattern of axonal degeneration in the sciatic nerves, which was rightly correlated with possible endoneurial ischemia [76].

Inflammatory oedema and increased EFP of sciatic nerve are changes initially detected in early EAN induced in Lewis rats with intradermal inoculation of an emulsion of peripheral nerve in complete Freund's adjuvant [77]. Several years later, the same American group re-examined the issue in Lewis rats by inoculation with autoreactive T cell lines sensitized to residue 57–81 of P_2 myelin protein [78]. Both oedema and inflammation in sciatic nerves paralleled the time of the EFP increase, reaching peak levels at 7 days pi and declining to near-normal values after 11 days. Intriguingly, axonal damage appeared at the height of the inflammatory process, when oedema and increased EFP were maximal, which are believed "to stretch the perineurium and constrict the transperineurial microcirculation, compromising nerve blood flow and producing the potential for ischemic nerve injury". In AIDP, this pathogenic proposal was corroborated with further description of peripheral nerve trunks (ventral rami of lumbar roots and lumbosacral trunk) showing centrofascicular or wedge-shaped regions with marked loss of large myelinated fibres, which are characteristic of nerve ischemia [69, 79] (Fig. 5).

Finally and continuing with adoptive transfer of P_2-EAN, L5 root histological study at peak disease (day 6) showed inflammation with a mean number of demyelinated axons of 79/mm^2 (0.7% of the total number), and a mean number of degenerating axons of 121/mm^2 (1.0% of the total) [80]; certainly, such low percentage of nerve fibre degeneration does not seem sufficient to explain maximal neurologic deficit (complete limb paralysis). Once again, these findings give strong support to the pathogenic role of inaugural inflammatory oedema.

e) Axonal pathology in EAN induced by anti-ganglioside antibodies

EAN models mediated by antibodies against glycolipids, either demyelinating or axonal, have recently been reviewed [16, 81]. I will focus on selected EAN studies resulting in early Wallerian-like degeneration.

Yuki and colleagues developed an AMAN model in rabbits after administering bovine brain ganglioside (BBG) or GM1 with Freund's complete adjuvant (CFA) [82]. Both experiments resulted in flaccid limb weakness of acute onset. In peripheral nerves, there was Wallerian-like degeneration, macrophage invasion and endoneurial oedema (see their Fig. 1c), with neither lymphocytic infiltration nor demyelination. IgG was deposited on the axons of the anterior roots that apparently exhibit lesser degree of axonal degeneration than that of sciatic nerves (cf. their Fig. 1c and d). The protocol used by Yuki and colleagues was severely criticized, as repeated injection CFA they used could lead to systemic inflammatory response that

contributed to the success of the model [83]. A few years later, Moyano and colleagues validated the Yuki's rabbit model of axonal neuropathy induced by immunization with gangliosides [84]. Interestingly, the authors carried out five different experiments during a period of two years by different operator, using different batches of drugs, in a total of 26 rabbits. A serious objection to this paper is interpretation of their Fig. 3c, semithin section of sciatic nerve, from a rabbit immunized with BBG/Cronassial©/Keyhole limpet hemocyanine, which is described as follows: "note that fibres with axonal degeneration (arrows)", when the great majority of myelinated fibres (around 120 in this image) show normal axons sometimes surrounded by myelin with plumping appearance (just the two arrowed fibres exhibiting myelin collapse suggest active axonal degeneration). There are several endoneurial lipid-laden macrophages. I am persuaded that a diagnosis of axonal neuropathy cannot be accepted without reserve; quite to the contrary, I would suggest that the observed histological changes point to a primary demyelinating process.

Susuki and colleagues provided an AMAN model in rabbits immunized with BBG or GM1, which included the presence of macrophages in the periaxonal space, and IgG deposited on nerve root axons. Initial lesions were located

