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วารสาร ประสาทวิทยา แห่งประเทศไทย

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บรรณาธิการแถลง

สวัสดีครับท่านสมาชิกสมาคมประสาทวิทยาแห่งประเทศไทย และผู้สนใจทุกท่าน วารสารสมาคมประสาทวิทยาที่ท่านกำลังอ่านนี้ได้เผยแพร่ออกมาสู่แวดวงวิชาการครบ 40 ปีในวารสารฉบับนี้ และกำลังก้าวเข้าสู่ปีที่ 41 ในฉบับต่อไป การที่วารสารได้มีอายุถึง 40 ปีนี้ไม่ใช่เรื่องง่ายเลย ถ้าไม่ได้รับความร่วมมือจากท่านสมาชิกทุกท่านและผู้สนใจในวงวิชาการประสาทวิทยาทุกท่านที่ร่วมกันสร้างสรรผลงานวิชาการเผยแพร่ในวารสารสมาคมประสาทวิทยาตั้งแต่วารสารฉบับที่ 1 ปีที่ 1 จนกระทั่งมาถึงวารสารฉบับที่ 4 ปีที่ 40 เล่มนี้

วารสารเล่มนี้มีผลงานวิจัยของแพทย์ประจำบ้านประสาทวิทยาที่น่าสนใจ หลากหลายโรคที่น่าสนใจทั้งสิ้น ผมสังเกตว่างานวิจัยของแพทย์ประจำบ้านมีความน่าสนใจมากขึ้นเรื่อยๆ และมีมาตรฐานสูงขึ้น ต้องขอขอบพระคุณอาจารย์ที่ปรึกษาและอาจารย์ในทุกๆ สถาบันฝึกอบรมที่ร่วมมือกันดูแลแพทย์ประจำบ้านให้บรรลุเป้าหมายในการฝึกอบรม จบเป็นอายุรแพทย์ระบบประสาทที่ดี ให้การดูแลสุขภาพประชาชนให้มีคุณภาพชีวิตที่สูงขึ้น

ผมในนามของบรรณาธิการวารสารสมาคมประสาทวิทยาแห่งประเทศไทย ขอขอบพระคุณผู้เผยแพร่ผลงานวิจัยทุกท่านที่ร่วมกันเผยแพร่ผลงานทางวิชาการ และบทความที่มีประโยชน์ต่อผู้อ่านตั้งแต่วารสารฉบับที่ 1 ปีที่ 1 จนถึงฉบับที่ 4 ปีที่ 40 เล่มที่ท่านกำลังอ่านอยู่ กองบรรณาธิการหวังว่าสมาชิกสมาคมประสาทวิทยาทุกท่านจะร่วมมือกันเผยแพร่ผลงานวิจัยและบทความที่มีประโยชน์ต่อสังคมตลอดไป

ศ.นพ.สมศักดิ์ เทียมเก่า
บรรณาธิการวารสารสมาคมประสาทวิทยาแห่งประเทศไทย

คำแนะนำสำหรับผู้นิพนธ์ในการส่งบทความทางวิชาการเพื่อรับการพิจารณาลงในวารสารประสาทวิทยาแห่งประเทศไทย (Thai Journal of Neurology)

วารสารประสาทวิทยาแห่งประเทศไทย หรือ Thai Journal of Neurology เป็นวารสารที่จัดทำขึ้นเพื่อเผยแพร่ความรู้โรคทางระบบประสาทและความรู้ทางประสาทวิทยาศาสตร์ในทุกสาขาที่เกี่ยวข้อง เช่น การเรียนรู้ พฤติกรรม สารสนเทศ ความปวด จิตเวชศาสตร์ และอื่นๆ ต่อสมาชิกสมาคมฯ แพทย์สาขาวิชาที่เกี่ยวข้อง นักวิทยาศาสตร์ ผู้สนใจด้านประสาทวิทยาศาสตร์ เป็นสื่อกลางระหว่างสมาชิกสมาคมฯ และผู้สนใจ เผยแพร่ผลงานทางวิชาการและผลงานวิจัยของสมาชิกสมาคมฯ แพทย์ประจำบ้านและแพทย์ต่อยอดด้านประสาทวิทยา นักศึกษาสาขาประสาทวิทยาศาสตร์ และเพื่อพัฒนาองค์ความรู้ใหม่ ส่งเสริมการศึกษาต่อเนื่อง โดยกองบรรณาธิการสงวนสิทธิ์ในการตรวจทางแก้ไขต้นฉบับและพิจารณาตีพิมพ์ตามความเหมาะสม บทความทุกประเภท จะได้รับการพิจารณาถึงความถูกต้อง ความน่าเชื่อถือ ความน่าสนใจ ตลอดจนความเหมาะสมของเนื้อหาจากผู้ทรงคุณวุฒิจากในหรือนอกกองบรรณาธิการ วารสารมีหลักเกณฑ์และคำแนะนำทั่วไป ดังต่อไปนี้

1. **ประเภทของบทความ** บทความที่จะได้รับการตีพิมพ์ในวารสารอาจเป็นบทความประเภทใดประเภทหนึ่งดังต่อไปนี้

1.1 **บทบรรณาธิการ** (Editorial) เป็นบทความสั้น ๆ ที่บรรณาธิการและผู้ทรงคุณวุฒิที่กองบรรณาธิการเห็นสมควร เขียนแสดงความคิดเห็นในแง่มุมต่าง ๆ เกี่ยวกับบทความในวารสารหรือเรื่องที่บุคคลนั้นเชี่ยวชาญ

1.2 **บทความทั่วไป** (General article) เป็นบทความวิชาการด้านประสาทวิทยาและประสาทวิทยาศาสตร์ และสาขาวิชาอื่นที่เกี่ยวข้อง

1.3 **บทความปริทัศน์** (Review article) เป็นบทความที่เขียนจากการรวบรวมความรู้ในเรื่องใดเรื่องหนึ่งทางประสาทวิทยาและประสาทวิทยาศาสตร์ และสาขาวิชาอื่นที่เกี่ยวข้อง ที่ผู้เขียนได้จากการอ่านและวิเคราะห์จากวารสารต่าง ๆ ควรเป็นบทความที่รวบรวมความรู้ใหม่ ๆ ที่น่าสนใจที่ผู้อ่านสามารถนำไปประยุกต์ได้ โดยอาจมีบทสรุปหรือข้อคิดเห็นของผู้เขียนด้วยก็ได้

1.4 **นิพนธ์ต้นฉบับ** (Original article) เป็นเรื่องรายงานผลการศึกษาวิจัยทางประสาทวิทยาและประสาทวิทยาศาสตร์ และสาขาวิชาอื่นที่เกี่ยวข้องของผู้เขียนเอง ประกอบด้วยบทคัดย่อ บทนำ วัสดุและวิธีการ ผลการศึกษา สรุปแบะวิจารณ์ผลการศึกษา และเอกสารอ้างอิง

1.5 **ย่อวารสาร** (Journal reading) เป็นเรื่องย่อของบทความที่น่าสนใจทางประสาทวิทยาและประสาทวิทยาศาสตร์ และสาขาวิชาอื่นที่เกี่ยวข้อง

1.6 **วิทยาการก้าวหน้า** (Recent advance) เป็นบทความสั้น ๆ ที่น่าสนใจแสดงถึงความรู้ ความก้าวหน้าทางวิชาการด้านประสาทวิทยาและประสาทวิทยาศาสตร์ และสาขาวิชาอื่นที่เกี่ยวข้อง

1.7 **จดหมายถึงบรรณาธิการ** (Letter to the editor) อาจเป็นข้อคิดเห็นเกี่ยวกับบทความที่ตีพิมพ์ไปแล้วในวารสารและกองบรรณาธิการได้พิจารณาเห็นว่าจะเป็นประโยชน์ต่อผู้อ่านท่านอื่น หรืออาจเป็นผลการศึกษาการค้นพบความรู้ใหม่ ๆ ที่สั้นและสมบูรณ์ในตัว

1.8 **กรณีศึกษาน่าสนใจ** (Interesting case) เป็นรายงานผู้ป่วยที่น่าสนใจหรือผู้ป่วยที่มีการวินิจฉัยที่พบไม่บ่อยผู้อ่านจะได้เรียนรู้จากตัวอย่างผู้ป่วย

1.9 **บทความอื่น ๆ** ที่กองบรรณาธิการเห็นสมควรเผยแพร่

2. **การเตรียมต้นฉบับ**

2.1 ให้พิมพ์ต้นฉบับด้วย font Angsana New ขนาดอักษร 14 โดยพิมพ์เว้นระยะห่างระหว่างบรรทัด 2 ช่วง (double space) และใส่เลขหน้ากำกับไว้ทุกหน้า

2.2 หน้าแรกประกอบด้วย ชื่อเรื่อง ชื่อผู้เขียน และสถานที่ทำงานภาษาไทยและภาษาอังกฤษ และ

ระบุชื่อผู้เขียนที่รับผิดชอบในการติดต่อ (corresponding author) ไว้ให้ชัดเจน ชื่อเรื่องควรสั้นและได้ใจความตรงตามเนื้อเรื่อง

2.3 เนื้อเรื่องและการใช้ภาษา เนื้อเรื่องอาจเป็นภาษาไทยหรือภาษาอังกฤษ ถ้าเป็นภาษาไทยให้ยึดหลักพจนานุกรมฉบับราชบัณฑิตยสถานและควรใช้ภาษาไทยให้มากที่สุด ยกเว้นคำภาษาอังกฤษที่แปลแล้วได้ใจความไม่ชัดเจน

2.4 รูปภาพและตาราง ให้พิมพ์แยกต่างหากหน้าละ 1 รายการ โดยมีคำอธิบายรูปภาพเขียนแยกไว้ต่างหาก รูปภาพที่ใช้ถ้าเป็นรูปจริงให้ใช้รูปถ่ายสี ขนาด 3" x 5" ถ้าเป็นภาพเขียนให้เขียนด้วยหมึกดำบนกระดาษมันสีขาวหรือเตรียมในรูปแบบ digital file ที่มีความคมชัดสูง

2.5 นิพนธ์ต้นฉบับให้เรียงลำดับเนื้อหาดังนี้

บทคัดย่อภาษาไทยและภาษาอังกฤษพร้อมคำสำคัญ (keyword) ไม่เกิน 5 คำ บทนำ (introduction) วัสดุและวิธีการ (material and methods) ผลการศึกษา (results) สรุปและวิจารณ์ผลการศึกษา (conclusion and discussion) กิตติกรรมประกาศ (acknowledgement) และเอกสารอ้างอิง (references)

2.6 เอกสารอ้างอิงใช้ตามระบบ Vancouver's International Committee of Medical Journal โดยใส่หมายเลขเรียงลำดับที่อ้างอิงในเนื้อเรื่อง (superscript) โดยบทความที่มีผู้เขียนจำนวน 3 คน หรือน้อยกว่าให้ใส่ชื่อผู้เขียนทุกคน ถ้ามากกว่า 3 คน ให้ใส่ชื่อเฉพาะ 3 คนแรก ตามด้วยอักษร et al ดังตัวอย่าง

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3. การส่งต้นฉบับ

ส่งต้นฉบับของบทความทุกประเภทในรูปแบบไฟล์เอกสารไปที่ www.thaijoneuro.com

4. เงื่อนไขในการพิมพ์

4.1 เรื่องที่ส่งมาลงพิมพ์ต้องไม่เคยตีพิมพ์หรือกำลังรอตีพิมพ์ในวารสารอื่น หากเคยนำเสนอในที่ประชุมวิชาการใดให้ระบุเป็นเชิงอรรถ (foot note) ไว้ในหน้าแรกของบทความ ลิขสิทธิ์ในการพิมพ์เผยแพร่ของบทความที่ได้รับการตีพิมพ์เป็นของวารสาร

บทความจะต้องผ่านการพิจารณาจากผู้เชี่ยวชาญ 3 ท่าน (reviewer) ซึ่งผู้เชี่ยวชาญทั้ง 3 ท่านนั้นจะไม่ทราบผลการพิจารณาของท่านอื่น ผู้รับผิดชอบบทความจะต้องตอบข้อสงสัยและคำแนะนำของผู้เชี่ยวชาญทุกประเด็น ส่งกลับให้บรรณาธิการพิจารณาอีกครั้งว่ามีความเหมาะสมในการเผยแพร่ในวารสารหรือไม่

4.2 ข้อความหรือข้อคิดเห็นต่าง ๆ เป็นของผู้เขียนบทความนั้น ๆ ไม่ใช่ความเห็นของกองบรรณาธิการหรือของวารสาร และไม่ใช่ความเห็นของสมาคมประสาทวิทยาแห่งประเทศไทย

4.3 สมาคมฯจะมอบวารสาร 5 เล่ม ให้กับผู้เขียนที่รับผิดชอบในการติดต่อเป็นอภินันทนาการ

4.4 สมาคมฯ จะมอบค่าเผยแพร่ผลงานวิจัยนิพนธ์ต้นฉบับกรณีผู้รับผิดชอบบทความหรือผู้นิพนธ์หลักเป็นแพทย์ประจำบ้านหรือแพทย์ต่อยอดประสาทวิทยา

สารบัญ

ORIGINAL ARTICLE

INTERESTING CASE

Prevalence and Associated Factors of Ischemic Stroke in the Young Patients

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ABSTRACT

Introduction: Ischemic stroke can cause major disability in any patient affected. Ischemic stroke in the young patients in Rajavithi hospital have not been well studied. This study aimed to determine prevalence and associated factor of ischemic stroke in the young patients.

Objectives:

1. To study the prevalence of ischemic stroke in the young patients in Rajavithi hospital.
2. To study any factors associated with acute ischemic stroke in the young patients.

Materials and Methods: Retrospective cross-sectional study in ischemic stroke patients admitted in Rajavithi Hospital during July 1, 2021 - June 30, 2023.

Results: From 770 ischemic stroke patients, 100 patients (12.99 %) were stroke in the young (age≤ 45years). Their mean age was 37.56 + 7.52 years old. Fifty-five patients (55%) were male. Mean BMI in stroke in the young group is 25.99 $\pm$ 5.39 kg/m^2, which is statistically significantly higher than in the older group(p=0.003). Hypertension is statistically significant(p<0.001) more common in stroke in the young group. According to Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, type of strokes was undetermined in 32%, large artery atherosclerosis in 25%, small artery occlusion in 21%, other determined cause in 15% and cardioembolism in 7% of ischemic stroke in the young patients.

Conclusion: Prevalence of ischemic stroke in the young is 12.99% among all stroke patients. Stroke of undetermined etiology was the most common type. Further prospective study in a larger population with more complete investigations is needed.

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Keyword: Stroke in the young, Ischemic stroke, Cerebral infarction, Stroke etiology, Stroke risk factor

Introduction

Ischemic stroke is a disease found globally affecting more than 5.7 million people, with approximately 2.1 million cases in the Asian region[1,2]. It is a significant public health problem, with a mortality rate of 10% and a disability rate of 50-60%, and there is a rising trend in the future[3,4].

Ischemic stroke in the young refers to cases occurring in individuals under the age of 45[5-7], constituting about 5% of all ischemic stroke cases[5]. The incidence varies in different countries. According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification[8], the majority of cases in the young fall into the category of 'stroke of undetermined etiology.' Other causes include cardioembolic and large artery atherosclerosis[7,9-12].

This study aims to accurately determine prevalence and causes of ischemic stroke in young patients through practical laboratory examinations. Identifying the etiology will aid in planning appropriate treatment, reducing mortality rates, and preventing recurrence[13].

Materials and Methods

Study design: Retrospective cross-sectional study of ischemic stroke patients admitted in Rajavithi hospital during July 1, 2021 - June 30, 2023.

Characteristics of study samples:

Inclusion criteria

1. First-ever ischemic stroke patients who were admitted in Rajavithi hospital during July 1, 2021 - June 30, 2023, and divided into two groups: aged ≤ 45 years, and aged > 45 years.

2. The patients aged 18 and over.

Exclusion criteria

1. Incomplete information in the medical record

Sample size calculation:

Sample size was calculated using an approximate formula based on proportions[13].

$$n = \frac{Z_{\alpha/2}^2 \; P(1-P)}{d^2}$$

n = number of sample sizes for each group

$Z_{\alpha/2}$ = Statistical value under the standard curve when determining the level of statistical significance

α = 0.05 is 1.96

P = the incidence of ischemic stroke in patients with a young age is 13.6%, as referenced in the study by Guidetti D et al[14] in 2013, p = 0.136

d = the allowable margin of error should not exceed 20% of the P

Therefore, (d) = 0.20 x 0.20 = 0.04

The number of samples can be calculated as follows.

$$n = \frac{1.96^2 \times 0.136 \times (1-0.136)}{0.03^2}$$

n = 502 + missing data 10%

= 550

In this study, the researchers will collect data from a total of 550 patients as the sample size.

Outcome

The primary outcome is prevalence of ischemic stroke in the young in Rajavithi hospital.

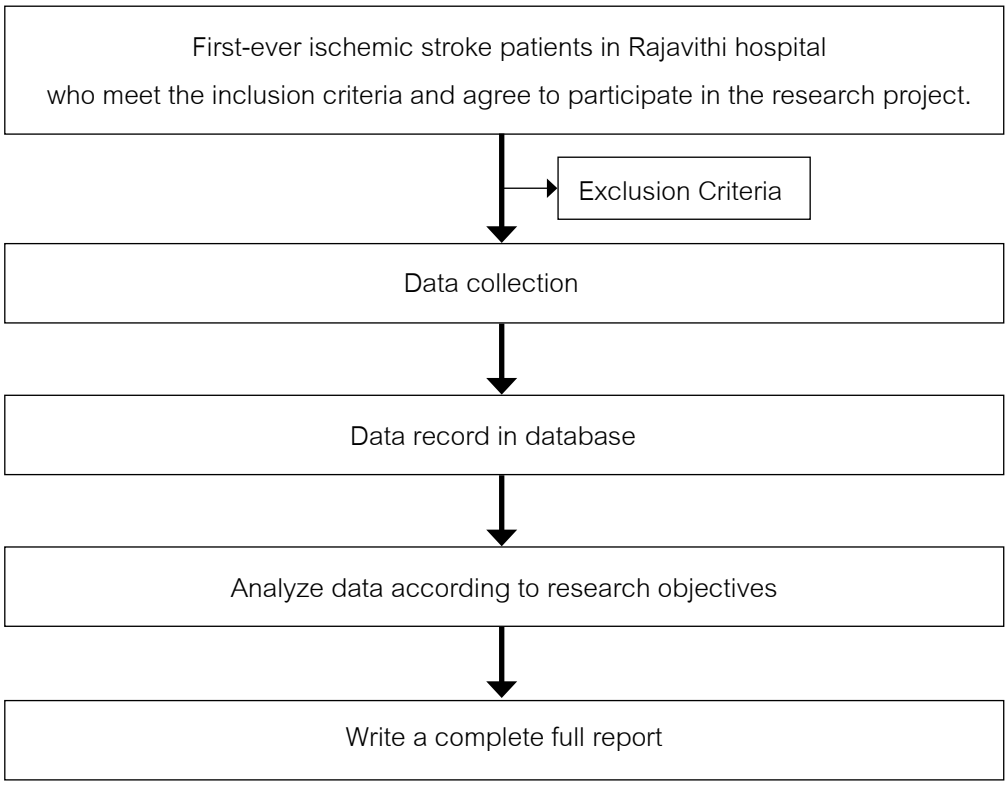
The secondary outcome is associating factors of ischemic stroke in the young in Rajavithi hospital.