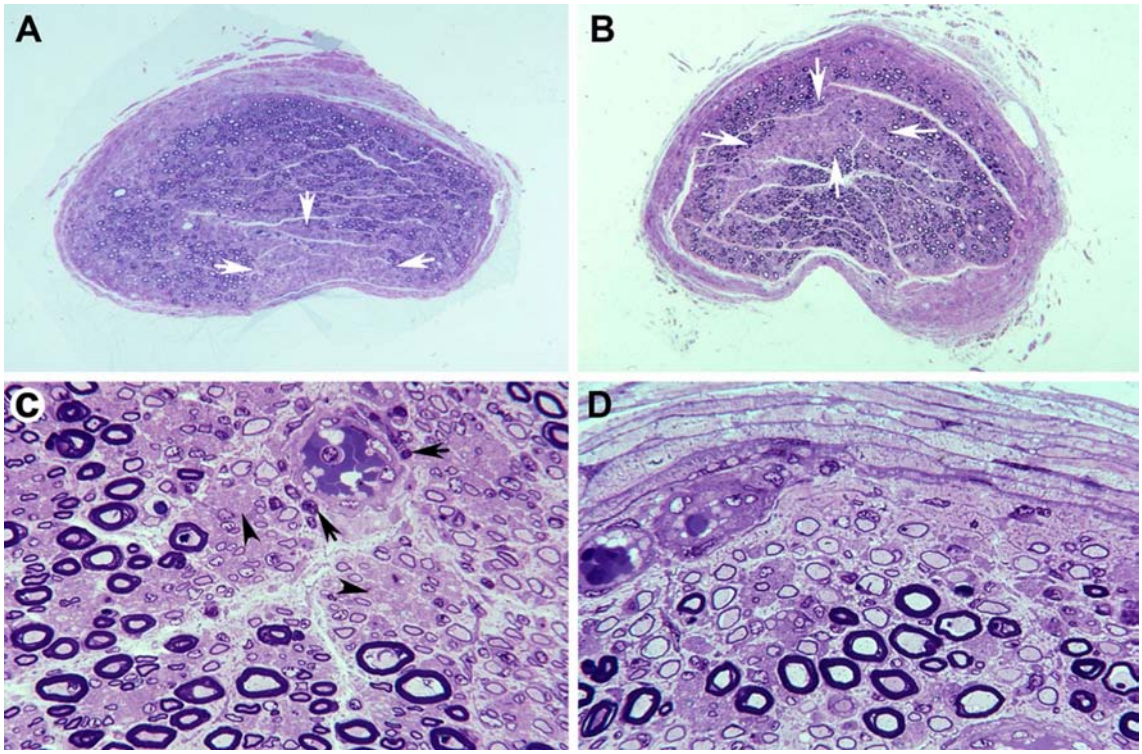

Fig. 5: Ischemic nerve lesions in AIDP. Adapted from Berciano et al. [69]. Semithin sections of the ventral ramus of the third lumbar nerve (a) and lumbosacral trunk (b) illustrating wedge-shaped and centrofascicular areas with marked loss of myelinated fibres (arrows) (Toluidine blue; original magnification × 62 before reduction). c This semithin section of the central region of the lumbosacral trunk illustrates severe reduction of large myelinated fibres, thinly myelinated small axons, preserved unmyelinated axons (arrowheads), and endoneurial mononuclear cells and lymphocytes (arrows) (Toluidine blue; original magnification 470 before reduction). d This semithin section of the subperineurial area of the lumbosacral trunk shows numerous thinly myelinated fibres and occasional mononuclear cells; such extensive de-remyelination accounts, to some degree, for the apparent widespread loss of myelinated fibres perceptible in image B (Toluidine blue; original magnification × 375 before reduction)

mainly on nerve roots, as in AMAN (see above) [85]. Electrophysiology showed that distal motor conduction was preserved, whereas F wave latency could be absent or exceptionally delayed. As wisely indicated by the authors, this electrophysiological finding may indicate demyelination, remyelination, or a wide-paranodes, consistent with the pathology of nerve root specimens. Subsequently, the authors examined the molecular organizations of nodes in this same EAN model associated with antiGM1 antibodies [86]. At the acute phase with progressing animal limb weakness, Na_v channel clusters were disrupted or disappeared at abnormally lengthened nodes concomitant with deposition of IgG and complement; paranodal axoglial structures were also disrupted. The nodal molecules disappear in lesions with complement deposition but not in association with macrophagic infiltration. During recovery, complement deposition at nodes decreased,

and Na_v channels redistributed on both sides of affected nodes. In short, these findings give strong support to the notion that AMAN is a disease that specifically disrupts the nodes of Ranvier.

Using a rabbit EAN model, Yuki and colleagues verified that carbohydrate mimicry between GM1 and the *Campylobacter jejuni* lipooligosaccharide induces the production of pathogenic autoantibodies, and the development of axonal GBS [87]. Although the antecedent of *Campylobacter jejuni* infection and GBS, particularly AMAN/AMSAN, is well established, the concordance between disease in humanbeings and domestic animals, suffering from such infection, is less clear. Li and colleagues analysed the occurrence of spontaneous paralytic neuropathy induced by *Campylobacter* infection in five chicken flocks, whose farm families had recently developed GBS [88]. The only two paralyzed chickens showing florid Wallerian-like degeneration in sciatic nerve belonged to a flock whose farmer had AIDP.

The Willison's Group extended EAN studies focusing on the motor terminal as target site, using both MFS-associated anti-GQ1b antibodies, and AMAN-associated anti-GM1 and -GD1a antibodies [6, 12, 89, 90]. The authors demonstrated that the motor terminal is indeed a vulnerable site for anti-ganglioside antibody attack that resulted in complement fixation. Deposition of MAC pores would allow uncontrolled calcium ingress triggering a sequence of destructive events, including calpain activation, with subsequent paralysis. Undoubtedly, such biological events represent the basis of distal nerve conduction block or RCF reported in AMAN (see above). Nevertheless, the hypothesis that anti-GM1 or -GD1a antibodies alter the presynaptic motor nerve terminal at the neuromuscular junction has not entirely been supported by axonal-stimulating single-fibre electromyography studies. While Spaans and colleagues reported increased jitter and intermittent blocking of muscle fibre action potentials to a varying degree in all 9 examined GBS patients in the acute stage of illness [91], Kuwabara and colleagues found normal jitter in all 23 GBS patients, 13 of them categorized as AMAN [92]. Furthermore, in early axonal GBS, Brown and colleagues carried out electrophysiological recording of M responses in several motor nerves advancing the site of stimulation closer to the point motor [93]. Particularly illustrative is their Fig. 1 showing changes in the extensor digitorum brevis maximum M potentials in response to supramaximal stimulation of the deep (anterior) tibial nerve at 20, 40, 60, 80 and 100 mm proximal to the innervation zone. The greatest M amplitude is that obtained with most distal stimulation. So, this electrophysiological study points to failure, not in terminal motor segments but in pre-terminal ones.