Data collection

1. Demographic data of all ischemic stroke patients and associated factors of ischemic stroke included age, sex, BMI, systolic blood pressure, smoking, underlying disease, laboratory tests

2. Clinical outcome of all ischemic stroke patients included the severity of stroke using the National Institutes of Health Stroke Scale (NIHSS), and the etiology of stroke based on TOAST classification

Research Methodology



Statistical Analysis

Descriptive statistics: The categorical data is reported by percentage. Continuous data with normal distribution is reported as means and standard deviation. If the data is not a normal distribution data, it is reported with median, minimum, maximum, and interquartile range and percentile Rank.

Inferential statistics: Categorical data were compared using the Chi-square test or Fisher's exact test or McNemar test. The uncorrelated data is compared with Student t-test for normal distribution data and Mann-Whitney U-test was used for non-normal distribution data. All tests were assigned a level of statistical significance at a p-value < 0.05.

Results

Baseline characteristics, underlying disease, and laboratory testing were demonstrated in Table 1. There were 770 ischemic stroke patients included in this study, which comprised 100 patients(12.99%) in ischemic stroke age ≤ 45 years group, and 660 patients(87.01%) in ischemic stroke age>45 years group. In ischemic stroke in the young group, 55.0% are male, and mean age is 37.56 years (SD 7.52). In the age >45 years group,

57.9% are male and mean age is 65.56 years (SD 11.07). Age is a statistically significant difference between the two groups(p<0.001). Common risk factors in all stroke patients were smoking, hypertension, dyslipidemia and diabetes. Mean BMI in stroke in the young group is 25.99 ± 5.39, which is statistically significantly higher than in the older group(p=0.003). Mean systolic blood pressure in stroke in the young group is 148.62 ± 30.14, which is statistically significantly lower than in the older group (p=0.001). The underlying disease were statistically significant difference between the two group(p<0.001), which hypertension is statistically significant(p<0.001) more common in stroke in the young group(89.1%) compared to the older group(86.2%), whereas dyslipidemia in stroke in the young group is 63%, and diabetes mellitus in the stroke in the young group is 39%, which are statistically significant less common than in the older group(p<0.001 and p=0.003, respectively).

Table 1 Demographic data of the patients (n = 770)

Factors	Total	Age≤45 years (n=100)	Age>45 years (n=670)	p-value
Sex				0.583
Male	443 (57.5)	55 (55.0)	388 (57.9)	
Female	327 (42.5)	45 (45.0)	282 (42.1)	
Age (years)	61.92 ± 14.24	37.56 ± 7.52	65.56 ± 11.07	<0.001*
BMI	24.51 ± 4.48	25.99 ± 5.39	24.29 ± 4.29	0.003*
Systolic blood pressure	157.33 ± 29.45	148.62 ± 30.14	158.63 ± 29.15	0.001*
Smoking	358 (46.5)	45 (45.0)	313 (46.7)	0.748
Underlying disease	564 (73.2)	46 (46.0)	518 (77.3)	<0.001*
Hypertension	486 (86.2)	41 (89.1)	445 (85.9)	<0.001*
Dyslipidemia	368 (65.2)	29 (63.0)	339 (65.4)	<0.001*
Diabetes mellitus	238 (42.2)	18 (39.1)	220 (42.4)	0.003*
Atrial fibrillation	66 (11.7)	7 (15.2)	59 (11.4)	0.547
Coronary heart disease	62 (11.0)	4 (8.7)	58 (11.2)	0.110
Laboratory Testing				
HbA1C ≥ 7.0 mg%	192 (24.9)	23 (23.0)	169 (25.2)	0.632
LDL ≥ 70 mg/dL	688 (89.4)	87 (87.0)	601 (89.7)	0.414

Value are represented as number (percent), Mean±SD,* significant as p<0.05

Clinical outcomes of the ischemic stroke patients in this study including the severity of stroke and etiology of stroke were demonstrated in Table 2. The severity of stroke according to NIHSS score are similar between stroke in the young and the older group in mild(72% and 70.9%) and moderate stroke(23% and 26.7%), but there are more patients in stroke in the young group are in severe stroke(5% and 2.4%). However, there is no statistically significant difference of the severity between the two groups (p=2.666).

Table 2 Clinical outcomes of the patient (n = 770)

Factors	Total	Age≤ 45 years (n=100)	Age> 45 years (n=670)	p-value
NIHSS				2.666
1 - 4	547 (71.0)	72 (72.0)	475 (70.9)	
5 - 15	202 (26.3)	23 (23.0)	179 (26.7)	
16 - 20	21 (2.7)	5 (5.0)	16 (2.4)	
21 - 42	0 (0.0)	0 (0.0)	0 (0.0)	
TOAST classification				<0.001*
Small artery occlusion	427 (55.5)	21 (21.0)	406 (60.6)	
Large artery atherosclerosis	228 (29.6)	25 (25.0)	203 (30.3)	
Cardioembolism	63 (8.2)	7 (7.0)	56 (8.4)	
Undetermined cause	34 (4.4)	32 (32.0)	2 (0.3)	
Other determined cause	18 (2.3)	15 (15.0)	3 (0.4)	
Hematologic conditions	7 (38.9)	6 (40.0)	1 (33.3)	
Noninflammatory	5 (27.8)	3 (20.0)	2 (66.7)	
Inflammatory and infectious	4 (22.1)	4 (26.6)	0 (0.0)	
Genetic	1 (5.6)	1 (6.7)	0 (0.0)	
Cardiac abnormalities	1 (5.6)	1 (6.7)	0 (0.0)	

Value is represented as number (percent), * significant as p<0.05

The etiology of stroke according to the TOAST classification in stroke in the young group are as followed; undetermined cause (32.0%), large artery atherosclerosis (25%), small artery occlusion (21%), other determined cause (15%), and cardioembolism (7%), while the most common etiology of stroke in the older age group is small artery occlusion (60.6%), followed by large artery atherosclerosis (30.3%), and cardioembolism(8.4%). The difference of stroke etiology is statistically significant between the two groups (p<0.001). In stroke in the young group, the cause of other determined etiology was cerebral venous sinus thrombosis, antiphospholipid syndrome, polycythemia vera, vasospasm, Moyamoya disease, vasculitis, HIV-related, neurofibromatosis, and atrial septal defect.

Specific investigations in stroke in the young patients were demonstrated in Table 3. ANA is positive in 13% of patients, echocardiogram or Holter monitoring is positive in 8% of patients, ESR is positive in 6% of patients, lupus anticoagulant is positive in 2% of patients, urine substance is positive in 2% of patients, and anti-HIV is positive in 1% of patient. However, tests for urine substances were not done in 72% of patients.

Table 3. Specific investigations (n = 100)

Specific investigations	Positive	Negative	Not done
ANA	13 (13)	81 (81)	6 (6)
Echocardiogram/Holter	8 (8)	84 (84)	8 (8)
ESR	6 (6)	88 (88)	6 (6)
Lupus Anticoagulant	2 (2)	92 (92)	6 (6)
Urine substance	2 (2)	26 (26)	72 (72)
Anti-HIV	1 (1)	93 (93)	6 (6)
Anti Beta2 Glycoprotein	0 (0)	94 (94)	6 (6)
Anti Cardiolipin	0 (0)	94 (94)	6 (6)
Anti Thrombin III	0 (0)	86 (86)	14 (14)
Protein C	0 (0)	86 (86)	14 (14)
Protein S	0 (0)	86 (86)	14 (14)
RPR	0 (0)	94 (94)	6 (6)

Value is represented as number (percent)

Discussion

The prevalence of ischemic stroke in the young in this study was 12.99%, which was similar to the prevalence in the previous study[14]. In ischemic stroke in the young group, BMI was significantly higher and hypertension was more common than the older age group, which both are the traditional cardiovascular risk factors.

The cause of stroke in this study was undetermined in 32% of cases, which was higher than the other study[15], due to limited availability of the diagnostic investigation in our hospital, some investigations were done only in clinically suspected cases, and sometimes due to financial problems. Small artery occlusion and large artery atherosclerosis were more common in this study than the previous study[16], in which BMI, high blood pressure, diabetes mellitus and other atherosclerotic risk are associated with these types of strokes.

The limitation of this study included incomplete information related to family history and incomplete investigation as the study was a retrospective cross-sectional study. Further prospective study in a larger population should be able to collect more data and do broader investigations for stroke in the young patients.

However, the results from this study could emphasize the importance of modifying stroke risk factors as a preventive strategy even in the people of young age.

Conclusion

Prevalence of ischemic stroke in the young is 12.99% among all stroke patients. Stroke of undetermined etiology was the most common type according to TOAST classification. Further prospective study in a larger population with more complete investigations is needed.

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Prevalence of Ischemic Stroke Subtype and Relationship Between Patient Factors and Each Subtype in Taksin Hospital

Potchara Veerarattakul

ABSTRACT

Background: Ischemic stroke is a global health issue. Prevention strategies depend on its subtype, the standard criterion is a TOAST classification. Few studies in Thailand clarified stroke of undetermined etiology into incomplete evaluation subtype that reflecting care service quality.

Objectives: This study aims to establish local prevalence in hospital that cerebrovascular imaging not routinely done as reference for improving protocol of comprehensive evaluation and predictors for each subtype.

Materials and Methods: This retrospective cross-sectional study included acute ischemic stroke patients who admitted in stroke unit between October 1st, 2021 and September 30th, 2022. All patients were classified into 7 subtypes and then analysed relationship between patient factors and each subtype.

Results: A total of 382 patients are categorised as follow: Incomplete evaluation, 218 (57%); LAA, 55 (14%); SVO, 42 (11%); CE, 25 (7%); Negative evaluation, 19 (5%); Two or more causes identified, 12 (3%); and SOE, 11 (3%). Lack of cerebrovascular assessments is the cause of incomplete evaluation related with aged 45 years or older, beyond fast-track period, cortical NIHSS ratio <0.1, and lacunar infarction. Incomplete evaluation consists of lacunar infarction (38%), known specific cause (10%), poor prognosis (2%) and denial (1%) and unspecified reason (6%). To LAA, moderately high LDL-c and current smoking more likely relate with aOR 3.65 and 3.15 (p value=0.04) but lacunar infarction least likely relates with aOR 0.04 (p value <0.001).

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Conclusion: Stroke of undetermined etiology with incomplete evaluation is around a half in the setting of non-routine cerebrovascular assessment and mostly consists of the lacunar infarction. Local prevalence should be established for enhancing cerebrovascular accessibility, the implementation of vascular study protocol should apply for current smoking patient who has not in optimal range of LDL-c presenting with non-lacunar infarction.

Keyword: Ischemic stroke subtype prevalence, TOAST classification, Relationship between patient factors and stroke subtype, Incomplete evaluation with lacunar infarction, Cerebrovascular assessment

Introduction

Stroke is the global health issue, the second of mortality rate and the third of disability rate because the exposure of vascular risk factor such as aging, hypertension, diabetes mellitus, dyslipidemia, smoking or pollution for a period of time causes inadequate perfusion or occlusion of blood clot from local chronic inflammatory vasculature or upstream source[1,2]. Prevention by antiplatelets, anticoagulants or carotid intervention beside optimization of vascular risk factor needs identifying subtype of ischemic stroke that TOAST classification is a standard, simple, and high inter-rater reliable system[3].

In Thailand, the first study of stroke prevalence was published without ischemic stroke subtype distribution[4]. There were a few studies regarding to the prevalence of ischemic stroke subtype. These previous studies reported ischemic stroke prevalence according to TOAST classification with SUE ranges from 3.6% to 18% but They did not clarify SUE into 3 categories namely two or more causes identified, negative evaluation, and incomplete evaluation[5-7]. Incomplete evaluation was low about 1.7% in the high-rate cerebrovascular imaging center that both intra and extracranial magnetic resonance angiography was performed up to 98.7%[8]. Patient who is ignored for cerebrovascular assessment could be losing benefit of carotid intervention or high intensity antiplatelet regimens. The data of incomplete evaluation are important to promote cerebrovascular assessment protocol.

This study focuses on prevalence of incomplete evaluation subtype that is expected high because cerebrovascular assessment is not routinely performed in all ischemic stroke patients unlike the residency or fellowship training hospitals. Furthermore, the cause of incomplete evaluation and the predictors of other subtypes are also explored.

Methods

Study design

This study is a single center, retrospective cross-sectional study describing the prevalence of all ischemic stroke subtype according to TOAST classification in the hospital that cerebrovascular imaging is not routinely performed. Moreover, relationship between patient factors and each subtype is assessed for predictive factors of each subtype (Figure 1).

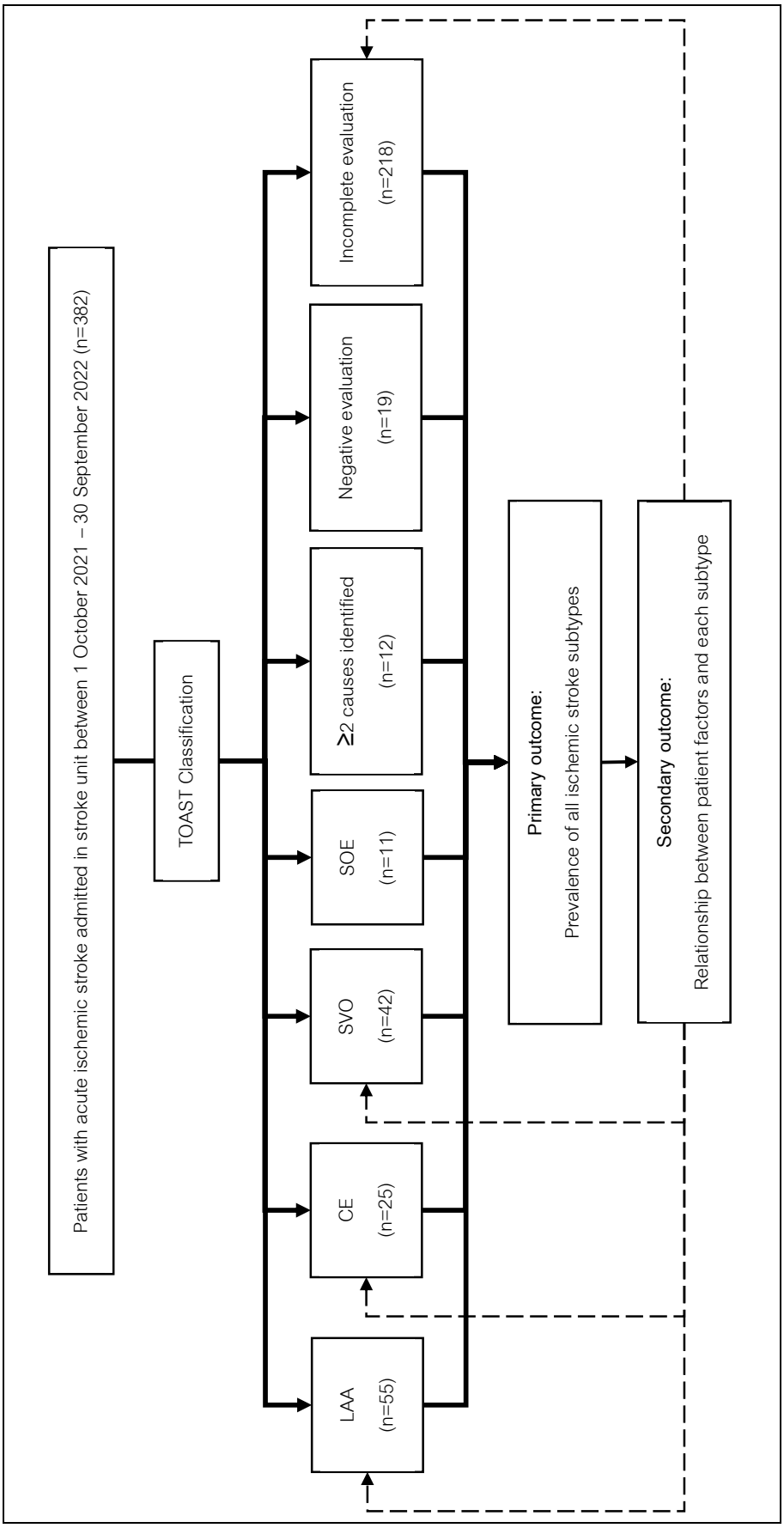

Figure 1 Patient flow chart

Study population

All patients were diagnosed acute ischemic stroke and admitted in stroke unit at Taksin hospital between October 1st, 2021, and September 30th, 2022. Patients presented with transient ischemic attack (TIA) and hemorrhagic stroke were excluded. The collected data were extracted from the patients' medical records and Thai Neurological Information Center stroke registry while neuroimaging studies were reviewed from PACS by neurologist. Demographic characteristics, vascular related medical history, clinical presentation, cardiac investigation (EKG and/or echocardiography), neuroimaging characteristics and laboratory values were collected. The recanalization procedures were also assessed in patients who presented within 6 hours or stroke fast track period.

Measurements

Subtypes of ischemic stroke using original TOAST criteria were identified by neurologist using clinical history, results of diagnostic tests including EKG, echocardiography, CT or MR brain, cerebrovascular imaging and compatible laboratory findings. Patients were classified into 7 categories as follows; LAA: upstream intra or extracranial stenosis ≥50%; CE: high risk sources such as atrial fibrillation, valvular heart disease and left-side thrombus; SVO: recent area of infarction ≤15mm with upstream intra or extracranial stenosis <50%; SOE: uncommon identified cause such as non-atherosclerotic vasculopathy, hypercoagulable state, hypoperfusion, or iatrogenic cause; Two or more causes identified of SUE; Negative evaluation of SUE: recent area of infarction >15mm without upstream intra or extracranial stenosis ≥50% or high risk cardioembolic source by EKG and/or echocardiography; and Incomplete evaluation of SUE.

Factors that might be associated in each category were defined as follows; age, sex, vascular risk factors including hypertension (patient' s self-report, or use of antihypertensive medication), diabetes mellitus (patient' s self-report, use of antihyperglycemic agent, or HbA1C >6.5%), and dyslipidemia (LDL-c >130mg/dL), history of end organ damage including old CVD (patient' s self-report, or old vascular brain lesion in CT scan), IHD (patient' s self-report and medical records), and CKD (eGFR <60mL/min/1.73m^2), atrial fibrillation (medical records, detection by screening EKG or 24-hour EKG monitor), smoking habit (current smoker within previous 6 months, yes or no), alcohol consumption behavior (> 1 drink per week, yes or no), activation of stroke fast track (yes or no), referral stroke (transferring from other hospital, yes or no), clinical characteristics including NIHSS (range from 0 to 42, with higher scores indicating more severe neurologic deficit) and cortical NIHSS (ratio ≥0.1 by summation of part 2-best gaze (score 0-2), part 3-visual field (score 0-3), part 9-best language (score 0-3) and part 11-extinction and inattention (score 0-2) divided by total NIHSS, yes or no), lacunar infarction (recent area of infarction ≤15mm, yes or no) and laboratory values including HbA1C, LDL-c and eGFR.

Ethical considerations

This study was approved by the Bangkok Metropolitan Administration Ethics Committee for Human Research (BMAEC-S017hc66_EXP). The data were collected and analysed in Taksin hospital computer without extracting to personal computer. Information was kept anonymous without name or hospital number when extracting outside stroke unit. The researcher collected every eligible patient even missing some data for avoiding selection bias.

Statistical analysis

Using n4Studies calculated sample size by the infinite population proportion method from a previous study including missing rate 10% resulting in 349 patients[7,9]. Categorical variables were presented as number and percentage, and continuous variables were presented as median and interquartile. Relationship was tested between patient factors and all subtypes by Chi-square and Kruskal-Wallis. Using Stata software, predictors for each subtype were analysed by logistic regression with $p<0.05$ considered statistically significant.

Results

A total of 382 patients with acute ischemic stroke admitted in stroke unit at Taksin hospital from October 2021 through September 2022 were included. The median age was 66 years (min=23 and max=96), and 57.6% were male. Around one-fourths were current smoking. Hypertension was the most common vascular risk factors by 61.5%, and history of previous stroke was the most common underlying end organ damage by 23.3%. Atrial fibrillation was found in 17.3% that around two-thirds were firstly detected in this admission. Most patients had moderate severity (Median NIHSS 5) with low cortical NIHSS ratio (72%). Almost all were performed CT scan and a half was lacunar infarction. Most of them were in a normal range of HbA1C 6.1%, LDL-c 112mg/dL and eGFR 81mL/min/1.73m^2 (Table 1).

Among 112 patients were activated stroke fast track. They had median of stroke duration as 155 minutes, ASPECTS as 9, and posterior ASPECTS as 8.5. Recanalized procedures were given in 65 patients (17%) consisted of intravenous alteplase in 62 patients (16%) and mechanical thrombectomy in 18 patients (5%). Seven patients had symptomatic intracerebral hemorrhage. All of them received IV alteplase that median ASPECTS as 3 (Table 2).

Table 1 Baseline characteristics

	Total N=382	TOAST Classification							*p*-value
		LAA n=55	CE n=25	SVO n=42	SOE n=11	SUE* 5.1 n=12	5.2 n=19	5.3 n=218	
General characteristics									
Age - y Median [IQR]	66 [57-74.5]	66 [54.5-72]	77 [57-83]	59.5 [50.25-66]	60 [57.5-73]	70.5 [63.75-78.5]	61 [51-69.5]	67 [59-75]	**<0.001**
Male sex - no. (%)	220 (57.6)	39 (70.9)	10 (40)	24 (57.1)	3 (27.3)	6 (50)	9 (47.4)	129 (59.2)	**0.049**
Vascular risk factors lifestyle									
Current smoking - no. (%) †	94 (24.6)	23 (46)	4 (18.2)	11 (30.6)	1 (16.7)	2 (18.2)	2 (11.8)	51 (25.5)	**0.042**
High and moderate alcohol consumption - no. (%) ‡	39 (10.2)	8 (16)	3 (13.6)	3 (8.3)	0	2 (18.2)	3 (17.6)	20 (10.1)	0.708
Medical history									
Vascular risk factors									
Hypertension - no. (%)	235 (61.5)	30 (54.5)	11 (44)	24 (57.1)	8 (72.7)	9 (75)	11 (57.9)	142 (65.1)	0.275
Diabetes mellitus - no. (%)	161 (42.1)	20 (36.4)	8 (32)	18 (42.9)	1 (9.1)	2 (16.7)	9 (47.4)	103 (47.2)	0.052
Dyslipidaemia - no. (%)	136 (35.6)	25 (45.5)	6 (24)	18 (42.9)	4 (36.4)	3 (25)	7 (36.8)	73 (33.5)	0.447
End organ damage									
Old cerebrovascular disease - no. (%)	89 (23.3)	10 (18.2)	10 (40)	9 (21.4)	4 (36.4)	6 (50)	1 (5.3)	49 (22.5)	**0.021**
Ischemic heart disease - no. (%)	36 (9.4)	4 (7.3)	4 (16)	2 (4.8)	1 (9.1)	1 (8.3)	1 (5.3)	23 (10.6)	0.762
Chronic kidney disease - no. (%)	53 (13.9)	4 (7.3)	5 (20)	3 (7.1)	2 (18.2)	3 (25)	2 (10.5)	34 (15.6)	0.051
Atrial fibrillation - no. (%)	66 (17.3)	0	21 (84)	0	0	11 (91.7)	0	34 (15.6)	-
Known - no.	25	0	6	0	0	4	0	15	
At admission - no.	41	0	15	0	0	7	0	19	
Presentation									
Within 6h/stroke fast track - no. (%)	112 (29.3)	21 (38.2)	19 (76)	18 (42.9)	3 (27.3)	4 (33.3)	12 (63.2)	35 (16.1)	<0.001
Median - minute [IQR]	155 [91.5-241.25]	128 [75-216]	110 [58.5-202.5]	139 [90-208.75]	195 [119-257.5]	304 [254.25-312.5]	152.5 [135.5-216.5]	219 [138.5-267.5]	-
Referral stroke - no. (%)	67 (17.5)	16 (29.1)	5 (20)	7 (16.7)	3 (27.3)	4 (33.3)	9 (47.4)	23 (10.6)	<0.001

Table1 Baseline characteristics (continue)

	Total N=382	TOAST Classification							*p*-value
		LAA n=55	CE n=25	SVO n=42	SOE n=11	SUE* 5.1 n=12	5.2 n=19	5.3 n=218	
Clinical characteristics									
NIHSS - Median [IQR] §	5 [3-10]	9 [5-17]	16 [6.75-23.75]	5 [2-7]	6 [3-16.5]	10 [6.5-20]	11 [6-21]	4 [3-7]	<0.001
Cortical NIHSS ratio ≥0.1 - no. (%) ¶	96 (25.1)	28 (50.9)	16 (64)	6 (14.3)	4 (36.4)	5 (41.7)	9 (47.4)	28 (12.8)	<0.001
Imaging characteristic									
Lacunar infarction - no. (%)	203 (53.1)	6 (10.9)	7 (28)	42 (100)	3 (27.3)	2 (16.7)	0	143 (65.6)	<0.001
Laboratory values ‖									
HbA1C - Median [IQR]	6.1 [5.6-7.1]	5.8 [5.5-7.1]	6.0 [5.7-6.6]	6.3 [5.6-7.5]	5.45 [5.3-5.825]	6.3 [5.8-6.5]	6.1 [5.8-7.8]	6.1 [5.6-7.2]	0.128
LDL-c - Median [IQR]	112 [84.75-140.25]	125 [101-143]	87 [77.5-119]	127 [99-142]	129 [80-153]	75 [69.5-112]	110 [95.25-132.25]	108 [84-140]	0.015
eGFR - Median [IQR]	81 [60.25-94]	83 [69-97]	81 [51.75-97.75]	85 [74-101]	78 [53.5-87.25]	79 [50.5-82]	84 [58.25-97.25]	78 [57.5-93]	0.13

* SUE denotes Stroke of undetermined etiology including 5.1 Two or more etiologies, 5.2 Negative evaluation and 5.3 Incomplete evaluation.

† For the current smoking or smoking within previous 6 months, data were missing for 40 patients, 342 patients were included in the analysis.

‡ For more than moderate alcohol consumption or >1 drink per week, data were missing for 41 patients, 341 patients were included in the analysis.

§ Score on NIHSS range from 0 to 42, with higher scores indicating more severe neurologic deficits. For NIHSS, data were missing for 18 patients, 364 patients were included in the analysis.

¶ Summation of part 2-best gaze (score 0-2), part 3-visual field (score 0-3), part 9-best language (score 0-3) and part 11-extinction and inattention (score 0-2) divided by total NIHSS. For cortical NIHSS ratio, data were missing for 45 patients, 337 patients were included in the analysis.

‖ For laboratory value, data were missing for 12 patients in HbA1C, 14 patients in LDL-c, and 20 patients in eGFR. 370 patients for HbA1C, 368 patients for LDL-c, and 362 patients for eGFR were included in the analysis.

Table 2 Recanalized procedure in stroke fast track

	Total n=112	TOAST Classification						
		LAA n=21	CE n=19	SVO n=18	SOE n=3	SUE 5.1 n=4	SUE 5.2 n=12	SUE 5.3 n=35
Clinical characteristics								
NIHSS score - Median [IQR]	7 [4-17]	17 [9-24]	18 [11-26]	5 [3.25-7.75]	16.5 [15.25-17.75]	8 [5.5-16.5]	11 [6-19]	4.5 [2-6]
Imaging characteristics								
Within 6 hours/stroke fast track								
ASPECTS †† - Median [IQR]	9 [8-10]	7 [4-9]	9 [6.5-10]	10 [10-10]	10 [7.5-10]	8 [4.5-9]	6 [3-8.5]	10 [9-10]
Pc-ASPECTS †† - Median [IQR]	8.5 [8-9]	7.5 [7.25-7.75]	-	-	-	10 [10-10]	8.5 [8.25-8.75]	9 [9-9]
Recanalization procedure - no. (%)								
IV alteplase and/or thrombectomy	65	15	13	11	1	2	10	13
IV alteplase	62	15	11	11	1	1	10	13
Thrombectomy	18	6**	7	0	0	1	4**	0
Symptomatic intracerebral haemorrhage	7	2	2	0	0	0	3	0
After IV alteplase	7	2	2	0	0	0	3	0
After thrombectomy	4	1	2	0	0	0	1	0
Failure of thrombectomy	2	1	0	0	0	1	0	0

†† The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is an imaging measure of the extent of ischemic stroke. Scores ranges from 0 to 10 that higher scores indicating a smaller infarct core with 6 patients had pc-ASPECTS (details are available at www.aspectsinstroke.com).

** Only 1 patient from LAA and 5.2 were performed thrombectomy beyond 6 hours.

Among 382 patients, all had screening EKG or 24-h EKG monitor but only 160 patients (42%) had CT or MR angiography. The distribution of subtype was as followed: Incomplete evaluation, 218 (57%); LAA, 55 (14%); SVO, 42 (11%); CE, 25 (7%); Negative evaluation, 19 (5%); Two or more causes identified 19 (5%); and SOE, 11 (3%). Incomplete evaluation was the most common subtype, and no one had cerebrovascular assessment in both extra and intracranial artery. This group consisted of lacunar infarction (38%), known specific cause (10%) mainly AF (the others: valvular heart disease, 2; apical aneurysm, 1; acute anemia, 1; and polycythemia vera, 1), poor prognosis (2%) (previous bed ridden status, 5; large infarction, 3; and active hepatocellular carcinoma, 1, denial of further investigation (1%) (lack of caregiver, 2; and lack of health coverage scheme, 2), and unspecified reason (6%) (Figure 2).

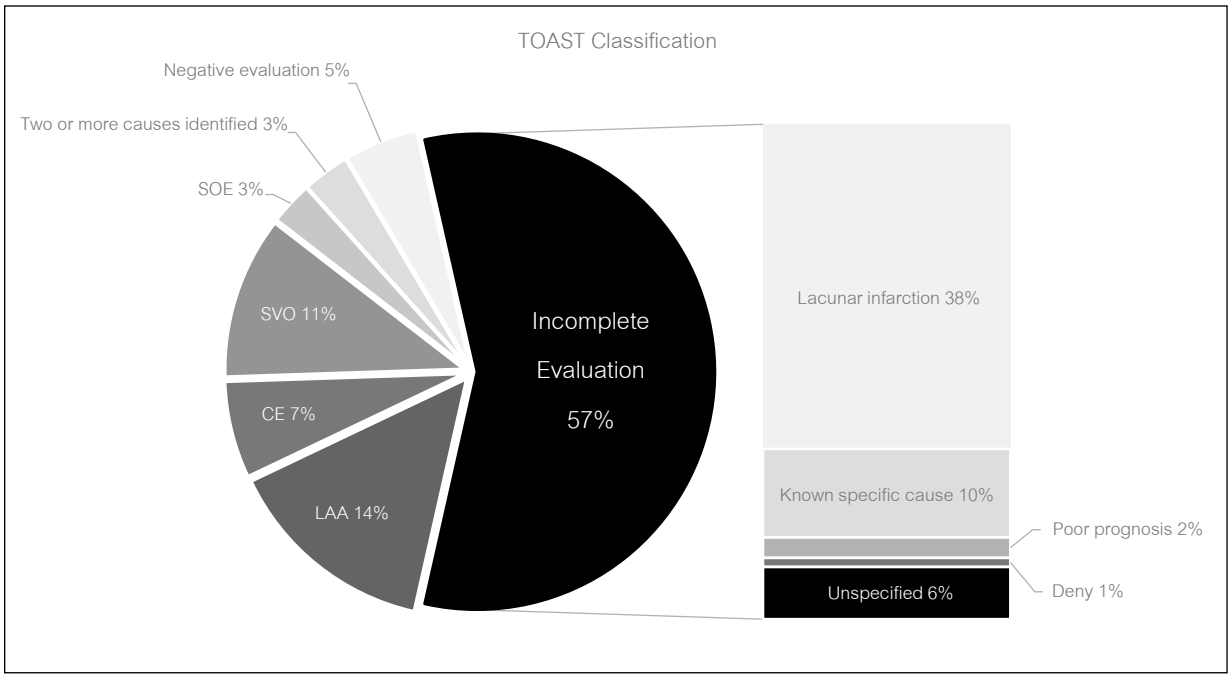

Figure 2 Prevalence of ischemic stroke subtype

The second most common was LAA including carotid stenosis in 7 patients [13%] and the rest of intracranial LAA as followed; MCA, 32 [58%]; ICA, 7 [13%]; VA, 4 [7%]; BA, 3 [6%]; ACA, 1 [2%]; and PCA, 1 [2%] respectively. Third was lacunar infarction without upstream significant stenosis and high risk cardioembolic source identified, the other lacunar infarction in 161 patients were also found in other subtypes as followed: Incomplete evaluation, 143; CE, 7; LAA, 6; SOE, 3; and two or more causes identified, 2. Almost high risk cardioembolic sources were AF in 21 patients [84%] followed by cardiomyopathy in 3 patients [12%] and acute myocardial infarction in 1 patient. For two or more causes identified, almost all were combination of LAA and CE but the only one was combination of LAA and SOE with acute anemia. The least was SOE or stroke of uncommon cause consisted of septicaemia, 3;

vascular malformation, 2; and cryptococcal meningitis, 1; advanced stage hepatocellular carcinoma, 1; acute anemia, 1; polycythemia vera, 1; essential thrombocytosis, 1; and vaccination, 1.

Median age in SVO (59.5 years) had lower than CE, two or more causes identified, incomplete evaluation and LAA (77, 70.5, 67, and 66 years respectively). Male and current smoking had more proportion in LAA (70.9% and 46%). Medical history of old cerebrovascular disease had more proportion in two or more causes identified, CE and SOE (50%, 40% and 36.4% respectively). Not only non-stroke fast track and non-referral stroke had the most (84% and 89.4%) but also median NIHSS and high cortical NIHSS ratio had the least (4 point and 12.8%) in incomplete evaluation. For lacunar infarction excluding SVO and negative evaluation by definition, incomplete evaluation had the most (65.6%) and LAA had the least (10.9%). Lastly median LDL-c level in SVO and LAA (127mg/dL and 125mg/dL) had higher than incomplete evaluation, CE and two or more causes identified (108, 87 and 75mg/dL respectively) (Table 1).

To LAA, current smoking and LDL-c level of 130-159mg/dL relate but lacunar infarction does not. To CE, stroke fast track and high cortical NIHSS ratio relate but age 45-64 years and LDL-c level of 130-159mg/dL do not. To SVO, stroke fast track and LDL-c level of 100-159mg/dL relate. Finally, age 45 years or older and lacunar infarction relate but stroke fast track and high cortical NIHSS ratio do not relate to incomplete evaluation (Table 3).

Table 3 Logistic regression for patient factors and each subtype

Variable	LAA		CE		SVO		Incomplete evaluation	
	p-value	Adjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)
Age 18 - 44	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Age 45 - 64	0.65	1.49 (0.27 - 8.21)	0.02	0.01 (0.00 - 0.43)	0.12	0.31 (0.07 - 1.38)	<0.01	5.06 (1.68 - 15.24)
Age 65 - 74	0.18	3.36 (0.58 - 19.66)	0.26	0.26 (0.02 - 2.72)	0.11	0.25 (0.05 - 1.34)	0.01	4.46 (1.41 - 14.14)
Age ≥75	0.5	0.45 (0.05 - 4.46)	0.18	6.63 (0.42 - 105.84)	0.09	0.13 (0.01 - 1.40)	<0.01	9.11 (2.30 - 36.08)
Male sex	0.09	2.71 (0.87 - 8.39)	0.2	3.58 (0.52 - 24.73)	0.52	0.68 (0.21 - 2.19)	0.49	0.78 (0.39 - 1.58)
Current smoking	0.04	3.15 (1.05 - 9.43)	0.5	0.40 (0.03 - 5.85)	0.95	1.04 (0.31 - 3.49)	0.85	1.08 (0.50 - 2.34)
Old cerebrovascular disease	0.46	0.64 (0.20 - 2.08)	1.0	1.00 (0.15 - 6.50)	0.17	2.62 (0.66 - 10.38)	0.44	0.74 (0.35 - 1.58)
Stroke fast track	0.61	1.29 (0.49 - 3.41)	<0.01	121.45 (8.89 - 1658.55)	0.03	3.53 (1.15 - 10.83)	<0.01	0.20 (0.10 - 0.40)
Referral stroke	0.24	1.94 (0.65 - 5.84)	0.49	1.99 (0.28 - 13.95)	0.19	3.44 (0.55 - 21.29)	0.18	0.54 (0.22 - 1.33)
NIHSS 0-4	Ref	Ref	Ref	Ref	0.6	0.42 (0.02 - 10.59)	0.32	1.96 (0.52 - 7.35)
NIHSS 5-15	0.86	0.91 (0.32 - 2.62)	0.35	0.32 (0.03 - 3.39)	0.88	1.27 (0.05 - 29.87)	0.7	1.28 (0.37 - 4.43)
NIHSS 16-20	0.12	4.57 (0.68 - 30.64)	0.38	0.23 (0.01 - 5.91)	0.5	0.21 (0.00 - 19.31)	0.43	0.47 (0.07 - 3.07)
NIHSS 21-42	0.55	0.60 (0.11 - 3.24)	0.89	0.81 (0.05 - 14.29)	Ref	Ref	Ref	Ref
Cortical NIHSS ratio ≥10%	0.18	2.16 (0.70 - 6.62)	0.03	25.86 (1.37 - 489.7)	0.24	2.50 (0.54 - 11.59)	<0.01	0.29 (0.12 - 0.69)
Lacunar infarction	<0.01	0.04 (0.01 - 0.14)	0.99	0.98 (0.14 - 6.85)	-	-	<0.01	2.34 (1.24 - 4.43)
LDL-c <100	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
LDL-c 100-129	0.23	2.10 (0.63 - 6.99)	0.08	0.11 (0.01 - 1.26)	0.03	4.84 (1.21 - 19.35)	0.22	0.61 (0.28 - 1.34)
LDL-c 130-159	0.04	3.69 (1.10 - 12.43)	0.01	0.01 (0.00 - 0.36)	0.01	8.05 (1.68 - 38.58)	0.32	0.64 (0.26 - 1.55)
LDL ≥160	0.23	2.34 (0.58 - 9.42)	0.92	1.11 (0.13 - 9.09)	0.89	1.12 (0.23 - 5.35)	0.67	0.82 (0.33 - 2.05)

Discussion

The result shows very high prevalence of incomplete evaluation because the case performed further CTA/MRA brain and neck is selected by uncommon presentation or LAA-like characteristics such as stroke in the young, moderate or severe stroke severity, cortical lobe sign presentation, recurrent episode of previous symptom, asymmetrical or territorial infarction appearance. This is emphasized by the result of relationship that age 45 years or older (not be stroke in the young), non-stroke fast track, low cortical NIHSS ratio, and lacunar infarction more likely do not go on cerebrovascular assessment. The large amount of incomplete evaluation is still expected in the hospital that cerebrovascular accessibility is limited whether it is insufficient radiologist, technician, or facility. By the way, this limitation could be improving if the data are illustrated. The main reason for no further vascular study is lacunar infarction. Some patients with lacunar infarction could uncommonly have coexisted LAA as same as some patients with known specific disease especially AF. They might lose benefit of carotid intervention.