In the context of experimental ganglioside-induced neuromuscular synaptopathy [90], ex vivo and in vivo nerve–muscle preparations exposed to anti-ganglioside antibodies have revealed that peri-synaptic Schawnn cells rapidly become phagocytic and engulf axonal debris [94]. Intriguingly, in proximal nerve trunks of patients died with AIDP harbouring secondary axonal degeneration, we have reported large myelinated fibres with apparently normal myelin sheath that surrounded a dark content often with a light core [69, 70], bringing to mind dark swollen axons [95, 96] (Fig. 6). Ultrastructural study revealed, however, that dark areas corresponded not to swollen axons but to ridges of adaxonal Schwann cells replete with degenerated organelles; axons, though sometimes attenuated, were preserved. Comparable Schwann cell/axon interactions had been reported in other neuropathies and likely represent a nonspecific mechanism by which the Schwann cell clears debris and help maintain the integrity of the axon under normal and pathologic conditions [97].

f) Topography of initial GBS lesions: pathophysiological considerations

As aforementioned, in any GBS subtype, early lesions predominate in spinal roots and spinal nerves; furthermore, in ganglioside-mediated EAN, the outstanding early finding is nerve terminal damage. As a whole, this is so because blood–nerve interface is less efficient in several important structures in the peripheral nervous system, including from the spinal cord to root-nerve junction (spinal nerve), dorsal root ganglia and neuromuscular junctions [98, 99]. Variations in permeability between such areas are presumably important for the distribution of lesions caused by various blood-borne agents of a toxic, immunologic or infectious nature [100], as is the case of GBS and EAN.

Knowledge of the microscopic anatomy of the peripheral nervous system is essential for an adequate understanding of the pathogenic relevance of early pathological events in GBS [101]. Spinal roots traverse the subarachnoid space covered by an elastic multicellular root sheath derived from the arachnoid and penetrate the dura at the subarachnoid angle. As of the subarachnoid angle, where motor and sensory roots join to form the spinal nerve, dura mater is in continuity with epineurium, whereas the arachnoid turns into perineurium. Therefore, intrathecal nerve roots are covered by an elastic root sheath, whereas spinal nerves and more distant nerve trunks till their pre-terminal segments possess epi-perineurium that is relatively inelastic. Conceivably, initial inflammatory oedema may be accommodated in intrathecal nerve roots enlarging their size but without this implying significant increase of EFP. Conversely, in nerve trunks surrounded by epi-perineurium, such oedema may cause a critical elevation of EFP that constricts transperineurial vessels by stretching the perineurium beyond the compliance limits, which lead to ischemic conduction failure, and eventually to Wallerian-like

degeneration [11]. Although this phenomenon may occur in any segment of peripheral nerve trunks, pathological and US studies indicate that spinal nerves are the hotspot in any early GBS subtype, thus explaining the high prevalence of electrophysiological changes pointing to pathology in proximal nerve segments (see above and Fig. 3). In any case, inflammatory oedema is also a histological feature of intermediate and pre-terminal nerve segments, potential cause of partial conduction block, nerve inexcitability or RCF [67, 69] (see Fig. 3).

g) Neurofilament light chain concentration and GBS

Neurofilament light chain (NfL) is a neuronal cytoplasmic protein highly expressed in large calibre myelinated axons. Its levels increase in cerebrospinal fluid and serum (sNfL) proportionally to the degree of axonal damage in a variety of neurological disorders, including inflammatory, neurodegenerative, traumatic and cerebrovascular diseases [102].

Altmann and colleagues recently reported sNfL concentrations in 27 GBS patients, 17 being categorized as AIDP, 5 as primary axonal GBS, and the remaining 5 as equivocal [15]. Serum samples were obtained within 5 days after onset. The median sNfL concentration in GBS patients on admission was 85.5 pg/ml versus 9.1 pg/ml in controls. High sNfL levels correlated with poor outcome, but, intriguingly, no significant differences were observed between AIDP and primary axonal GBS. Wisely, the authors commented on that "though sample size is too small to draw any conclusions, we believe that sNfLs are elevated even in primarily demyelinating disease which might be attributed to axonal damage below the threshold detectable by nerve electrophysiology. Neurophysiology may not represent what is really happening at the pathology level". Although agreeing with this assertion, I wish to propose that so very early sNfL elevations might be associated with inflammatory oedema with subsequent ischemic endoneurial events mainly occurring in proximal nerve trunks, which may cause conduction failure and eventually Wallerian-like degeneration. Detection of such pathologic hallmark calls for further ultrasonographic or special electrophysiological studies (see above). Furthermore, in very early AMAN, there may be a dual mechanism of muscle weakness and elevation of sNfL: ganglioside-mediated distal motor conduction block implying axonal dysfunction and potential Wallerian-like degeneration; and (ii) conduction block at ventral rami of spinal nerves caused by above-mentioned endoneurial ischemia [69].

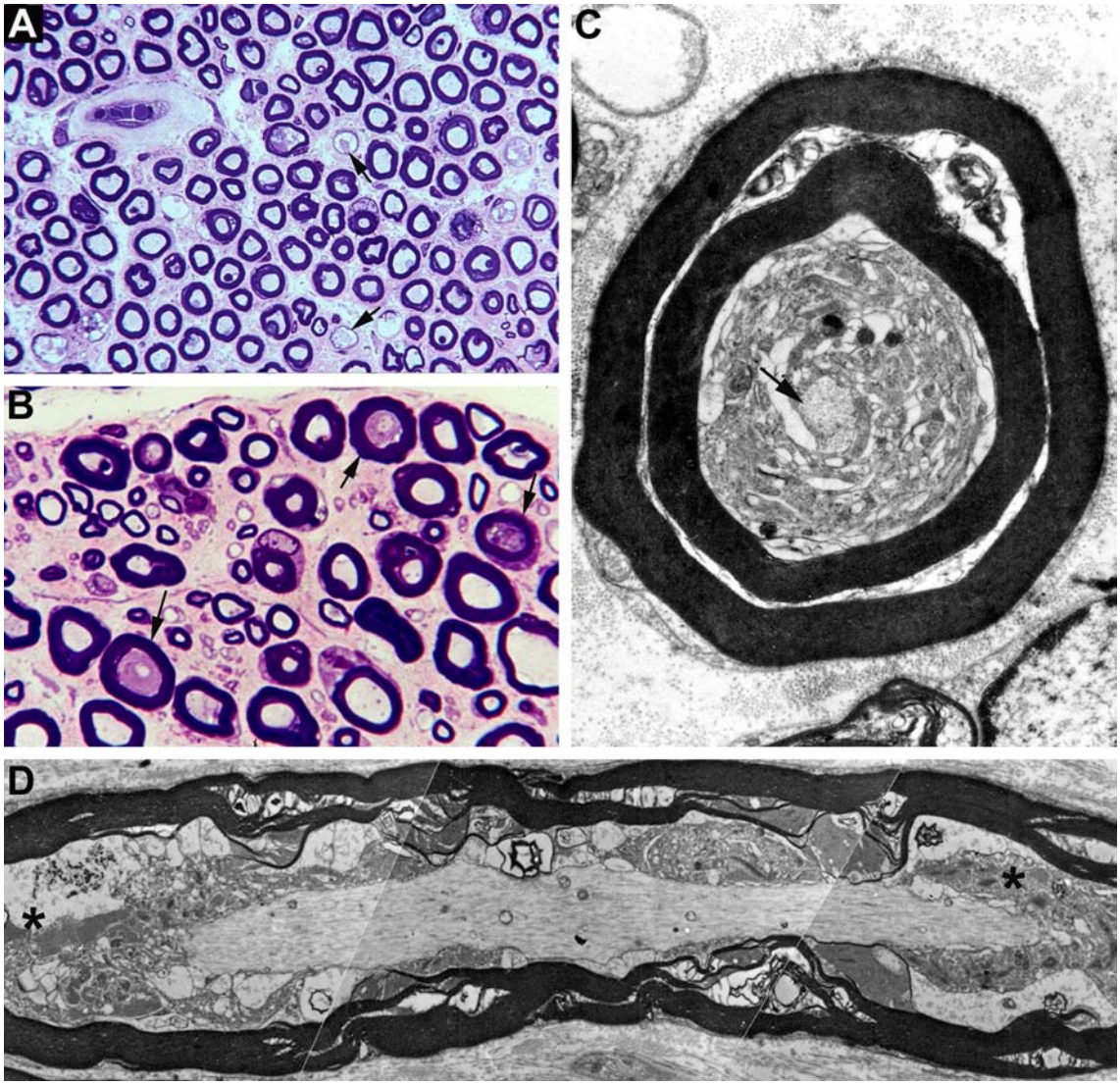

Fig. 6: Axonal repair in AIDP. Adapted from Berciano et al. [69]. a This semithin section of L5 ventral root shows that the density of myelinated fibres is preserved, although there are thinly myelinated fibres and fibres with vacuolated myelin (arrows) (Toluidine blue; original magnification ×375 before reduction). b This semithin section of L5 dorsal root illustrates three dark fibres (arrows) (Toluidine blue; original magnification ×750 before reduction). c This electron micrograph shows the morphology of a dark fibre characterized by an attenuated axon (arrow) surrounded by complex adaxonal Schwann cell processes and normal myelin (×5900 before reduction). d This longitudinal electron micrograph section shows extensive accumulation of vacuoles, degenerated organelles, and amorphous material in the adaxonal Schwann cell cytoplasm. Such accumulation is more pronounced in the paranodal regions (asterisks), though involving the internodal regions. Note that the axon is variably displaced but otherwise preserved (×2200 before reduction)

III. Therapeutic Considerations

GBS treatment is based upon the use of either intravenous high doses of human immunoglobulin (IVIG) or plasmapheresis [1, 2]. The rationale of both treatments is their capacity to remove pathogenic antibodies.

New complement inhibitors successfully prevented damage by anti-GQ1b antibodies at mouse neuromuscular junctions [103, 104]. Eculizumab, a humanized monoclonal antibody against terminal complement protein C5 that inhibits terminal complement activation, is an effective therapy for paroxysmal nocturnal hemoglobinuria [105]. All these data were the rationale for trials with eculizumab in GBS [106]. Regrettably, a recent meta-analysis of two trials comparing eculizumab and placebo demonstrated uncertain results [107].

As already stated, inflammatory oedema is pathogenic in early stages of GBS and EAN; in this regard, timely comment is made by Powell and Myers [108], "whereas brain edema is universally understood as a medical emergency, the destructive impact on the peripheral nervous system of endoneurial edema is less appreciated. Measures to inhibit edema and to ameliorate its effects have potential importance in protecting nerve fibers from ischemic injury". Given the

narrow therapeutic window to avoid the impact of oedema on axons, such measures should be implemented as soon as possible, including the use of boluses of intravenous methylprednisolone in subgroups with severe early GBS.

a) Pain in pure motor GBS including AMAN

Asbury and Fields distinguished two major forms of neuropathic pain: (i) dysesthetic pain (ie, causalgia, small nerve neuropathy and post-herpetic neuralgia); and (ii) nerve trunk pain (eg, spinal nerve compression and inflammatory neuritis including GBS) [109].

In the original AMAN description [57], it is stated that "many patients had neck and back stiffness and pain; one father said that his son seemed as though he had a rod up his spine" (their composed Fig. 1 is an impressive picture displaying weakness of neck flexor muscles and displaying resistance to passive neck flexion).

In a series of 55 consecutive GBS patients, 49 (89%) described pain during the course of their illness; in around half of them, it was described as excruciating [110]. Back and leg pain was commonly exacerbated by straight leg raising, which provides indirect evidence that traction on inflamed nerve roots could be responsible for some of the pain. The authors argued that irritation of the nervi nervorum, which innervates nerve trunks, may also refer pain to the paraspinal region via dorsal rami of spinal nerves.