Prevalence of other subtypes is similar to a previous Korean study in order of frequency as follows: LAA (37.3%) had more common than SVO, CE, negative evaluation, two or more causes identified and SOE (22.9, 20.6, 11.1, 3.4 and 2.9% respectively). However, they had no study of relationship despite they could performed cerebrovascular imaging in almost all patients with the least prevalence of incomplete evaluation[8].

This study demonstrates relationship corresponding to the previous studies. Unlike CE in younger than 65 years corresponds to the association between atrial fibrillation and the elder who are 75 years or older[7]. In addition, current smoking and LAA is consistent with Kim et al that shown regular cigarette smoking within the last 5 years associated with significant stenosis of intracranial atherosclerosis[10].

Moreover, Patients present during stroke fast track period or with high cortical NIHSS ratio are more likely CE. This may be because the ischemia from CE occurs without time to prepare for collaterals causing more severe stroke (median NIHSS 18) and more cortical involvement (64%). Stroke fast track also relates to SVO that could be impairment of collateral recruitment[11]. Lastly, relationship between LDL-c and each subtype shows moderately high LDL-c level related to atherosclerotic vasculopathy in contrast to CE (Table 3).

For application, cerebrovascular assessment should be assessed for current smoking patient who has not in optimal range of LDL-c presents with non-lacunar infarction. There's no need to be moderately high LDL-c because of cross-related SVO. However, vascular study should perform for all later when resources are ready.

Limitation of this study; First, although there is the risk of misclassification, the data are double corrected by medical record and stroke registry, the raw picture of cerebrovascular assessment need to present in PACS, and the degree of stenosis is reviewed strictly on standard criteria. Second, the proportion of incomplete evaluation is too high for generalizing proper dominant ischemic stroke subtypes in this area but in terms of care service, the prevalence of incomplete evaluation should be reported in individual hospital for improving protocol even further. Third, there are quite small proportion in LAA, CE, SVO and SOE subtypes for analyzing the relationship but these is comparable to a previous study in the number of patients[6].

This is the first study demonstrating complete TOAST classification subtypes and analyzing relationship between multiple categorized factors and each subtype. Basic information of stroke unit was established as a baseline profile that could be a reference and encouraged cerebrovascular accessibility in the future such as carotid and transcranial ultrasound for reducing proportion of incomplete evaluation and improving stroke prevention protocol. The next study should re-analyzes relationship with a few proportions of incomplete evaluation, however even optimized protocol, there is still an incomplete evaluation around 3% owing to poor prognosis and denial for further investigation but the prevalence should be reported in individual hospital for improving the stroke prevention service even further.

Conclusion

Stroke of undetermined etiology with incomplete evaluation is around a half in the setting of non-routine cerebrovascular assessment and mostly consists of the lacunar infarction. Local prevalence should be established for enhancing cerebrovascular accessibility, the implementation of vascular study protocol should apply for current smoking patient who has not in optimal range of LDL-c presenting with non-lacunar infarction.

Abbreviations

TOAST: Trial of Org 10,172 in Acute Stroke Treatment; LAA: Large artery atherosclerosis; CE: Cardioembolism; SVO: Small vessel occlusion; SOE: Stroke of other determined etiology; SUE: Stroke of undetermined etiology; CT: computer tomography; MRI: Magnetic resonance imaging; PACS: Picture archiving and communication system; EKG: Electrocardiogram; old CVD: old Cerebrovascular disease; IHD: Ischemic heart disease; CKD: Chronic kidney disease; NIHSS: National Institute of Health Stroke Scale; ASPECTS: Alberta Stroke Program Early Computed Tomography Score; HbA1c: Hemoglobin A1c; LDL-c: Low-density lipoprotein cholesterol; eGFR: Estimated glomerular filtration rate; IQR: Interquartile range

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Availability of data and materials

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Outcome of Second Immunomodulatory Treatment in Guillain-Barré Syndrome Patients with Poor Response to Initial Treatment in Neurological Institute of Thailand: A Single-Center Retrospective Observational Study

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ABSTRACT

Background : Guillain-Barré syndrome (GBS) is an immune-mediated polyneuropathy. The majority of patients have a good response to standard treatments which are intravenous immunoglobulin (IVIG) and plasma exchange (PE). However, some patients have poor responses, which do not improve and may deteriorate. Therefore, the second immunomodulatory treatment is considered for these patients.

Objectives : This research aimed to study the outcome of a second immunomodulatory treatment in GBS patients with poor response to initial treatment at the Neurological Institute of Thailand.

Materials and Methods : An observational retrospective review was performed, including patients with GBS between January 2017 and June 2023. Demographic data, clinical features, CSF profiles, electrodiagnostic classifications, MRC sum scores, and GBS disability scores at admission, 4 weeks, 8 weeks, 12 weeks, and 24 weeks were analyzed.

Results : A total of 64 patients with GBS were included. 17 patients (26.6%) had a poor response to the initial treatment. 7 patients (41.2%) received the second treatment. There were 6 patients (85.7%) who had PE followed by IVIG and 1 patient (14.3%) had a second dose of IVIG. The results showed no significant difference in the MRC sum score and GBS disability score during follow-up between the two groups. The patients in the second treatment group had higher serious complications including 1 patient (14.3%) had a catheter-related bloodstream infection and 1 patient (14.3%) had a thromboembolic event.

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Conclusion : The second immunomodulatory treatment in GBS patients with poor response to the initial treatment is not associated with an improvement in MRC sum scores and GBS disability scores, intubation periods, length of hospital stay, and mortality. There are increased risks of treatment-related complications, including catheter-related bloodstream infections, and thromboembolic events.

Keywords : Guillain-Barré syndrome; Second immunomodulatory treatment; Intravenous immunoglobulin; Plasma exchange

Introduction

Guillain-Barré syndrome (GBS) is an immune-mediated peripheral neuropathy and is the most common cause of acute flaccid paralysis with an annual worldwide incidence of approximately 1-2 per 100,000 person-year. GBS incidence increases around 20% in every 10 years of age, which is more frequently in male than female patients.[1-3]

GBS typically presents with acute progressive bilateral limb weakness, distal paresthesias or sensory loss, absence of reflex, and cranial nerve involvement. GBS is usually a monophasic disease reaching its nadir within two to four weeks after the onset. The clinical course of the disease ranges from mild or no disability to severe with bedridden, autonomic disturbance, and respiratory failure requiring a mechanical ventilator in 25% of them. The mortality rate is about 4-10% within 1 year of symptom onset, most commonly due to cardiovascular and respiratory complications.[1-3]

Intravenous immunoglobulin (IVIG) and plasma exchange (PE) are the standard immunomodulatory treatments of GBS, proven equal benefit for the patients.[4,5] Practically, IVIG is easier to administer and more available, so it is usually the first choice of treatment. The majority of patients about 80% have a good response to the standard immunomodulatory treatment. They can regain the ability to walk independently at 6 months after disease onset and 60% of GBS patients completely recover motor function at 1 year. The relapse episode is rare, affecting 2-5% of patients.[1-5]

However, 40-50% of GBS patients do not respond to the initial immunomodulatory treatment either IVIG or PE, which does not improve on GBS disability score at 4 weeks and may even further deteriorate.[6-9] Therefore, the second immunomodulatory treatments including repeating the same previous treatment or changing to another therapy are considered for these patients, although there is no consensus evidence about the best treatment for the patients who have a poor response or deteriorate after the primary treatment course.[10]

In current evidence, only a few studies have evaluated the outcome of the second course of treatment in GBS patients.[10-14] A double-blind, randomized, placebo-controlled trial evaluating the second IVIG in GBS patients in the Netherlands with poor prognosis (SID-GBS) was recently published in 2018 and showed no significant benefit from the second IVIG. Furthermore, it had a higher risk of thrombosis and infectious complications.[14] On the other hand, PE after IVIG remains unclear because PE would probably wash out the IVIG previously administered.[10] Only one small retrospective study in the U.S. reported that IVIG followed by PE was not better than IVIG as well as the patients who received both treatments had a worse GBS disability grade at discharge and longer length of hospital stay.[13]

There are many questions about whether subtypes of GBS patients in Western are different from Asia including Thailand. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is the most common subtype in the United States and Europe presenting in about 60-90% of GBS patients while axonal forms, acute motor axonal neuropathy (AMAN) and acute motor sensory axonal neuropathy (AMSAN), are more prevalent in China and South-east Asia.[1,2,15] Generally, axonal subtypes are different from AIDP. They tend to have a poor prognosis compared with AIDP. The therapeutic response to IVIG is good in the case of AIDP, but is unsatisfactory in the patients with the axonal forms.[16-18] Moreover, there are few case reports shown that some patients with axonal subtypes were likely to improve with PE after failing IVIG treatment.[17-19]

Therefore, this research aimed (1) to determine the clinical predictors are associated with poor response in GBS patients, (2) to study the outcome of a second immunomodulatory treatment in GBS patients with poor response to initial treatment in the Neurological Institute of Thailand.

Materials and Methods

Study design

An observational retrospective study was conducted at the Neurological Institute of Thailand, including all patients diagnosed with GBS between January 2017 and June 2023. The study was reviewed and approved by Institutional Review Board (IRB).

Study population

The study population included patients aged 18 years or more diagnosed with GBS according to Brighton criteria 2011.[1,20] The inclusion criteria are (1) progressive bilateral flaccid weakness of limbs, (2) Absent or decreased tendon reflexed in affected limbs, (3) time between onset to nadir within 4 weeks, (4) evidence of albuminocytologic dissociation defined as the combination of cerebrospinal fluid (CSF) protein level more than 45 mg/dl and cell count less than 50 cells/ul, (4) the reported electrodiagnostic features are compatible with the subtypes of GBS. We accepted in case protein levels are normal or electrodiagnostic studies are normal, especially within the first week of symptom onset.[1,20] In addition, the electrodiagnostic criteria are based on Uncini's criteria 2017, classified as AIDP, AMAN, AMSAN, inexcitable, equivocal, and normal.[21] The exclusion criteria are (1) the patients were finally diagnosed with another diagnosis; (2) medical data were incompletely recorded.

Data collection

The data recorded including age, gender, comorbidity, antecedent events within the 4 weeks preceding the onset of symptoms, date of onset, clinical manifestations, Medical Research Council (MRC) sum score, GBS disability score, CSF profiles, electrodiagnostic studies, an option of immunomodulatory treatment, treatment response, complications, and length of hospital stay.

The MRC sum score was used to assess muscle strength ranging from 0 (complete paralysis) to 60 (normal). The GBS disability score is a widely accepted scale for accessing the functional status of patients with GBS (0: normal; 1: minor symptoms but able to run; 2: able to walk 10 meters or more without assistance but unable to run; 3: able to walk 10 meters across an open space with help; 4: bedridden or chairbound; 5: requiring assisted ventilation for at least part of the day; 6: death)

Furthermore, immunomodulatory treatments are defined as the treatments that modulate the immune system including IVIG, and PE. The second immunomodulatory treatment is the second course of treatment in GBS patients who poorly respond to initial treatment such as a second dose of IVIG, PE followed by IVIG. In addition, the definition of poor response is an improvement in GBS disability score less than one grade at 4 weeks after the initial course of treatment.

Outcome

The clinical outcomes were presented by an improvement in GBS disability score, MRC sum score at 8 weeks, at 12 weeks, and 24 weeks after the start of treatment, duration of hospital stay, intubation period, and mortality.

Statistical analysis

Continuous variables were presented as the median and interquartile range, while categorical variables were described as percentages. The differences between groups were analyzed using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. All probability values were two-sided and the level of significance was set at p-value < 0.05. Statistical analyses were performed using SPSS for Windows version 16.0 (SPSS Inc., Chicago, Illinois, USA)

Results

Demographics and clinical features

A total of 64 patients with GBS were included in the present study. The demographics and clinical features of the GBS patients are shown in Table 1. Male patients were slightly predominant (53.1%). The male-to-female ratio was 1.2:1. Median age at onset was 53.5 years (range from 42-64 years). Underlying diseases were hypertension (45.3%), diabetic mellitus (21.9%), coronary artery disease (7.8%), and HIV (6.3%). The most common antecedent events were URI (15.6%), diarrhea (7.8%), vaccination (7.8%), and fever of unknown origin (6.3%). The mean duration before the first evaluation was 7 days (range from 5 to 14 days).

Table 1 Demographic data and clinical manifestations of patients with GBS (n=64).

Variable	Total (n=64)	Good response (n=47)	Poor response (n=17)	p-valve
Demographic data				
Sex, male: female	1.2: 1	1: 1.1	2.4: 1	0.092
Age (years); median (IQR)	53.5 (42.0-64.0)	55.0 (38.0-64.0)	53.0 (46.5-65.0)	0.503
Comorbidity; n (%)				
Diabetic mellitus	14 (21.9)	11 (23.4)	3 (17.6)	0.742
Hypertension	29 (45.3)	20 (42.6)	9 (52.9)	0.461
HIV	4 (6.3)	3 (6.4)	1 (5.9)	1.000
Coronary artery disease	5 (7.8)	1 (2.1)	4 (23.5)	0.015*
Antecedent event; n (%)				
Diarrhea	5 (7.8)	4 (8.5)	1 (5.9)	1.000
URI	10 (15.6)	10 (21.3)	0	0.051
Vaccination	5 (7.8)	4 (8.5)	1 (5.9)	1.000
Fever unknown origin	4 (6.3)	3 (6.4)	1 (5.9)	1.000

Variable	Total (n=64)	Good response (n=47)	Poor response (n=17)	p-valve
Clinical manifestations				
Duration from symptom onset to admission (days); median (IQR)	7.0 (5.0-14.0)	7.0 (5.0-14.0)	8.0 (4.0-14.0)	0.830
Clinical features at admission; n (%)				
Weakness	64 (100)	47 (100.0)	17 (100.0)	NA
Sensory disturbance	50 (78.1)	38 (80.9)	12 (70.6)	0.495
Facial weakness	29 (45.3)	19 (40.4)	10 (58.8)	0.192
Ophthalmoplegia	16 (25.0)	11 (23.4)	5 (29.4)	0.745
Oropharyngeal weakness	31 (48.4)	18 (38.3)	13 (76.5)	0.007*
Hyporeflexia or areflexia	62 (96.9)	46 (97.9)	16 (94.1)	0.464
Radicular pain	6 (9.4)	4 (8.5)	2 (11.8)	0.652
Respiratory failure	25 (39.1)	12 (25.5)	13 (76.5)	<0.001*
Autonomic dysfunction	14 (21.9)	9 (19.1)	5 (29.4)	0.380
Alteration of mental status	3 (4.7)	1 (2.1)	2 (11.8)	0.170
MRC score at admission; median(IQR)	36.0 (30.0-48.0)	38.0 (30.0-48.0)	12.0 (5.0-19.0)	<0.001*
GBS score at admission; median (IQR)	4.0 (3.0-5.0)	4.0 (3.0-5.0)	5.0 (5.0-5.0)	<0.001*

The majority of GBS patients presented with sensorimotor polyneuropathy. Almost all patients had a symmetrical, proximal, and distal weakness with hyporeflexia or areflexia. Other clinical features were oropharyngeal weakness (48.4%), facial weakness (45.3%), respiratory failure (39.1%), ophthalmoplegia (25.0%), autonomic dysfunction (21.9%), radicular pain (9.4%) and altered mental status (4.7%)

For further analysis, the author classified the patients into 2 groups which are a good response group and a poor response group. There were 47 patients (73.4%) who had a good response to the initial treatment and 17 patients (26.6%) had a poor response to the initial treatment. There were no significant differences in gender, age, and antecedent events among the study group. However, GBS patients in the poor response group had higher comorbidity with coronary artery disease (23.5 vs. 2.1, p=0.015), higher oropharyngeal weakness (76.5% vs. 38.3%, p=0.007), and higher respiratory failure (76.5% vs. 25.5%, p<0.001) at admission. Furthermore, a low MRC sum score, especially less than 30 (100.0 vs. 27.7, p<0.001), low motor power grading, and high GBS disability score at the time of admission more than 4 (82.4 vs. 25.5, p<0.001) were associated with poor response to treatment.

Laboratory and electrophysiological findings

The CSF examination and electrodiagnostic studies were examined in all patients. The results are presented in Table 2. 81.3% of patients had albuminocytological dissociation with a median protein value of 113.5 mg/dl (range 53.0-146.5 mg/dl). There were no significant differences in the CSF profile between these study groups.

Table 2 CSF and electrodiagnostic features of patients with GBS (n=64).

Variable	Total (n=64)	Good response (n=47)	Poor response (n=17)	p-valve
CSF characteristics				
Albuminocytologic dissociation; n (%)	52 (81.3)	36 (76.6)	16. (94.1)	0.157
CSF protein (mg/dl); median (IQR)	113.5 (53.0-146.5)	112.0 (52.0-147.0)	115.0 (43.5-131.5)	0.676
Duration from symptom onset to LP (days); median (IQR)	7.0 (5.0-14.0)	7.0 (5.0-14.0)	8.0 (4.5-14.5)	0.825
Electrodiagnostic features				
Electrodiagnostic classification; n (%)				
AIDP	38 (59.4)	31 (66)	7 (41.2)	0.062
AMAN	8 (12.5)	6 (12.8)	2 (11.8)	0.062
AMSAN	8 (12.5)	6 (12.8)	2 (11.8)	0.062
Inexcitable	6 (9.4)	1 (2.1)	5 (29.4)	0.062
Normal	4 (6.3)	3 (6.4)	1 (5.9)	0.062
Conduction block; n (%)	10 (15.6)	8 (17.0)	2 (11.8)	1.000
Duration from symptom onset to study (days); median (IQR)	10.0 (5.2-15.8)	9.0 (5.0-14.0)	14.0 (10.0-20.5)	0.015*

For electrodiagnostic studies, the most frequent electrodiagnostic classifications were AIDP (59.4%), followed by AMAN (12.5%) and AMSAN (12.5%). Some patients were inexcitable (9.4%) and normal (6.3%). The electrodiagnostic study was performed at a median of 10 days (range from 5 to 15 days). There were no significant differences in the electrodiagnostic features between these study groups.

Treatment and outcomes

For initial treatment, 63 patients (98.4.%) were treated with 0.4 mg/kg/day intravenous immunoglobulin (IVIG) for 5 days and 1 patient (2.1%) received 5 cycles of plasma exchange (PE). Of all patients, 47 patients (73.4%) had a good response and 17 patients (26.6%) had a poor response to the initial treatment. For patients with a good response, the median times after treatment to the first clinical response were 8 days (ranging from 5-24 days). At 4, 8, 12, and 24 weeks after treatment, median MRC scores were 48.0 (range from 29.5-54.0), 56.0 (range from 44.5-60.0), 58.0 (range from 46.0-60.0), and 60.0 (range from 49.0-60.0) respectively, and GBS disabling scores were 3 (range from 2-4), 2 (range from 0-3), 1.0 (range from 0.0-2.5) and 0 (range from 0-2) respectively. Almost all patients (95.7%) were able to walk independently at 24 weeks after the treatment. The treatment outcome is shown in Table 3, Figure 1A, and Figure 1B.