Ruts and colleagues described that a high proportion of GBS patients with pure motor neuropathy reported pain, mostly localized in the extremities, and sometimes referred to as severe pain [111]. The authors proposed that pain in the acute phase of pure motor GBS is likely of nociceptive origin, probably due to activation of nervi nervorum. In the IGOS study, 77 (62%) of 125 patients from Bangladesh reported pain at the entry; worthy of note is that 74 (69%) of them had pure motor GBS [7].

Based on our sonographic and autopsy studies (see above), we offered an alternative pathophysiological explanation for acute pain in pure motor GBS/AMAN: early inflammatory oedema, located in the anterior spinal roots at the vertebral foramina entrance, the ventral rami of spinal nerves or both, could involve abutting dorsal rami, thus causing nerve trunk pain referred to their innervation territories, from neck to buttocks, eventually accompanied by neck and back stiffness [112].

Therapy of nerve trunk pain in GBS includes the use of non-steroidal anti-inflammatory drugs, simple analgesics, parental opioids, or even epidural morphine [110]; in spite of their combined use, pain may remain intractable. There have been at least 13 well-documented GBS patients with severe backache and rapid response to steroids (reviewed in reference [11]). In a randomized placebo-controlled study of 223 GBS patients, methylprednisolone had no significant effect on the presence and intensity of pain [113]. Given that this series included only 10 patients with radicular pain, wisely, the authors concluded that this number is too small to conclude about a possible favourable effect of methylprednisolone on this type of pain in GBS. Be that as it may, there appears to be an area of potential further therapeutic study.

IV. Conclusion

The analysis of GBS and EAN data allows for drawing the following conclusions:

- Both in severe AIDP and P_2-induced EAN, the pathologic background may be divergent: pure demyelination in intrathecal spinal roots, and a combination of Wallerian-like degeneration and demyelination in more distant nerve trunks.
- Initial pathogenic lesion in AIDP and P_2-induced EAN is inflammatory oedema mainly involving proximal nerve trunks, particularly spinal nerves. In nerve trunks pos- sessing epi- perineurium, such oedema may increase EFP causing nerve ischemia with conduction failure and eventually Wallerian-like degeneration accompanying demyelination. Having this in mind, serial NCS studies seem to be necessary for accurate GBS subtyping. Imaging techniques help delineate the topography of lesions.
- Revision of the original description of the axonal form of GBS strongly suggests that its pathologic background consists of a divergent pathology: demyelination and axonal degeneration in spinal roots, and pure axonal degeneration in more distant nerve trunks.
- In AMAN, Wallerian-like degeneration also predominates at the ventral root exit from the dura, namely in spinal nerves. Therefore, spinal nerve is an ultrasonographic and pathological hotspot in any GBS subtype.
- In ganglioside-induced axonal EAN, there may be demyelinating changes; consequently, separation between axonal and demyelination patterns does not seem to be absolute. In ganglioside-induced EAN, neuromuscular synaptopathy promotes a repair phenomenon from the perisynaptic Schwann cells. Similar features act on AIDP with secondary axonal damage, where proximal nerve trunks may exhibit exuberant proliferation of adaxonal Schwann cell cytoplasm.
- Knowledge of the microscopic anatomy of the peripheral nervous system and the variable efficiency of the blood–nerve barrier is essential for an accurate understanding of the topographic distribution of lesions both in GBS and EAN.

- There may be a potential therapeutic role of boluses of methylprednisolone in early severe GBS patients, or those with intractable pain.

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Compliance with ethical standards

Conflicts of interest The author declare no conflict of interest.

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Recurrent Arterial Thrombosis in Young Adult, as Complication of Covid-19 Infection: A Case Report and Review of Literature

By Kazim Mohammed, Abdullahi Bashir H Mohamud, Mulham Mustafa, A. Sumeen, R. Abdelgadir, Muhammad Mohsin Khan (MD) & Dr. Ali Raza

Abstract- A 30-year-old male with no significant past medical history developed a stroke on day 15th of his COVID-19 Positive result with investigations showing Thrombosis of Left ICA/MCA. The patient underwent mechanical thrombectomy with adequate recanalization yet presented with a recurrent thrombus the next day. Hypercoagulable state is one of the unusual complications seen in COVID-19 positive patients with multiple pieces of literature pointing towards increased risk of venous thromboembolism, with stress towards VTE prophylaxis[1,2]. Arterial thromboembolism is a lesser-known sequela, often involves larger blood vessels correlating with increased inflammatory markers and severity of the disease, and such patients may need prolonged anticoagulation therapy.

GJMR-A Classification: NLMC Code: WG 540

Recurrent Arterial Thrombosis in Young Adult, as Complication of Covid-19 Infection: A Case Report and Review of Literature

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Abstract- **A 30-year-old male with no significant past medical history developed a stroke on day 15th of his COVID-19 Positive result with investigations showing Thrombosis of Left ICA/MCA. The patient underwent mechanical thrombectomy with adequate recanalization yet presented with a recurrent thrombus the next day. Hypercoagulable state is one of the unusual complications seen in COVID-19 positive patients with multiple pieces of literature pointing towards increased risk of venous thromboembolism, with stress towards VTE prophylaxis[1,2]. Arterial thromboembolism is a lesser-known sequela, often involves larger blood vessels correlating with increased inflammatory markers and severity of the disease, and such patients may need prolonged anticoagulation therapy.**

I. Introduction/background

In late December 2019, the first case of the novel coronavirus was first identified in Wuhan, China, and on Mar 11, 2020, the WHO officially declared it a worldwide pandemic. Since then, the world has faced many challenges to overcome and adapt. The novel Coronavirus can present in a spectrum ranging from asymptomatic to the critically ill, with 81% exhibiting mild symptoms[3]. Its high infection rate has left the medical world at unprecedented times with new aspects of the virus observed in each specialty and requires a multi-disciplinary approach to treat the many organs affected. Many studies point to the primary pathogenesis in ARDS/Multiorgan failure in these patients is a Hypercoagulable/Prothrombotic state. We want to present an otherwise healthy 30-year-old COVID-19 positive patient developing an Acute Stroke involving the ICA/MCA.

II. Case Presentation

A 30-year-old male with no known significant past medical history works as a construction worker presented to the ED by complaining of a fever, dry cough, headache, and a sore throat. He has a history of contact with his roommate, who was also experiencing similar symptoms. He denied shortness of breath or chest pain and tested positive for COVID-19 by real-time reverse Transcriptase- Polymerase Chain reaction Swap test (RT-PCR). The examination was unremarkable, a selective blood workup including CBC, CMP, CRP, and a G6PD screening, all of which showed no significant abnormalities. An initial chest x-ray performed at admission was unremarkable, and the patient transferred to the quarantine facility as per the CDC protocol.

On admission to the quarantine facility, repeat blood work was done, including an ECG and a repeat chest x-ray, which showed patchy consolidation in the left lower lung zone. The patient has remained stable, and without any complaints until the day 15th post positive COVID-19 PCR test, the patient collapsed and was unresponsive initially with a GCS score of 11. Vital signs were measured, showing a blood pressure of 99/62 mmHg, Heart Rate of 107 bpm, Oxygen Saturation of 92%, Random Blood Sugar 100 mg/dL, and the patient was afebrile. On examination, the patient showed right-sided facial palsy and hemiplegia with a power of the right upper limb and right lower limb of 0/5 and 2/5, respectively, left upper and lower limbs were 5/5 with intact sensation. The patient was immediately transferred to a specialized stroke unit by ambulance.

III. Investigations

Upon arrival to the ED, vitals were as follows: BP 120 /72, HR 100, oxygen saturation 93 % on room air, and picked up to 97% on 3 L nasal cannula, respiratory rate of 23, and afebrile. On examination, the patient was confused with global aphasia and muteness, right hemianopia, right gaze deviation, right facial weakness, and right hemiplegia (arm 0/5, leg 2/5). NIHSS score- 22 and mRS – 0. A repeated chest x-ray was done, noting air space opacity in the middle and lower lung zones bilaterally (figure 4). His Labs showed WBC-7.8, HCT47.5, INR1.1, Pt-12.5, APTT-25.9, CPR-58.7, Ferritin-619. Unfortunately, the D-Dimer sample was not sent to the lab.

Stroke protocol was activated, and an urgent CT scan along with a perfusion scan. A plain CT scan showed subtle hyperdensity in the left MCA *(Figure 1a)* with no apparent intracerebral or subarachnoid

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hemorrhage with normal ventricles in position and size subarachnoid spaces looked unremarkable. CT perfusion revealed CBF and CBV *(Figure 1b and 1c)* apparent mismatch in the left cerebral hemisphere, mainly in the left frontoparietal region in the left MCA territory with a delay in MTT/T max images, suggestive of tissue at risk. While in CT angiogram, there was the small filling defect of in the left CCA in the neck proximal to the bifurcation, plus partial filling defect left ECA in the neck along with narrowing of the lumen of the left CCA in petrous and cavernous segments with no opacification in the supra-clinoid part of the left CCA and also non-visualized M1 segment of the left MCA, suggestive of a partial block. In contrast, the right ACA/MCA and posterior circulation looked unremarkable.

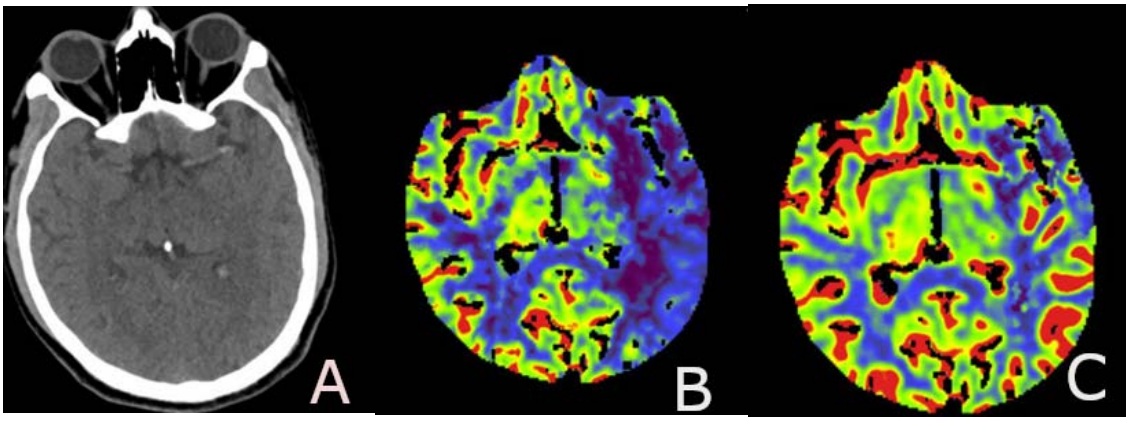

Figure 1A: Plain CT scan showed subtle hyperdensity in the left MCA

Figure 1b and 1c: CT perfusion revealed CBF and CBV apparent mismatch in the left cerebral hemisphere, mainly in the left frontoparietal region in the territory of the left MCA

IV Thrombolysis was initiated as per protocol with a bolus of Alteplase 6.3 mg, followed by an infusion of 56.7 mg. A neuro-interventionist was involved, and the patient underwent mechanical thrombectomy. Simultaneously, as per Qatar CDC guidelines, he was started on Azithromycin, Hydroxychloroquine, and Oseltamivir combination as part of his Covid-19 treatment based on worsened chest X-ray, after ensuring the QTC is below 450 on ECG in such patients.