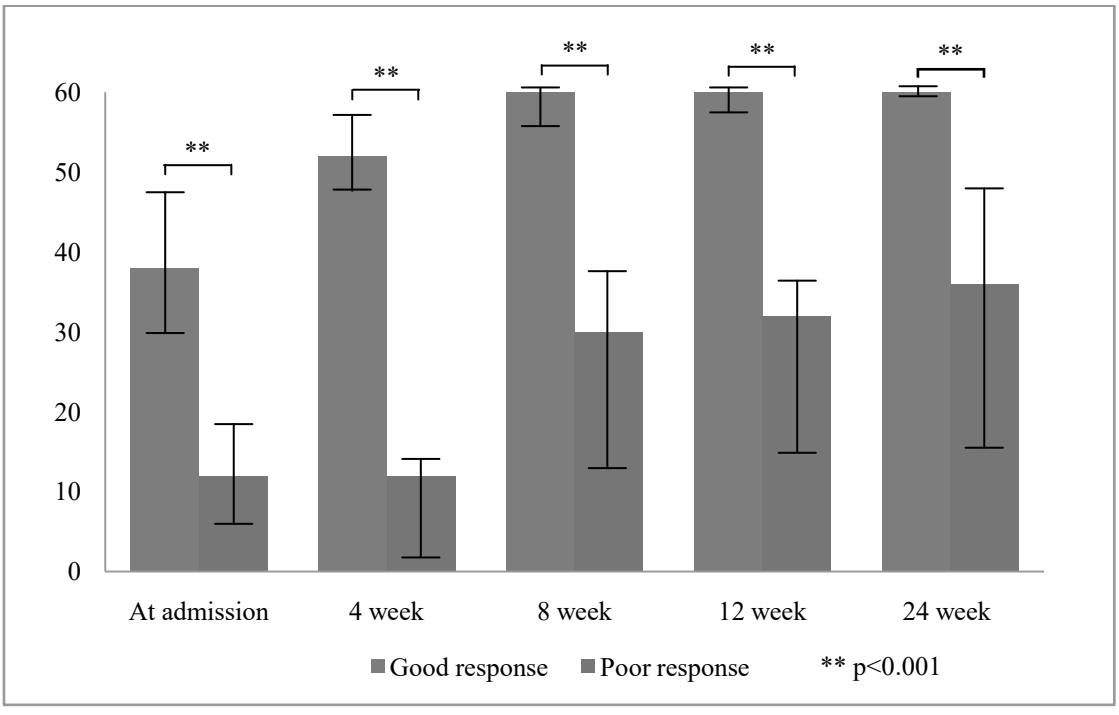


Figure 1A MRC sum score between good response group and poor response group.

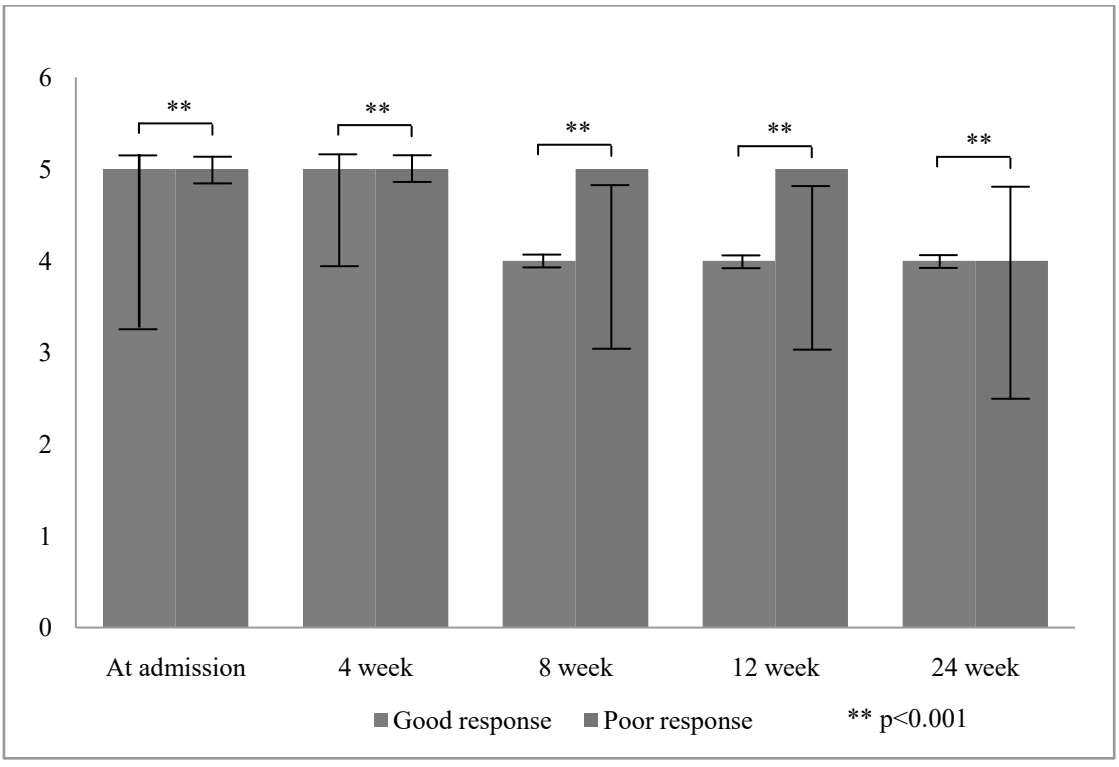


Figure 1B GBS disability score between good response group and poor response group.

Table 3 Treatment and outcome of patients with GBS (n=64).

Variable	Total (n=64)	Good response (n=47)	Poor response (n=17)	p-valve
Outcomes				
MRC score at 4 week; median (IQR)	48.0 (29.5-54.0)	52.0 (48.0-56.0)	12.0 (0.0-25.0)	<0.001*
MRC score at 8 week; median (IQR)	56.0 (44.5-60.0)	60.0 (54.0-60.0)	30.0 (12.0-38.0)	<0.001*
MRC score at 12 week; median (IQR)	58.0 (46.0-60.0)	60.0 (58.0-60.0)	32.0 (14.0-36.0)	<0.001*
MRC score at 24 week; median (IQR)	60.0 (49.0-60.0)	60.0 (60.0-60.0)	36.0 (15.0-48.0)	<0.001*
GBS score at 4 week; median (IQR)	3.0 (2.0-4.0)	2.0 (2.0-3.0)	5.0 (5.0-5.0)	<0.001*
GBS score at 8 week; median (IQR)	2.0 (0.0-3.0)	0.0 (0.0-2.0)	4.0 (3.0-5.0)	<0.001*
GBS score at 12 week; median (IQR)	1.0 (0.0-2.5)	0.0 (0.0-1.0)	4.0 (3.0-5.0)	<0.001*
GBS score at 24 week; median (IQR)	0.0 (0.0-2.0)	0.0 (0.0-0.0)	4.0 (2.5-5.0)	<0.001*
Duration from symptom onset to treatment (days); median (IQR)	9.5 (6.0-14.0)	8.0 (5.0-14.0)	14.0 (8.0-20.2)	0.120
Complications; n (%)				
Thromboembolism	1 (1.6)	0	1 (5.9)	0.266
Infection	20 (31.3)	7 (14.9)	13 (76.5)	<0.001*
Cardiovascular complication	4 (6.3)	2 (4.3)	2 (11.8)	0.285
Intubation (days); median (IQR)	12.0 (0.0-17.8)	4.0 (0.0-7.0)	38.0 (11.0-56.0)	<0.001*
Length of stay (days); median (IQR)	22.5 (8.5-43.0)	13.0 (7.0-25.0)	50.0 (38.5-64.5)	<0.001*
Death; n (%)	3 (4.7)	0	3 (17.6)	<0.001*

However, 17 patients (26.6%) had a poor response to the initial treatment. Median durations from symptom onset to treatment in this group were slightly longer, but non-significant difference (14 vs. 8, p=0.120). 10 patients (58.9%) received only a single course of IVIG and 7 patients (41.1%) received the second treatment. There were 6 patients (85.7%) who had PE after IVIG and 1 patient (14.3%) had a second dose of IVIG. Duration from the initial treatment to the second treatment was 21.5 days (range from 17.0 to 25.5 days). Patients with poor response had lower median MRC scores and higher GBS disabling scores during follow-up than other groups significantly. At 4 weeks, the median MRC score and GBS disabling score were 12.0 (0.0-25.0) and 5.0 (5.0-5.0) respectively. More than 76.5% of the patients required mechanical ventilation. At 8 weeks, the median MRC score and GBS disabling score were 30.0 (12.0-38.0) and 4.0 (3.0-5.0) respectively. About two-thirds of the patients (70.6%) were still bedbound. At 24 weeks, the median MRC score and GBS disabling score were 36.0 (15.0-48.0) and 4.0 (2.5-5.0) respectively. Only a few patients (23.5%) were able to walk independently. Moreover, there were significantly longer intubation periods (38.0 vs. 4.0, p<0.001), prolonged length of hospital stay (50.0 vs. 13.0, p<0.001), higher infectious complications (76.5% vs. 14.9%, p<0.001), and higher mortality (0 vs. 17.3%, p<0.001)

Comparison between single course and second course of immunomodulatory treatment in GBS patients with poor response to initial treatment

Of 17 patients with poor response to the initial treat-

ment, there were 10 patients (58.8%) received a single treatment of IVIG and 7 patients (41.2%) received a second treatment. 6 patients (85.7%) received PE followed by IVIG and 1 patient (14.3%) received a second dose of IVIG. The Majority of patients were male (85.7%) and had a median age of 54.5 years (range from 45.0-63.2 years). Underlying diseases were hypertension (42.9%), diabetic mellitus (14.3%), and coronary artery disease (14.3%). Median times from symptom onset to admission were 7.0 days (range from 2.5 to 18.5 days). The median MRC sum score and GBS disability score at admission were 12.0 (9.0-19.0) and 5.0 (4.75-5.0) respectively. All of them were albuminocytologic dissociation and median CSF protein levels were 122.5 mg/dl (93.5-191.7 mg/dl). Electrodiagnostic findings were AIDP (28.6%), AMAN (14.3%), and inexcitable (57.1%). Median times from the initial treatment to the second treatment were 21.5 days (range from 17.0 to 25.5 days). There were no significant differences in baseline characteristics including gender, age, comorbidities, clinical manifestations, MRC sum score and GBS disability score at admission, CSF profiles, and electrodiagnostic features among these patient groups. These results are demonstrated in Table 4, Figure 2A, and Figure 2B.

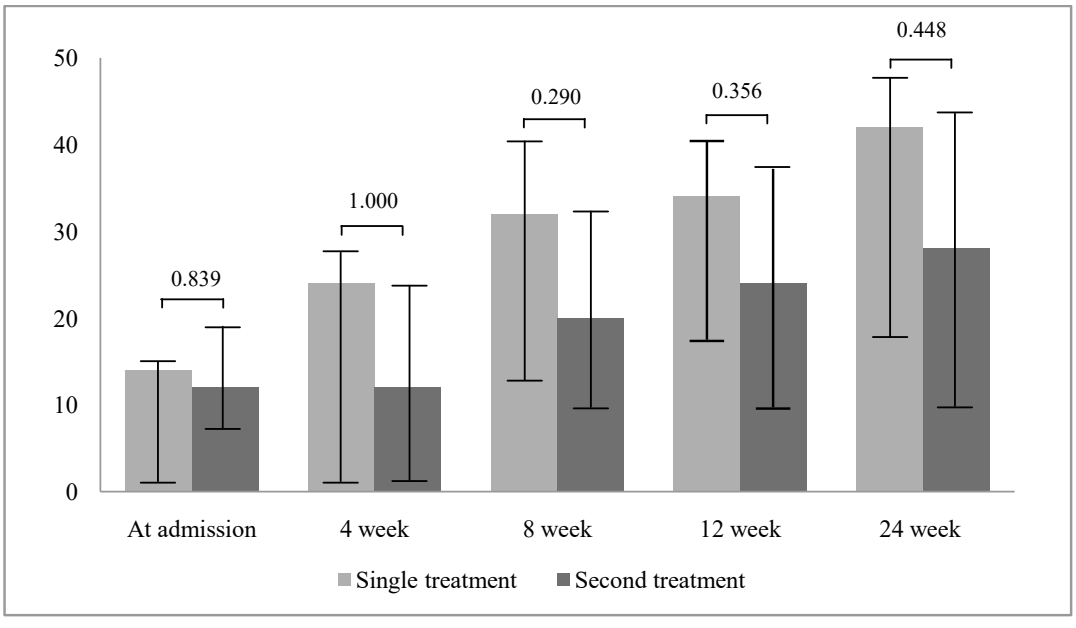


Figure 2A MRC sum score between GBS patients with poor response in single treatment group and second treatment group.

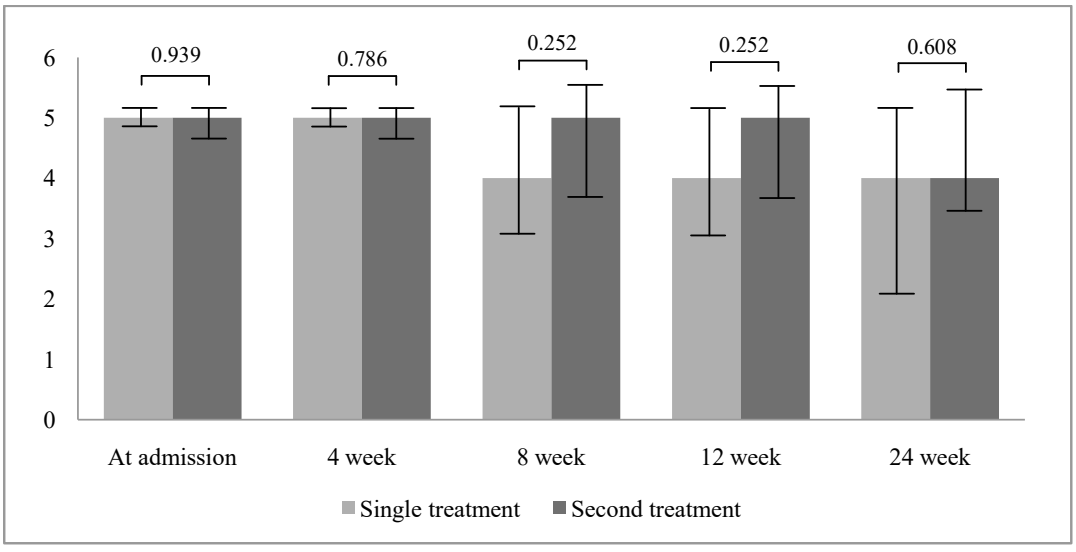


Figure 2B GBS disability score between GBS patients with poor response in single treatment group and second treatment group.

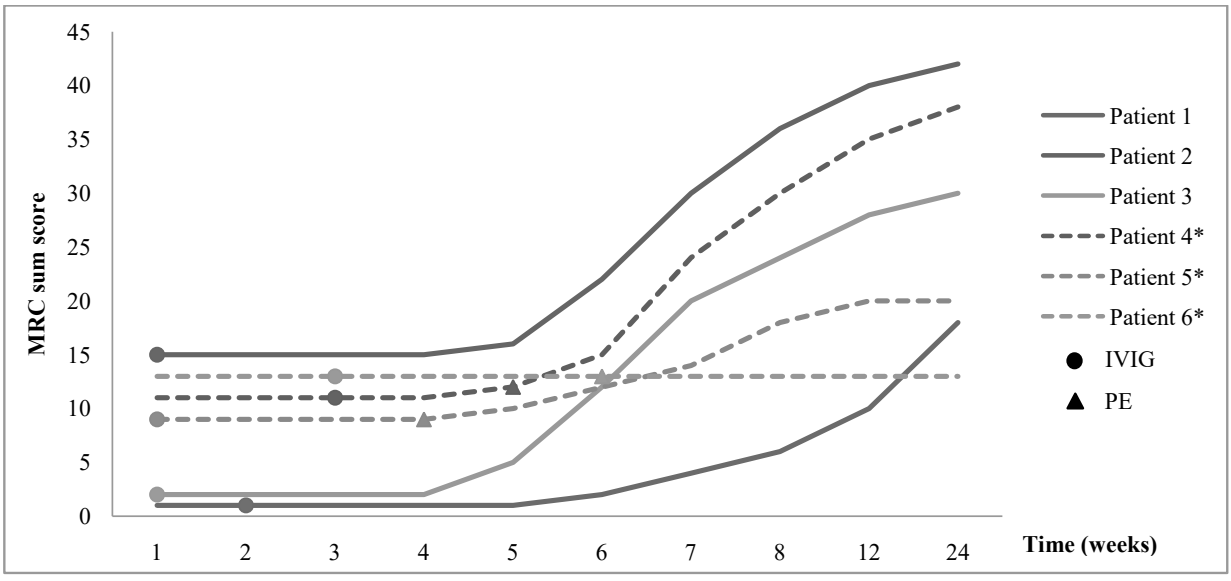
Table 4 Demographic data, clinical manifestations, CSF and electrodiagnostic features of GBS patient with poor response (n=17)

Variable	Single course (n=10)	Second course (n=7)	p-valve
Demographic data			
Male; n (%)	6 (54.5)	6 (100)	0.102
Age (years); median (IQR)	53.0 (47.0-71.0)	54.5 (45.0-63.2)	0.615
Comorbidity; n (%)			
Diabetic mellitus	2 (18.2)	1 (16.7)	1.000
Hypertension	7 (63.6)	2 (33.3)	0.335
HIV	1 (9.1)	0	1.000
Coronary artery disease	3 (27.3)	1 (16.7)	1.000
Clinical manifestations			
Duration from symptom onset to admission (days); median (IQR)	10.0 (5.0-14.0)	7.0 (2.5-18.5)	0.686
Clinical features at admission; n (%)			
Weakness	6 (100)	6 (100)	NA
Sensory disturbance	7 (63.6)	5 (83.3)	0.600
Facial weakness	6 (54.5)	4 (66.7)	1.000
Ophthalmoplegia	3 (27.3)	2 (33.3)	1.000
Oropharyngeal weakness	7 (63.6)	6 (100)	0.237
Absence or decrease of tendon reflex	10 (90.9)	6 (100)	1.000
Radicular pain	1 (9.1)	1 (16.7)	1.000
Respiratory failure	8 (72.7)	5 (83.3)	1.000
Autonomic dysfunction	3 (27.3)	2 (33.3)	1.000
Alteration of mental status	1 (9.1)	1 (16.7)	1.000

Variable	Single course (n=10)	Second course (n=7)	p-valve
MRC sum score at hospital admission; median (IQR)	14.0 (0.0-20.0)	12.0 (9.0-19.0)	0.839
GBS disability score at admission; median (IQR)	5.0 (5.0-5.0)	5.0 (4.75-5.0)	0.939
CSF characteristics			
Albuminocytologic dissociation; n (%)	10 (90.9)	6 (100)	1.000
CSF protein levels (mg/dl); median (IQR)	100.0 (27.0-128.0)	122.5 (93.5-191.7)	0.191
Duration from symptom onset to study (days); median (IQR)	7.0 (4.0-15.0)	9.0 (6.0-14.5)	0.724
Electrodiagnostic features			
Electrodiagnostic classification; n (%)			
AIDP	1 (9.1)	2 (33.3)	0.762
AMAN	5 (45.5)	1 (16.7)	0.762
AMSAN	1 (9.1)	0	0.762
Inexcitable	2 (18.2)	3 (50.0)	0.762
Normal	1 (9.1)	0	0.762
Conduction block; n (%)	1 (9.1)	1 (16.7)	1.000
Duration from symptom onset to study (days); median (IQR)	14.0 (7.0-19.0)	24.5 (10.75-36.0)	0.087

From the definition of poor response, it was defined as no improvement in GBS disability score at 4 weeks after the initial treatment. Most patients (64.7%) among both groups showed an improvement in the MRC sum score, although the GBS disability score did not change. There were 6 patients (35.3%) who had no change in GBS disability score and MRC sum score. 3 patients received a single treatment and 3 patients received a second treatment. Of these 6 patients, there were no significant difference in the MRC sum score and GBS disability score in patients who received single treatment or second treatment. The results are presented in Table 5, and Figure 3.