A filling defect (floating thrombus) noted in the distal left CCA before bifurcation. Total occlusion of the Left ICA and MCA by a large thrombus load starting from the distal cavernous segment. Aspiration thrombectomy; which cleared up the floating thrombus using Solumbra technique (combined aspiration and mechanical thrombectomy) using Solitaire 6X40mm stent; two trials were made and cleared up the ICA and MCA with a final control angiogram revealing adequate recanalization TICI 3. 10 mg Verapamil was injected to overcome spasm in the Left ICA and Left M1 segment. The clots recovered were sticky and soft, suggestive of the embolic source. The intracranial vessels did not show any atherosclerotic features, and there is no evidence of carotid dissection. *(Figure 2a, 2b and 2c)*.

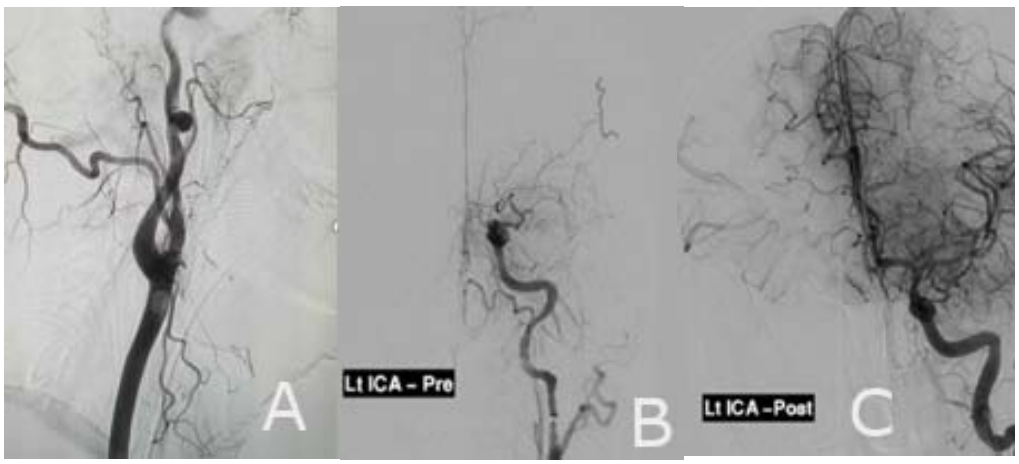

Figure: 2a showing a floating thrombus in the left CCA

Figure: 2b, and 2c show DSA Pre and Post Thrombectomy.

The patient was admitted to the ICU in a monitored bed and continued to receive care according to the stroke management protocol; he remained aphasic with right-sided hemiplegia. There were No arrhythmias or ECG abnormalities. Follow up CT scan done 24 hours after the thrombectomy showed hyper-density in the left MCA, suggestive of recurrent thrombus. Repeat CT and CTA showed a significant interval increase in the extent of vascular occlusion, involving the entirety of the left internal carotid artery beyond the bifurcation and the M2 and M3 segments of the left MCA (previously only in the M1). Redemonstrations of the small filling defect in the left external carotid artery with no significant interval change. The right CCA, ICA, MCA, and both ACAs appear patent with no evidence of occlusion, and the vertebrobasilar system appears patent with no evidence of occlusion as well *(figure 3)*.

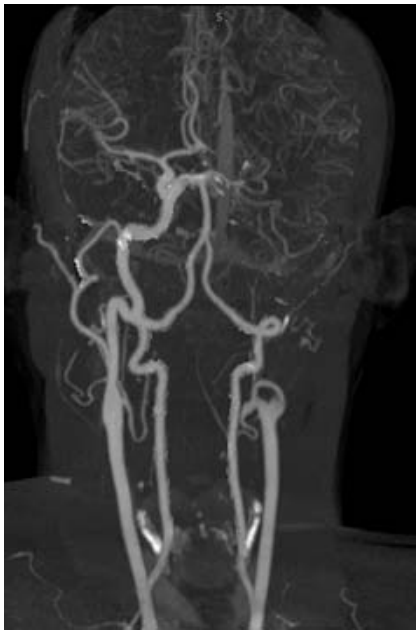

Figure 3: CTA done post thrombectomy reconfirming the recurrence of the thrombus in the Left ICA, MCA.

A cardiac echo done to rule out any source of thrombo-emboli was unremarkable. Serology work up for Lupus anticoagulant showed the first sample to be negative; however, the repeated sample tested positive with negative anticardiolipin and negative Anti Glycoprotein. His Protein C, Protein S, and ATA were normal. Connective Tissue disorder workup was done, with ANA, full ENA panel, which was healthy.

IV. Differential Diagnosis

In this case, the primary etiology of stroke is COVID 19 related thrombo-inflammation leading to stroke or coagulopathy related to the virus, less likely cause is ischemic stroke as the patient is young without any co-morbidities.

V. Treatment

The patient was started on anticoagulation (enoxaparin and followed by warfarin) with an INR target of 2-3, with a plan to repeat DSA after four weeks of anticoagulation treatment. He was tested negative on two samples of the COVID-PCR swab test, taken 24 hours apart on day 25th, with repeat chest x-ray showed regression of the bilateral pulmonary consolidation and infiltration, and the patient is more alert and awake, started verbalizing but has slurred speech.

VI. Outcome and Follow-up

The patient is still undergoing treatment understroke and rehab unit, with an active rehab session, and is expected to be transferred tothe rehabilitation unit.

VII. Discussion

Thromboinflammation or COVID-19-associated coagulopathy (CAC)[4], is a term coined for Hypercoagulable state in Covid-19, characterized by an elevation in procoagulant factor levels including fibrinogen, and an increase in D-dimers correlated with higher mortality. The occurrence of thromboembolic events in Covid-19 disease has been proven by Post-mortem examination of COVID19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings of lungs and other organs suggesting vascular dysfunction[5].

Oxley TJ et al. [6] presented 5 cases of Young adults (all aged between 33-40 years) who have developed stroke due to large vessel involvement and tested Coivd-19 PCR positive. While our example is also

a young adult without any co-morbidities, it is interesting to note that his chest X-ray progressed to worse on the day of the stroke and even the inflammatory markers were highest on the day of the stroke, raising a high level of suspicion of association between COVID-19 related inflammation and stroke *(Figure 4, & 5)*. Further investigational studies are required to know if early treatment in such a patient could prevent stroke, as in our case, even though he was tested positive, he was started on Covid-19 Treatment protocol only after he developed stroke and repeat X-ray showed B/L pneumonia.

Figure 4: Chest x ray done at Day 1 of Covid-19 PCR positive results, Day 3 showing Left basal Patch and Day 15 when patient developed Stroke, Showing Progression of the Pneumonia.

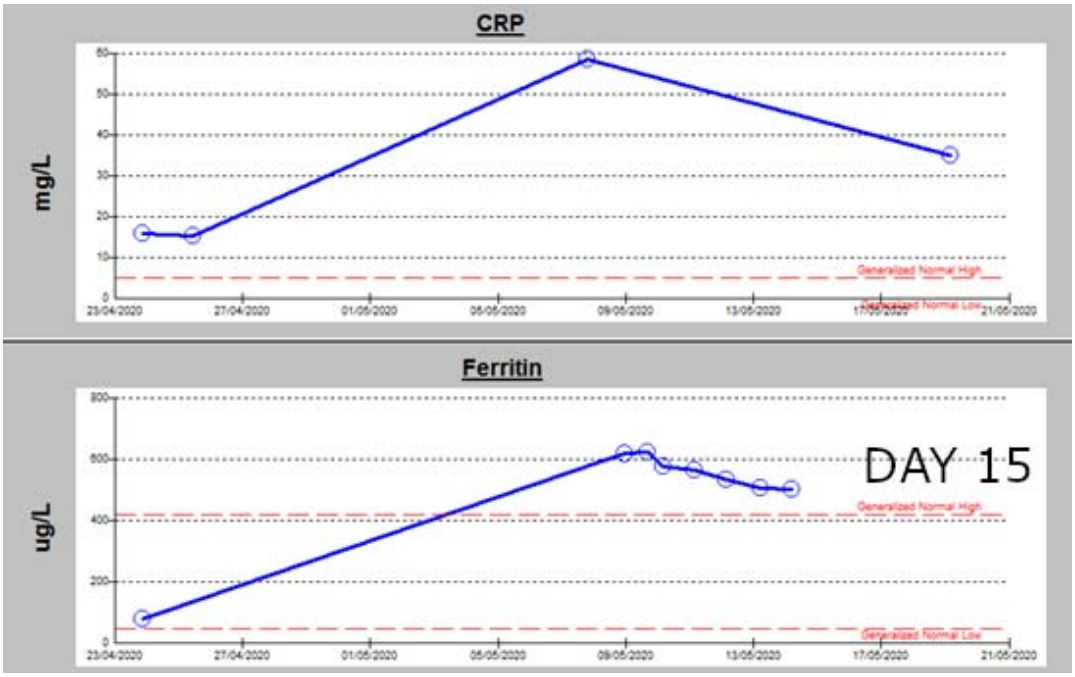

Figure 5: Graph co-relating the highest peak of inflammatory markers to the day of the stroke.

Although Serology workup for Lupus anticoagulant came positive on the repeated second with negative anticardiolipin and negative anti Glycoprotein, the underlying antiphospholipid syndrome (APS) is still suspicious considering the high rates of false positives rates of lupus anticoagulant, and the presence of Lupus antibodies (aPL) in other settings including infection, bacterial/Viral, Medications, Malignancy besides APS, either transiently or persistently[7]. McNally T,8, in his report, "The use of an anti-beta 2-glycoprotein-I assay for discrimination between anticardiolipin antibodies associated with infection and increased risk of thrombosis," concluded that the alpha-beta 2GPI assay is harmful in patients with transiently positive ACL assays associated with infection. We plan to repeat the Anti-lupus anticoagulant test after 12 weeks. However, it would be interesting to know if Covid-19 disease does increase the occurrence of Anti-phospholipid syndrome and related thrombotic events. Though limited data of just 6 cases of COVID infection-related large vessel stroke, including ours, Anterior circulation (ICA/MCA) is the most common site of thrombus occurrence. In contrast, just one case involving posterior circulation is reported in the cases described by Oxley TJ et al6.

Though Oxley et al6, in his case, reported complete resolution of the thrombus after ten days of anticoagulation, our situation was complicated with the recurrence of thrombus the next day. We plan to repeat DSA after four weeks of anticoagulation treatment.

VIII. Learning Points/Take Home Messages

- Large Vessel thrombus in Covid-19 positive patient could be a new etiology of stroke.
- The association between the Inflammatory peak, the formation of thrombus, and stroke occurrence need to be further investigated.
- Along with the effectiveness of anticoagulation and early treatment of Covid-19 infection in preventing such stroke is yet to be determined.

Conflict of Interest:

All authors declare no potential conflicts of interest to disclose related to the publication of this case series.

Author Contributions: KM, AH identified the cases, obtained informed consent and wrote the initial manuscript. MMK assisted in the literature review and manuscript writing. AH reviewed the case as infectious disease experts. Rest contributed to the manuscript writing, literature review and discussion. was also involved in image selection and critically revising the manuscript to its final form. All authors approved the final version for submission.

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Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.

Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

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.

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.

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

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

Please read the following rules and regulations carefully before submitting your research paper to Global Journals Inc. to avoid rejection.

Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

Criterion for Grading a Research Paper (Compilation) by Global Journals

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

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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