Furthermore, the patients who received the second treatment had higher treatment-related complications including 1 patient (14.3%) had a catheter-related bloodstream infection and 1 patient (14.3%) had a thromboembolic event. The results showed no significant differences in intubation periods (35.0 vs. 38.0, p=1.000), length of hospital stay (45.0 vs. 52.0, p=1.000), and mortality (28.6% vs. 18.2%, p=0.537).



Patient 1-3 represent single course of treatment, Patient 4*-6* represent second course of treatment Dots (●) represent IVIG, Triangles (▲) represent PE

Figure 3 Outcome of treatment in patients who did not change in MRC sum score at 4 week comparing between single treatment and second treatment

Table 5 Outcome of the second course immunomodulatory treatment in GBS patients with poor response to standard treatment compared to a single course of treatment (n=17).

Variable	Single course (n=10)	Second course (n=7)	p-valve
Outcomes			
MRC score at admission; median (IQR)	14.0 (0.0-20.0)	12.0 (9.0-19.0)	0.839
MRC sum score at 4 week; median (IQR)	24.0 (0.0-26.0)	12.0 (0.0-23.5)	1.000
MRC sum score at 8 week; median (IQR)	32.0 (12.0-40.0)	20.0 (9.0-33.5)	0.290
MRC sum score at 12 week; median (IQR)	34.0 (12.0-46.0)	24.0 (9.0-35.5)	0.356
MRC sum score at 24 week; median (IQR)	42.0 (18.0-48.0)	28.0 (9.0-41.5)	0.448
GBS score at admission; median (IQR)	5.0 (5.0-5.0)	5.0 (4.75-5.0)	0.939
GBS disability score at 4 week; median (IQR)	5.0 (5.0-5.0)	5.0 (4.75-5.0)	0.786
GBS disability score at 8 week; median (IQR)	4.0 (3.0-5.0)	5.0 (3.75-5.25)	0.252
GBS disability score at 12 week; median (IQR)	4.0 (3.0-5.0)	5.0 (3.75-5.25)	0.252
GBS disability score at 24 week; median (IQR)	4.0 (2.0-5.0)	4.0 (3.5-5.25)	0.608
Complications; n (%)			
Thromboembolism	0	1 (14.3)	1.000
Infection	6 (60.0)	7 (100.0)	0.237
Hospital acquired pneumonia	6 (100.0)	7 (100.0)	
Catheter-related bloodstream infection	0	1 (14.3)	
Cardiovascular complication	1 (10.0)	1 (14.3)	1.000
Intubation periods (days); median (IQR)	38.0 (5.0-60.0)	35.0 (12.7-52.0)	1.000
Length of stay (days); median (IQR)	52.0 (30.0-65.0)	45.0 (39.2-64.5)	1.000
Death; n (%)	1 (10.0%)	2 (28.6%)	0.537

Discussion

This study demonstrated overall demographic data, clinical manifestations, CSF profiles, electrodiagnostic characteristics, treatment outcomes, complications, and mortality were not different from previously published studies.[22-25] The majority of patients (73.4%) with GBS were a good response to treatment. The median time that showed the first clinical response was 8 days. Almost all patients (95.7%) were able to walk independently at 24 weeks. Unfortunately, 26.6% to 50% of GBS patients showed no improvements in GBS disability scores at 4 weeks after the treatment which reflects poor response to the initial treatment.[6-9] Only 23.5% of this group was able to walk independently at 24 weeks, and 4.6% died. In the present study, factors associated with poor response were underlying disease with coronary artery disease, oropharyngeal weakness, respiratory failure at admission, low MRC sum scores less than 30, and high GBS disability score at the time of admission more than 4. By comparison, low MRC sum scores of less than 40 at admission, high GBS disability score, presentation with bulbar weakness, respiratory failure requiring a mechanical ventilator, and severe motor weakness with inability to stand or lift elbow were significant predictors of poor outcomes in several studies.[26-30] Although many factors related to poor outcomes including high age more than 50 years, preceding diarrhea, and the short time from symptom onset to admission less than 7 days, it did not reach statistical significance in this study. Duration from symptom onset to treatment administration was also not significantly different. Moreover, electrodiagnostic predictors were not clear.

This study also demonstrated the outcome of the second course of treatment in the poor response group compared to a single treatment. There were 6 patients (85.7%) who had PE followed by IVIG and 1 patient (14.3%) had a second dose of IVIG. The median time from the initial treatment to the second treatment was 21.5 days. Most patients (64.7%) in both groups showed an improvement in MRC sum score during follow-up, even though the GBS disability scores did not change. Only 6 patients (35.3%) were not changed in the GBS disability scores and MRC sum scores. Of these groups, the results presented that there were no statistically significant differences in MRC sum scores, GBS disability scores during follow-up, intubation periods, duration of hospital stay, and mortality among these two groups. However, the patients with the second treatment had higher treatment-related complications, especially catheter-related bloodstream infections, and thromboembolic events.

These results were corresponding with the current studies. A double-blind, randomized, placebo-controlled trial evaluating the second IVIG in GBS patients in the Netherlands with poor prognosis (SID-GBS) was published in 2018 and showed no significant benefit from the second IVIG and it had a higher risk of thrombosis and infectious complications.[14] According to data from Oczko-Walker Malgorzata MD, this retrospective trial studied PE after initial IVIG in GBS. The results showed the patients who received both treatments had a worse GBS disability score at discharge with an increase in cost and hospitalization.[31]

The reason may explain about second immunomodulatory treatments do not show the obvious benefit because of severe axonal degeneration. The underlying pathogenesis of GBS is caused by

autoantibodies attack on myelin components, resulting in demyelination and secondary axonal injury or they can directly attack on axon, resulting in primary axonal injury. The recovery depends on the remyelination process and the degree of axonal degeneration.[2]

For this reason, there are severe axonal injury contribute to severe clinical features, poor response to treatment, and unpleasant clinical outcomes. Although the second immunomodulatory treatments are given, including neutralization of the autoantibodies by IVIG or removal by PE, they cannot restore the destroyed axon. Moreover, a second dose of IVIG may increase plasma viscosity and lead to an increased risk of serious adverse side effects, especially thromboembolic events.[14] Lastly, some expert opinions suggest that PE may be washed out of IVIG, as a result of preventing the therapeutic effect of IVIG.[32]

Limitation

There are several limitations in this study. Mainly, this is a retrospective study so it has many limitations when interpreting data on the chart reviews including missing data, lack of standard assessment, differences in timing of follow-up, and lack of long-term outcome data resulting from inconsistent follow-up of patients after discharge and some patients were referred back to their primary care physician. Secondly, there are no clear criteria to select patients who should receive the second immunomodulatory treatment after no clinical response to the initial treatment. Instead, the decision made by the attending physician depends on the patient's clinical situation. Finally, because of the limited sample size and single-center study, it cannot compare the effect of IVIG and PE on different subgroups, and it cannot accurately reflect the disease course in larger population samples. There is a need to multi-center study.

Conclusion

The second immunomodulatory treatment in GBS patients with poor response to the initial treatment is no significant differences in MRC scores, GBS disability scores during follow-up, intubation periods, length of hospital stay, and mortality compared to a single course of treatment. There are increased risks of serious treatment-related complications, including catheter-related bloodstream infections, and thromboembolic events.

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Sympathetic Hyperactivation as an Alternative Treatment of Orthostatic Hypotension in Parkinson's Disease: an Initial Report of an Ongoing Randomized Control Study

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Parnsiri Chairangsaris

ABSTRACT

Background: Orthostatic hypotension (OH) is a common non-motor condition in Parkinson's disease (PD). For these individuals, pyridostigmine and midodrine have not been well compared.

Objective: To determine the safety and short-term effectiveness of pyridostigmine monotherapy in comparison to midodrine for individuals with Parkinson's disease who met the criteria for orthostatic hypotension (OH).

Materials and Methods: An open label, randomized clinical study was conducted. A total of thirteen PD patients with OH were enrolled and randomized to receive midodrine (5 mg/day) or pyridostigmine (120 mg/day) over a two-week period. The primary objective measured the degree of improvement in OH in two weeks. The secondary outcomes include changes in supine blood pressure (BP), supine heart rate (HR), and the proportion of patients who meet the BP criteria for OH. Note that this report was an interim analysis.

Results: The orthostatic BP of both groups was improved over two weeks. In comparison between groups, systolic blood pressure changes during supine to upright position were -14.6 mmHg and -15.4 mmHg for pyridostigmine and midodrine group, the orthostatic systolic BP (SBP) drop was significantly lower in the pyridostigmine group ($p = 0.029$ for pyridostigmine group and $p = 0.048$ for midrodrine group). The changes in orthostatic HR, supine SBP, supine DBP, and supine HR did not significantly differ between the two groups. Mild to moderate side effects were observed by five participants. While 42.9% of patients using midodrine met the BP criteria for OH, 33.3% of patients taking pyridostigmine did.

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Conclusion: When treating orthostatic hypotension in Parkinson's disease patients, a single Pyridostigmine treatment was found to be safe and to be non-inferior to low dose Midodrine. Furthermore, it was discovered that pyridostigmine was better than midodrine in terms of enhancing orthostatic SBP change and reducing the number of OH patients.

Keywords: Pyridostigmine, Midodrine, Orthostatic hypotension, Parkinson's disease

Introduction

Blood pressure (BP) that drops further following a shift in upright position is known as orthostatic hypotension (OH). This condition is generally common in elderly people.[1] The sympathetic nervous system of the heart and the baroreflex are frequently affected in patients with Parkinson's disease (PD), which can result in OH. In addition to fatigue and shoulder or neck pain, the patient may develop syncope, unexplained falls, lightheadedness, cognitive impairment, impaired vision, and weakness. Orthostatic hypotension was detected in 40.2% of Parkinson's disease cases, according to a 10-month survey done at Phramongkutklao Hospital by Sithinamsuwan P, et al. In this group, the use of selegiline, a more advanced stage of Parkinson's disease, and a longer disease duration were risk factors for developing OH.[2]

Midodrine was the first medication licensed by the US Food and Drug Administration that was shown to relieve OH and clinical symptoms in double-blind, placebo-controlled trials.[3,4] The active metabolite of midodrine, desglymidodrine, hydrolyzes to decrease orthostatic blood pressure drops, raise peripheral vascular resistance, and diminish venous pooling in the legs and splanchnic circulation. It does this by directly activating the alph-1-adrenoreceptors.[3]

Pyridostigmine is an acetylcholinesterase inhibitor that raises cholinergic signals and promotes sympathetic ganglionic neurotransmission. Pyridostigmine may only increase adrenergic tone when the patient is upright since autonomic ganglionic traffic is primarily initiated by orthostatic pressure and is negligible when the patient is supine. According to a few brief investigations, pyridostigmine induced a reduction in diastolic blood pressure (DBP) while standing without exacerbating supine blood pressure.[5,6]

Midodrine and pyridostigmine have been shown in some randomized clinical trials to be both safe and effective in treating OH.[3-5] The majority of these studies were conducted for shorter than 24 hours, and the patients included in them had OH brought on by a variety of neurological conditions, which limited their applicability. Although previous studies have shown that over 65 percent of PD patients experience OH within seven years of diagnosis,[7] there were very few PD patients involved in the trials. This suggests that little attention has been paid to OH treatment in PD patients. Pyridostigmine and midodrine have not been extensively researched for the treatment of OH in Parkinson's disease patients. In Thailand, by Limwatthana C, et al., a small, open label, randomized clinical investigation, thirteen patients with OH who had Parkinson's disease (PD) were randomly assigned to take either pyridostigmine 30 mg twice day (60 mg/day) or midodrine 2.5 mg twice day (5 mg/day) for a month. Pyridostigmine and midodrine were found to be safe in patients with Parkinson's disease who had OH, and following treatment, OH diminished. Pyridostigmine was found to be superior

to midodrine in terms of improving orthostatic SBP change and lowering the proportion of patients who met the BP threshold for OH (-6.43 mmHg, -19 mmHg, respectively, p = 0.022).[8]

In the present study, we conducted a randomized open-label parallel clinical trial to assess the safety and short-term effectiveness of pyridostigmine 60 mg twice a day (with two-time higher dosage than the study of Limwatthana C, et al.[8] compared to midodrine (5 mg/day) in treating OH in patients with Parkinson's disease.

Objectives

To assess the safety and short-term (two weeks) effectiveness of pyridostigmine and midodrine as a therapy for Parkinson PD patients who met the diagnostic criteria for orthostatic hypotension (OH).

Materials and Methods Study design

This report was an interim analysis of an ongoing randomized, open-label clinical trial that was conducted at the Neurology Division of Phramongkutklao Hospital from January 2024 onwards. This project protocol was approved by the Institutional Review Board of the Royal Thai Army Medical Department (I0026/67).

Trial Population

The following patients met the inclusion criteria: 1) participants aged eighteen years old or older, 2) diagnosed with Parkinson's disease (PD) based on the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria, and 3) experiencing symptoms of orthostatic intolerance, such as headaches, dizziness, and fainting, when they visited the Neurology Division of Phramongkutklao Hospital. For patients to be eligible for OH, they had to have a drop in systolic blood pressure (SBP) of at least 20 mmHg or a decline in diastolic blood pressure (DBP) of at least 10 mmHg within three minutes of moving from a lying to a standing posture [9]. If the candidates were bedbound or unable to measure their blood pressure, those patients were excluded from the study.

Procedure

We collected medical histories and conducted physical examinations at baseline. Using a CARESCAPE TMV100 blood pressure monitor, orthostatic blood pressure (BP) and heart rate (HR) were recorded following 10 minutes of resting in the supine position and 3 minutes of moving from lying to the standing position.

Patients who were eligible were randomized to receive midodrine 2.5 mg twice daily (after breakfast and dinner) or pyridostigmine 60 mg twice daily (after breakfast and dinner) for a duration of two weeks in a 1:1 ratio by block of four, if they fulfilled the requirements for the OH diagnosis [9] and signed a consent form. The patients' PD medication regimens and dosages would not alter throughout the research. Orthostatic blood pressure and heart rate were rechecked two weeks after treatment. Monitoring and recording were taken on the patient's drug compliance, potential side effects, and concurrent medications.

Outcomes

Primary outcome was an improvement of orthostatic blood pressure within the following two weeks of treatment. The secondary outcomes

included the percentage of patients satisfying BP criteria for OH at 2 weeks, the change in supine blood pressure, and the change in orthostatic heart rate. What happened in terms of safety was an adverse outcome.

Statistical methods:

The primary and key secondary efficacy analyses included all PD patients who assigned randomization (intention-to-treat group) was done using the STATA/MP 12 in the model. All statistical data were shown as mean and standard deviation. The independent t-test, paired t-test, and Mann-Whitney test were used to measure the differences across groups. The Chi-square test, Fisher's exact test, and McNemar test were used to conduct discrete statistic data by percentage.

Results

Thirteen individuals (20.3%) out of the 64 individuals with Parkinson's were prior routinely identified for OH met the OH criteria at our Phramongkutklao Neurology clinic and Parkinson clinic cohort. Then, all the 13 patients were invited to participate in our study during January 2024. They were randomly allocated and enrolled (Figure 1). The patients on pyridostigmine and midodrine had mean ages of 71.5 and 69 years, respectively, with 66.7 and 57.1 percent of them being female. In terms of age and gender, the patients were well matched. The duration of PD lasted three years in the pyridostigmine group and eight years in the midodrine group. In comparison to the pyridostigmine group, the midodrine group showed greater supine SBP at baseline (p = 0.0035). From the supine to the upright position, all patients showed a significant drop in their DBP (-1.1, - 4.9 mmHg) and SBP (-14.5, -15.1 mmHg). At baseline, orthostatic blood pressure and heart rate fluctuations were similar throughout the groups. Demographic characteristics were shown in Table 1.

for the primary outcome, the orthostatic blood pressure declines in both groups, however, they were better at two weeks after the treatment. In comparison between groups, the pyridostigmine group experienced a considerably more orthostatic SBP change (-14.5 mmHg and -15.4 mmHg for pyridostigmine and midodrine groups. The decrease in orthostatic DBP drop was not significantly different between the two groups (-1.17 mmHg and -4.86 mmHg for pyridostigmine and midodrine respectively, p = 0.142).

for secondary outcomes. Two weeks following therapy, there was no discernible difference between the two groups' orthostatic HR change, supine SBP, supine DBP, or supine HR change from baseline. There was a substantially decrease supine SBP in the pyridostigmine group (-11.3 mmHg, p = 0.0035), Table 2. It was found that 33.3 percent of the pyridostigmine patients and 42.9 percent of the midrodrine patients met the BP requirement for OH after two weeks of treatment. None of the patients exhibited any signs of OH (Table 3).

Adverse events

Out of 13 patients, 5 (38.5%) experienced adverse events. All adverse events were mild and transient which disappeared within a few days. Four patients (57.1%) in the pyridostigmine group developed dizziness (n = 2) and gastrointestinal symptoms, including nausea and diarrhea (n = 2), while one patient (16.7%) in the midodrine group reported nauseated.

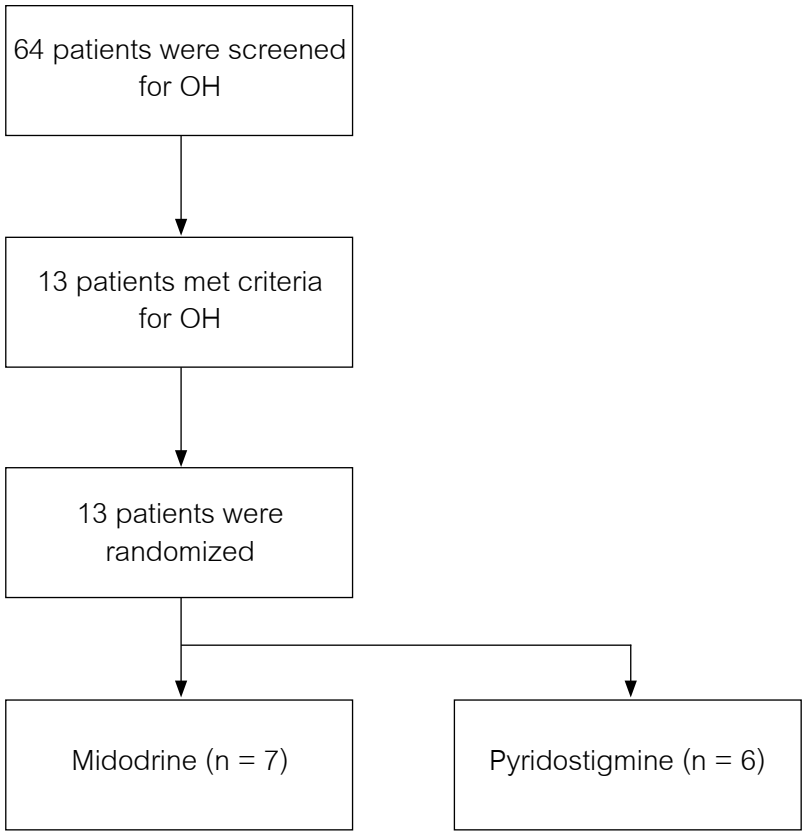

Figure 1. Flow diagram of the study

Table 1 Demographics of patients

	Pyridostigmine (n=6)	Midodrine (n=7)	p-value
Gender			
male	2 (33.33%)	3 (42.86%)	0.999
female	4 (66.67%)	4 (57.14%)	
Age			
Mean ± SD	71.50 ± 10.25	69.00 ± 13.54	0.719
median (Min - Max)	74 (58 - 85)	67 (54 - 88)	
Body weight (kg)			
Mean ± SD	55.5 ± 10.80	49.29 ± 5.44	0.206
median (Min - Max)	52 (44 - 69)	50 (42 - 58)	
Height (cm)			
Mean ± SD	158.67 ± 8.96	155.57 ± 8.06	0.525
median (Min - Max)	156.5 (149 - 170)	151 (149 - 171)	
BMI (kg/m2)			
Mean ± SD	22.11 ± 4.30	20.34 ± 1.39	0.372
median (Min - Max)	21.99 (16.61 - 28.3)	20.03 (18.86 - 22.22)	

	Pyridostigmine (n=6)	Midodrine (n=7)	p-value
Hypertension	3 (50.00%)	3 (42.86%)	0.999
Diabetic mellitus	2 (33.33%)	3 (42.86%)	0.999
Cardiovascular	1 (16.67%)	0 (0%)	0.462
Duration of Parkinson's disease (yr)			
Mean ± SD	2.67 ± 1.37	8.86 ± 6.12	
median (Min - Max)	2.5 (1 - 5)	8 (3 - 20)	0.014

Chi-square test or Fisher's exact test

Independent t-test or Mann-Whitney U test

significant iff p<0.05

Table 2 Baseline and follow-up orthostatic blood pressure and heart rate

	Pyridostigmine (n=6) Mean ± SD	Modrine (n=7) Mean ± SD	p-value**
Supine SBP, mmHg			
Baseline	140.17 ± 18.08	138.14 ± 16.1	0.835
2 weeks	128.83 ± 14.52	135.14 ± 13.57	0.435
p-value*	0.035	0.624	
Mean change (95% CI)	-11.33 (-21.46 , -1.21)	-3 (-17.23 , 11.23)	0.277
Orthostatic SBP drop, mmHg			
Baseline	-33.5 ± 15.37	-30.29 ± 12.58	0.686
2 weeks	-14.5 ± 7.34	-15.43 ± 10.37	0.858
p-value*	0.029	0.048	
Mean change (95% CI)	19 (2.95 , 35.05)	14.86 (0.16 , 29.55)	0.643
Supine DBP, mmHg			
Baseline	69.67 ± 13.28	74.57 ± 8.38	0.435
2 weeks	71 ± 11.66	76.14 ± 7.54	0.358
p-value*	0.563	0.376	
Mean change (95% CI)	1.33 (-4.21 , 6.87)	1.57 (-2.46 , 5.6)	0.931
Orthostatic DBP drop, mmHg			
Baseline	-1.17 ± 4.45	-6.29 ± 8.1	0.196
2 weeks	-1.17 ± 3.6	-4.86 ± 4.63	0.142
p-value*	0.999	0.578	
Mean change (95% CI)	0 (-4.3 , 4.3)	1.43 (-4.51 , 7.37)	0.649
supine HR, bpm			
Baseline	77.5 ± 21.49	81 ± 15.32	0.739
2 weeks	79.17 ± 19.54	81.86 ± 13.51	0.775
p-value*	0.153	0.744	
Mean change (95% CI)	1.67 (-0.88 , 4.21)	0.86 (-5.29 , 7)	0.784

* Paired t-test

** Independent t-test significant iff p<0.05

Table 3 Baseline and follow-up orthostatic hypotension

	Pyridostigmine (n=6)	Midodrine (n=7)	p-value
Patients met OH (n)			
Baseline	6 (100.00%)	7 (100.00%)	N/A
2 weeks	2 (33.33%)	3 (42.86%)	0.999
p-value	0.046	0.046	
Symptomatic OH (n)			
Baseline	1 (16.67%)	3 (42.86%)	0.559
2 weeks	0 (0%)	0 (0%)	N/A

Fisher's exact test

significant iff $p<0.05$

Discussion

The autonomic nerve system fails to regulate blood pressure in response to changes in posture because of insufficient norepinephrine release, which causes OH and supine hypertension, which is common in Parkinson's disease. However, there is still a deficiency in the treatment of symptomatic neurogenic orthostatic hypotension (nOH), which is sometimes complicated by significant rises in supine blood pressure. An effective treatment option for symptomatic nOH in Parkinson's disease (PD) is droxidopa, an oral prodrug that decarboxylates to norepinephrine. It improves nOH symptoms, falls, daily activities, and standing blood pressure.[10] Conversely, droxidopa is rather expensive and only available in a few nations. For PD patients, other drugs like midodrine or pyridostigmine may be a good substitute because they are more widely available and less expensive.

In this study, two weeks after therapy, orthostatic blood pressure changes and related symptoms were significantly alleviated by pyridostigmine and midodrine. After two weeks of medication, only 33.3% of the pyridostigmine group and 42.9% of the midodrine group experienced orthostatic hypotension. Overall, midodrine performed better at OH in DBP changes than pyridostigmine did, although pyridostigmine was better at OH in BP changes and reducing OH-associated symptoms, nevertheless, there were no statistic significant differences between studied groups.

Ours was one of the few studies to assess the safety and short-term effectiveness of pyridostigmine and midodrine for up to two weeks. In both groups, the SBP and DBP declines following standing were significantly reduced after two weeks. Pyridostigmine treatment decreased orthostatic blood pressure decline, although only slightly, up to six hours after delivery, according to short-term research.[5] Our research, pyridostigmine by far, it was recognized that both medications may be beneficial within a two-week period. Compared to another research from our division conducted earlier[8], Limwatthana C, et al. used a lower dosage of pyridostigmine (60 mg/day) for longer duration of follow up (4-week), which the results seemed not different.

When treating OH, supine hypertension is frequently a problem. Previous studies have demonstrated that pyridostigmine can lower the risk of supine hypertension.[5,6] In this study, there was a significant difference in the supine DBP change in

the midodrine group but not in the supine SBP change between the two groups. Long-term pyridostigmine treatment may raise supine SBP because it leads to occasional sympathetic hyperactivation[6]. Furthermore, the absence of supine hypertension in the midodrine group may be explained by the modest dose of midodrine used in this investigation.

Among the study's limitations were its small sample size (n = 13, as this report was the first initial assessment part from our ongoing trial), its short duration of Parkinson's disease, and its lack of a severity staging for PD patients, which we planned to further complete those measures in the next analysis. Therefore, not all PD patients may benefit from this study's results. The concomitant medication usage and dosage of the patients, which may have affected their blood pressure were not recorded in this initial part of the study.

Nevertheless, the therapies alleviated orthostatic blood pressure parameters change and symptoms related to OH for up to two weeks, even at low doses of midodrine. It's uncertain how long treatment will need to continue for combating OH. According to this study, midodrine or pyridostigmine therapy should be administered for a minimum of two weeks. It is necessary to complete our ongoing RCT to identify the effectiveness of treatment in individuals with various OH etiologies and to ascertain the optimum amount of time for pharmacologic treatment of OH.

Conclusion

Regarding the management of orthostatic hypotension in Parkinson's disease, pyridostigmine treatment has been shown to be safe and non-inferior to low dose Midodrine. Pyridostigmine was also found to be more effective than midodrine at improving orthostatic SBP change and reducing the number of patients with hypotension.

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Prevalence and Risk Factors of Myasthenia Gravis Exacerbation Related to COVID-19 Vaccination at Siriraj Hospital

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ABSTRACT

Objective: To study the prevalence and risk factors of MG exacerbation in relationship to COVID-19 vaccination at Siriraj Hospital.

Introduction: Various risk factors contribute to MG exacerbation, including infections, medications, and vaccination. In Thailand, 2.5 million people were affected by COVID-19 infection by the end of 2022. After COVID-19 vaccine approval, reports emerged of adverse events, particularly neurological complications. Despite Thailand's diverse use of COVID-19 vaccines and regimens, documentation of adverse events in MG patients in Thailand is lacking.

Materials and Methods: Our team conducted an observational retrospective study at Siriraj Hospital, Mahidol University, Thailand, to answer this issue. The data of patients in our MG clinic database from the established clinic until 31 December 2023 was reviewed. All patients who met the inclusion criteria were interviewed in person or via phone for information regarding COVID-19 vaccination and MG symptoms after the vaccination.

Results: Data collected from 209 MG clinic patients who attended the clinic from December 2019 to December 2023 revealed three episodes of MG exacerbation within six weeks after vaccination from a total of 633 vaccine events, comprising 0.47% of all COVID-19 vaccination events. Notably, two episodes of MG exacerbation occurred after the second dose, and one arose after the first. The factors associated with MG exacerbation after COVID vaccination from univariate analysis of patients with thymic carcinoma and patients with higher prednisolone dosage

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Conclusion: From the results of our study, given the low prevalence of MG exacerbation, MG patients should be encouraged to have COVID-19 vaccination with only minor concerns for MG exacerbation.

Keywords: COVID-19 vaccination, Myasthenia Gravis exacerbation, COVID-19 vaccination and Myasthenia Gravis exacerbation, Risk factors of Myasthenia Gravis exacerbation

Introduction

Myasthenia Gravis (MG) is a neuromuscular junction disorder caused by an autoimmune response against the post-synaptic neuromuscular junction, which later disrupts neural transmission to muscles, leading to muscle weakness. The incidence of MG in Thailand is approximately 2.17 per 100,000 population. Signs and symptoms of MG vary from extraocular muscle weakness, limb weakness, and facial muscle weakness to respiratory and pharyngeal muscle weakness, which can lead to respiratory failure, resulting in myasthenic crisis with a high mortality rate. The symptoms and severity of MG are individualized for each patient, depending on the structure of the neuromuscular junction (NMJ) damaged by immune cells and the disease stage.

Various risk factors contribute to MG exacerbation and MG crisis, including infections, medications, poor compliance, and vaccination. COVID-19 infection or vaccination can also result in worsening MG and MG crisis.

In Thailand, more than 2.5 million people were affected by COVID-19 infection by the end of 2022, ranking 30th globally[1]. COVID-19 primarily affects the respiratory tract, and the severity differs between each patient depending on patient co-morbidities, immunosuppressive drugs that lead to severe disease, COVID-19 vaccination, and the strain of COVID-19. The vaccine's efficacy against COVID-19 infection was 82.51% after one month of the first dose and up to 93.74% after one month of the complete second dose[2].

After COVID-19 vaccine approval, reports emerged of adverse events, particularly neurological complications such as Guillain-Barre syndrome, acute disseminated encephalomyelitis, MG exacerbation, and acute stroke. There were a few studies about the prevalence of MG exacerbation after COVID-19 vaccination, and most of them showed low event rates. About 5% of patients from a large cohort experienced worsening MG after COVID-19 vaccination[3]. Despite Thailand's diverse use of COVID-19 vaccines and regimens, documentation of adverse events, especially in MG patients, is lacking, leading our team to this study.

Method

Study design and population

This was a single-center observational retrospective study in MG Clinic, Siriraj Hospital, Mahidol University. The data of patients in our MG clinic database from the established clinic until 31 December 2023 was reviewed. The inclusion criteria of our population were 1.) Patients diagnosed with MG for at least three months; 2.) Age 18 years old or above; 3.) Patients who follow up in the MG clinic without documented loss to follow up; 4.) Good drug adherence and well-controlled disease; 5.) Documented any COVID-19 vaccination. The exclusion criteria were patients who were lost to follow-up or had incomplete medical records.

The primary outcome is the prevalence of MG exacerbation within six weeks of the COVID-19

vaccination, which is defined as the patient's subjectively reported worsening of symptoms by increasing MGFA grading and objective evident by physician examination that needs to be increased immunosuppressive dosage to control the symptom compared with before vaccination. The secondary outcome is a risk factor associated with MG exacerbation after COVID-19 vaccination.

Data collection and statistical analysis

We collected demographics data, MG clinical characteristics, COVID-19 vaccination information: gender, age, BMI, co-morbidities, age onset, age at diagnosis, the severity of symptoms at diagnosis and worst symptom by using MGFA, duration of follow-up, duration of follow-up to worst MGFA, MGFA at the beginning of 2020 through 2023, serological status, thymic pathology in patients undergoing thymectomy, adjuvant radiotherapy in patient experienced thymectomy, immunosup pressive and pyridostigmine usage, type of COVID-19 vaccines (inactivated virus, virus vector, mRNA), vaccine status (amount of vaccine that patient take, date of administration if possible, which vaccine that patients experience progression of MG symptom, duration from administration of vaccine to worsening MG symptom and severity of symptom, other precipitating factors that comprise to worsening of MG). The MGFA (Myasthenia Gravis Foundation of America) classification was used to classify the severity of the disease into five grades (I-V). All patients included in our study were interviewed in person or via phone for information regarding COVID-19 vaccination and MG symptoms after the vaccination.

Descriptive statistical analyses were performed to reveal qualitative data using percentages, frequencies and mean and standard deviations for quantitative data in a normal distribution. Median and IQR were utilized for quantitative data that were not in a normal distribution. Inferential analyses were applied to evaluate the prevalence of MG exacer bation after COVID-19 vaccinations. For the secondary outcome, Chi-square or Fisher's exact test was used for nominal scales such as gender. An independent t-test or Mann-Whitney-U test was applied for continuous data. P-value <0.05 was considered statistically significant.

Patient Consent and Protocol Approvals

All patients included in our study were informed consent via mobile phone or face-to-face before the interview session for information about COVID-19 vaccination and MG symptoms after getting the vaccination. The study was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (Si402/2023).

Results

A total of 209 patients met the inclusion criteria, and the total number of events of COVID-19 vaccination received by 209 MG patients were 633 events. Fifty-four patients were male (25.8%), the mean BMI (SD) was 24.1(4.6), the mean age (SD) was 55.4(14.9) years, the mean age onset was 42.65(15.9) years, the median time (IQR) of follow up was 11(5,17.5) years, the median time (IQR) of follow up to worst MGFA was 18 (7.75,60) months. Medical comorbidities are shown in Table 1. MGFA at onset, worst MGFA, and MGFA baseline each year are shown in Table 1.

Ninety-one patients (43.5%) were Acetylcholine receptor antibody positive, seven patients (3.3%)

were anti muscle-specific tyrosine kinase antibody positive, twenty-three patients (11%) were serological negative, and the rest of the patients did not have the serological testing. One hundred and twenty-eight patients (61.2%) underwent thymectomy; thirty-three of them had thymic hyperplasia, thirty-nine patients had thymic involution, thirty-nine patients had thymoma, six patients had thymic carcinoma, and eleven patients the thymic pathology was not noted. The mean prednisolone dosage for 2020 to 2023 is shown in Table 1. One hundred and sixteen patients were taking oral immunosuppressive drugs, including 99 patients on azathioprine, seven on mycophenolate mofetil, and ten on other immunomo dulating agents such as rituximab. The baseline demographic and clinical characteristics of included patients are summarized in Table 1.

Table 1: Baseline characteristics of patients in this study.

Characteristics	Total (N=209)
Gender, n (%)	
Male	54 (25.8)
Female	155 (74.2)
Age, year, mean (SD)	55.4 (14.9)
BMI, kg/m2, mean (SD)	24.1 (4.6)
Onset age, year, mean (SD)	42.7 (15.9)
Comorbidity, n (%)	
Type 2 diabetes mellitus	51 (24.4)
Essential hypertension	83 (39.7)
Dyslipidemia	93 (44.5)
Cerebrovascular disease	19 (9.1)
Cardiovascular disease	13 (6.2)
Chronic kidney disease	8 (3.8)
Obesity	111 (53.1)
Malignancy at any organ	18 (8.6)
Other	102 (48.8)
MGFA at onset, n (%)	
MGFA1	74 (35.4)
MGFA2	99 (47.3)
MGFA3	20 (9.6)
MGFA4	4 (2)
MGFA5	12 (5.7)
Duration of follow up, year, median (IQR)	11 (5,17.5)
Duration of follow up to worst MGFA, months, median (IQR)	18 (7.75,60)
Serological status, n (%)	
Anti-Ach receptor	91 (43.5)
Anti-MusK	7 (3.3)
Seronegative	23 (11)
Not test	88 (42.1)
Thymectomy, n (%)	
Yes	128 (61.2)
No	81 (38.8)

Table 1: Baseline characteristics of patients in this study.

Characteristics	Total (N=209)
Thymus histopathology, n (%)	33 (15.8)
Hyperplasia	39 (18.7)
Involution	39 (18.7)
Thymoma	6 (2.9)
Carcinoma	11 (5.3)
No data	
Radiation, n (%)	23 (11)
Yes	186 (89)
No	
Prednisolone dosage, mg/d, mean (SD)	4.6 (5.4)
Prednisolone dosage in 2020	4.7 (5.3)
Prednisolone dosage in 2021	4.8 (4.8)
Prednisolone dosage in 2022	5 (5.2)
Prednisolone dosage in 2023	
Immunosuppressive drug, n (%)	99 (47.4)
Azathioprine	7 (3.3)
Mycophenolate mofetil	10 (4.8)
Others	93 (44.5)
None	
MG exacerbation, n (%)	3 (1.4)
Yes	0 (98.6)
No	
MGFA at exacerbation, n (%)	1 (33.3)
MGFA1	0
MGFA2	0
MGFA3	0
MGFA4	2 (66.7)
MGFA5	6.7 (7.6)
Prednisolone dosage at exacerbation, mg/d, mean(SD)	
Severity of exacerbation, n (%)	1 (0.5)
Worsening MG	1 (0.5)
Impending MG crisis	1 (0.5)
MG crisis	
Other precipitating factor, n (%)	2 (1)
Infection	0
Drugs	0
Surgery	0
Trauma	0
Others	1 (0.5)
None	

All patients included in our study received various vaccine regimens, varying from one to six doses

of vaccines and from one to multiple types of vaccines (Figure1). The vaccination information was gathered from a vaccine passport of each patient who received vaccine at the government healthcare service outside Siriraj hospital, and from the medical record of Siriraj in patients who received vaccine at Siriraj hospital. The prevalence of MG exacerbation after vaccination was found in 3 of 633 vaccine events (0.47%) from three different patients. MG exacerbation was documented by history and physical examination by neurologists in the MG clinic. The exacerbation was within the postulated risk period of 6 weeks from each vaccine administration (patients No.1-3 in Table 2). Two of three got exacerbation after the second dose of vaccine (patients no.1 and no.2) and one had exacerbation after the first dose of vaccine (patient no.3). All events occurred within 14 days after vaccination. Three events of MG exacerbation happened after mRNA, inactivated virus, and virus vector vaccination in Patients No.1,2,3, respectively. Patients no.1 and no.2 required hospitalization after an exacerbation, and patient no.3 needed to adjust the immunosuppressive drug to relieve symptoms without hospitalization.

For the secondary outcome of the study, the factors associated with MG exacerbation after COVID vaccination from univariate analysis of patients with thymic carcinoma and patients with higher prednisolone dosage as shown in Table 3.

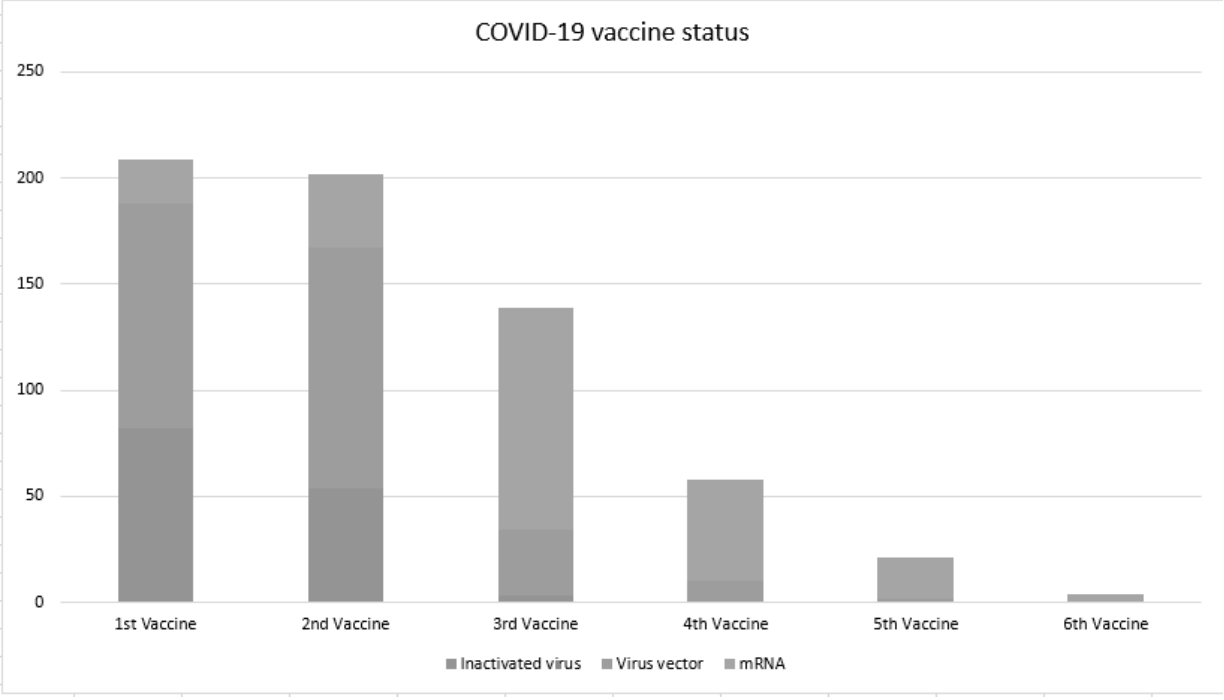

Figure 1 : COVID-19 vaccine status.

Table 2: Characteristics of the cases with MG exacerbation.

Pt	Sex	Age	BMI	Comorbidity	Age onset (Years)	MGFA at onset	Worst MGFA	Duration of follow up (months)	Duration from follow up to worst MGFA (years)	Serology	Thymectomy
1	M	44	18.9	Others	21	1	5	23	48	Anti-Ach	Yes
2	M	41	18.7	Others	33	1	5	8	60	Anti-MusK	No
3	F	59	24.7	Essential hypertension, Dyslipidemia	45	5	5	14	At onset	Seronegative	Yes

PtP	Thymic pathology	Radiation	MGFA during follow up	Mean prednisolone dosage (mg/d)	IS	Vaccine dose before exacerbation	MGFA at exacerbation	Vaccine type	Days from vaccine (ds)	Prednisolone dosage at exacerbation , mg/d	Symptom severity	Other precipitating factor
1	Thymic carcinoma	No	2020 : 1 2021 : 5 2022 : 1 2023 : 1	2020 : 5.5 2021 : 17 2022 : 16.4 2023 : 8.8	AZA	2nd dose	5	mRNA	3	15	MG crisis	Infection
2	-	No	2020 : 1 2021 : 2 2022 : 1 2023 : 1	2020 : 4.9 2021 : 13.5 2022 : 13.8 2023 : 8.6	AZA	2nd dose	5	Inactivated virus	10	5	MG crisis	Infection
3	Thymic carcinoma	Yes	2020 : 1 2021 : 1 2022 : 1 2023 : 1	2020 : 0 2021 : 0 2022 : 6.9 2023 : 4.4	None	1st dose	3	Virus vector	13	0	Worsening MG	None

Table 3: Comparison of multiple factors between exacerbation and non-exacerbation groups.

Characteristics	No exacerbation (N=206)	Exacerbation (N=3)	P-value (95% CI)
Gender, n (%)	52/54 (96.3)	2/54 (3.7)	
Male	154/155 (99.4)	1/155 (0.6)	0.164
Female	55.5 (14.9)	48 (9.6)	0.388
Age, year, mean (SD)	24.1 (4.6)	21.8 (3.7)	0.393
BMI, kg/m2, mean (SD)	42.8 (16)	33 (12)	0.292
Onset age, year, mean (SD)			
Comorbidity, n (%)	51 (100)	0	1
Type 2 diabetes mellitus	82/83 (98.8)	1 (1.2)	1
Essential hypertension	92/93 (98.9)	1 (1.1)	1
Dyslipidemia	19 (100)	0	1
Cerebrovascular disease	13 (100)	0	1
Cardiovascular disease	8 (100)	0	1
Chronic kidney disease	110/111 (99.1)	1/111 (0.9)	0.601
Obesity	18 (100)	0	1
Malignancy at any organ	100/102 (98)	2/102 (2)	0.614
Other			
MGFA at onset, n (%)	72/74 (97.3)	2/74 (2.7)	0.286
MGFA1	99 (100)	0	1
MGFA2	20 (100)	0	1
MGFA3	4 (100)	0	1
MGFA4	11/12 (91.7)	1/12 (8.3)	0.163
MGFA5			
Worst MGFA during follow up, n (%)	43 (100)	0	1
MGFA1	101 (100)	0	1
MGFA2	21 (100)	0	1
MGFA3	5 (100)	0	1
MGFA4	36/39 (92.3)	3/39 (7.7)	0.006(0.989-1.186)
MGFA5	11 (5,17)	14 (8,23)	0.447
Duration of follow up, year, median (IQR)			
Duration of follow up to worst MGFA, year, median (IQR)	12 (7.5,60)	60 (48,72)	0.197
Serological status, n (%)			
Anti-Ach receptor			
Anti-MusK	90/91 (98.9)	1/91 (1.1)	1
Seronegative	6/7 (85.7)	1/7 (14.3)	0.098
Not test	22/23 (95.7)	1/23 (4.3)	0.296
	88 (100)	0	0.265
Thymectomy, n (%)			
Yes			
No	126/128 (98.4)	2/128 (1.6)	1
	80/81 (98.8)	1/81 (1.2)	1

Table 3: Comparison of multiple factors between exacerbation and non-exacerbation groups.

Characteristics	No exacerbation (N=206)	Exacerbation (N=3)	P-value (95% CI)
Thymus histopathology, n (%)			
Hyperplasia	33 (100)	0	1
Involution	39 (100)	0	1
Thymoma	39 (100)	0	1
Carcinoma	4/6 (68.7)	2/6 (33.3)	**0.002(0.02-0.14)**
No data	11 (100)	0	1
Radiation, n (%)			
Yes	22/23 (95.7)	1/23 (4.3)	
No	184/186 (98.9)	2/186 (1.1)	0.296
Prednisolone dosage, mg/d, mean(SD)			
Prednisolone dosage in 2020	4.6 (5.5)	3.5 (3)	0.728
Prednisolone dosage in 2021	4.6 (5.3)	10.2 (9)	0.072
Prednisolone dosage in 2022	4.7 (4.7)	12.4 (4.9)	**0.006(-13.08,-2.28)**
Prednisolone dosage in 2023	4.9 (5.2)	7.3 (2.5)	0.438
Immunosuppressive drug, n (%)			
Azathioprine	97/99 (98)	2/99 (2)	0.604
Mycophenolate mofetil	7 (100)	0	1
Others	10 (100)	0	1
Other precipitating factor, n (%)			
Infection	0	2 (100)	**<0.001(0.001-0.34)**
Drug	0	0	-
Surgery	0	0	-
Trauma	0	0	-
Others	0	0	-
None	0	1 (100)	0.014(0.002-0.038)

Discussion

After the COVID-19 vaccine was introduced, reports about adverse events, especially neurological symptoms, raised concern in neurological patients. Individuals with pre-existing health conditions such as MG who were on immunosuppressive agents were potentially at higher risk for developing severe forms of infection requiring hospitalization and may lead to unfavorable outcomes[4-10].

There were only a few studies regarding the prevalence of neurological adverse events after COVID-19 vaccination in MG patients. One prior study found that as high as approximately 5% of all MG patients experienced worsening MG after COVID-19 vaccination[3]. In this study, we aimed to look for the prevalence of MG exacerbation after COVID-19 vaccination and risk factors associated with COVID-19 vaccination in a single medical center. From our study, there were only 3 MG exacerbation events out of 633 vaccination events that comprised only 0.47%, which was not a high prevalence. Two of three cases had MG exacerbation after the second dose of the vaccine, similar to the large cohort study of Sansone et al[2] and Patone et al.[8], in which most of the events

occurred after the second dose of the vaccine. When looking into the clinical characteristics between non-exacerbated and exacerbated groups, this study found that patients using higher doses of prednisolone and patients with confirmed thymic carcinoma had higher tendencies to get MG exacerbation after COVID-19 vaccination. This may be explained by poor disease control and higher severity of disease in patients with thymic carcinoma; these findings correlate with a study by Kato et al.[11] that found a high-grade thymoma was an independent risk factor of MG exacerbation after surgery. The strength of our study was the opportunity to study the prevalence of MG exacerbation after the various types of COVID-19 vaccination, given the fact that in Thailand, there were many types of COVID-19 vaccine. The other strength was that in our study, we personally interviewed each patient for the type of COVID-19 vaccination and symptoms of MG after the COVID-19 exacerbation. However, the main limitation of our study was the small number of patients, which limited the analysis of clinical risk factors for MG exacerbation after the COVID-19 vaccination.

Conclusion

Our study's results were correlated with previous studies that the prevalence of MG exacerbation after COVID-19 vaccination was low, although the drawback of our study was the small population, which has limitations on the analysis for clinical risk factors for MG exacerbation after COVID-19 vaccination. From the results of our study, given the low prevalence of MG exacerbation, the benefits of COVID-19 vaccination appeared to outweigh the risks, and MG patients should be encouraged to have COVID-19 vaccination with only minor concerns for exacerbation.

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Effect of Prior Statin Therapy on Outcomes in Large and Medium Vessel Occlusion Stroke with Endovascular Thrombectomy

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ABSTRACT

Introduction: The influence of prior statin therapy uses on the outcomes of patients with acute ischemic stroke treated with endovascular therapy is unclear. We compared procedural and clinical outcomes of endovascular therapy in patients on statin therapy or not before stroke onset.

Objectives: To assess effect of prior statin therapy on outcome in large and medium vessel occlusion stroke with endovascular thrombectomy

Methods: A retrospective observational study of 168 patients diagnosed with acute ischemic stroke within 7 days and received endovascular therapy with or without intravenous thrombolysis was conducted in Ramathibodi hospital between January 1, 2013 and December 31, 2022. Baseline characteristics, comorbidities, clinical and radiographic features, treatment were collected. Patients were divided into three groups according to statin therapy status category as patients without prior statin (no statin), patients with prior high intensity statin therapy (HIS) and patients with prior low or moderate intensity statin therapy (LIS). Multilevel mixed-effects logistic models including center as random effect were used to compare angiographic (rates of reperfusion at the end of procedure, procedural complications) and clinical outcomes according to statin subgroups. Comparisons were adjusted for prespecified confounders (age, admission National Institutes of Health Stroke Scale score, Alberta Stroke Program Early CT Score, intravenous thrombolysis, and time from onset to puncture), as well as for meaningful baseline between-group differences.

Results: A total of 168 patients were analyzed, of whom 97 patients (58%) had never taken any

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statin, 25 patients (15%) were on HIS and 46 patients (27%) were on LIS. No significant difference in recanalization rates, number of passes and periprocedural complication was found between patients with high intensity statin and without statin. Patients without statin therapy, HIS and LIS had similar discharge mRS and 90 days mRS, parenchymal hematoma. Symptomatic ICH is significantly higher in the high intensity statin group, compared with no statin group [OR 1.725 (95% CI, 3.5-11);P value = 0.003].

Conclusion: This study demonstrates the neutral effect of statin treatment with angiographic outcomes and clinical outcomes in acute ischemic stroke patient undergoing endovascular thrombectomy with or without intravenous thrombolysis.

Keyword: Stroke, Statin, Large vessel occlusion, Endovascular thrombectomy

Introduction

Acute ischemic stroke is a neurological emergency. Focal neurological disorders are observed immediately and last for up to 24 hours[1]. Statistically, stroke is the 4th leading cause of death and disability in the United States[2]. In Thailand, stroke is the leading cause of death and second most common cause of disability and disability[3,4].

Endovascular treatment alone or in combination with intravenous thrombolysis is the most effective treatment in treating acute ischemic stroke caused by large vessel occlusion in anterior circulation[5]. Successful recanalization in a timely manner is the most important factor that affects functional outcomes. However, more than a third of patients undergo successful recanalization unable to return to functional independent[6]. Stent retriever is widely used in the treatment of arterial catheter, which the stent is expanded to extract blood clots. This results in arterial intimal injury caused by friction between the inner artery wall and the stents[7]. Studies in patients and laboratory animals was found that the inner vessel wall was injured after treatment through an artery catheter with stent retriever resulting in vasospasm, intimal denudation, intimal hyperplasia, medial thickening and inflammatory reaction[8, 9].

High intensity statin is one of the most effective treatments for good prognosis in patients with ischemic stroke[10]. In addition to the LDL-reducing effect, statins also result in improve endothelial function, Increase the durability of atherosclerotic plaque, reduce inflammation and inhibit clotting of blood[11]. Animal studies have shown that statins contribute to the prevention of vascular injury in endovascular thrombectomy procedures[12]. According to a study conducted by Seblani et al in patients who received statins prior to the procedure, showed that among those who received statins, there was higher in 30 days survival rate than the non-statin group[13].

However, studies on the effects of statins on the outcomes of endovascular thrombectomy treatment are still sparse, both abroad and especially in Thailand. The procedure is not yet widely popular, and past studies have had limitations, such as no angiographic outcome studies, Intensity type of statin and fasting LDL level, this makes such studies limited. Therefore, we are interested in studying the relationship of statin therapy with the outcomes of endovascular thrombectomy, so that the results of the research suggest the importance of statins. To reduce disability and death of acute ischemic stroke patients caused by large vessel occlusion.

Objective

To assess effect of prior statin therapy on outcome in large and medium vessel occlusion stroke with endovascular thrombectomy

Methods

Study Population

We compile a list of hospital numbers and data of patients diagnosed with acute cerebral ischemia from large vessel occlusion and treatment with endovascular thrombectomy from Ramathibodi Stroke registry from 1 January 2013 to 31 December 2022. We include patients whose duration from the onset of abnormal symptoms to hospital arrival occurs within 24 hours, aged over 15 years, detects a medium or large vessel occlusion and is treated through endovascular thrombectomy within a 24-hour period. After the onset of symptoms, patients treated with High intensity statin or low to moderate intensity for 3 months will be identified as a statin group. Exclusion criteria were the following: patients younger than 15 years of age, patients treated with Carotid endarterectomy or Carotid artery stenting within 24 hours of symptom onset, patients with a previous history of large vessel chronic occlusion, undefined statin therapy status and unknown initial and final modified Thrombolysis in Cerebral Infarction (mTICI).

Data recorded

The following variables were recorded: baseline characteristics such as age and sex, baseline mRS, cardiovascular risk factors (diabetes, hypertension, smoking, dyslipidemia), medical history (prior ischemic heart disease and atrial fibrillation), use of APT at the time of stroke onset, stroke severity assessed by the National Institutes of Health Stroke Scale score before EVT, arterial systolic and diastolic pressure, Trial of ORG 10172 in Acute Stroke Treatment etiologic classification of ischemic stroke, Alberta Stroke Program Early CT Score, occlusion site (divided into 5 groups: internal carotid artery, M1 and M2 portion of the middle cerebral artery, basilar artery and vertebral artery occlusion), as well as times from symptom onset to groin puncture and from symptom onset to revascularization. The full stroke diagnosis workup was up to the decision of the clinician included an ECG, a 48-hour cardiac rhythm recording in the acute stroke unit and a standard biological evaluation. All patients underwent non-contrast CT scan brain imaging within 24 hours post-treatment; additional non-contrast CT scan imaging could be performed at any time in case of neurological deterioration. Intracranial hemorrhages (ICHs) on post-treatment imaging were also studied. mTICI at the end of the procedure, the number of passes, and procedural complications were also recorded. Radiographic outcome measures were adjudicated by individual site investigators.

Outcomes

The primary study outcome was the percentage of patients who achieved a favorable after discharge outcome, defined as an mRS score of 0 to 2. Secondary outcomes included clinical outcomes (excellent 90-day outcome defined as an mRS score of 0–1, mRS score of 0-2, the degree of disability assessed by the overall distribution of 90-day mRS, any hemorrhagic complications, parenchymal hematoma, sICH and procedural outcomes [reperfusion rates at the end of endovascular procedure: successful reperfusion (mTICI

score 2b), complete reperfusion (mTICI score 3)], >1 passes, procedural complications [defined as arterial perforation, arterial dissection, embolization in a new territory, and subarachnoid hemorrhage]

Statistical analysis

Quantitative variables are expressed as mean (SD) in case of normal distribution or median (interquartile range) otherwise. Categorical variables are expressed as numbers (percentage). Patients were divided into 3 groups according to their medication (no statin, high intensity statin and low to moderate intensity statin groups) before EVT. Baseline characteristics were compared between the no statin and HIS study groups, as well as between the no statin and LIS study groups using the Student t test for gaussian continuous variables, the Mann-Whitney U test for nongaussian continuous variables, or the χ_2 test (or Fisher exact test when the expected cell frequency was <5) for categorical variables, as appropriate. Between-group imbalances in baseline characteristics were also assessed by calculating absolute standardized differences. Comparison in binary outcomes between groups was made using multilevel mixed-effects logistic models by including center as random effect, and odds ratios were calculated.

Results

Of the 258 patients analyzed, 45 were excluded because they did not have previous drug acquisition data, and 26 were excluded because they were not treated with the mechanical thrombectomy (only angiography) and 19 were excluded because there were no angiographic outcomes (Figure 1). A total of 168 patients were analyzed, of whom 25 (15%) were on high intensity statin (HIS) and 46 (27%) were on low to moderate intensity statin (LIS). Patients on HIS were male predominance, were more likely to have hypertension, hypercholesterolemia, diabetes, a history of ischemic stroke, ischemic heart disease, malignancy, antiplatelet treatment, lower mean NIHSS and less stent retriever in endovascular therapy (Table 1). Both populations showed differences in the location of occlusions while there were no differences in thrombectomy time metrics and stroke mechanisms.

Table 1 Baseline characteristics

Demographics	No Statin (n=97)	HIS (n=25)	LIS (n=46)	Total (n=168)	*P*-value
Age, y; mean (SD)	65.95	68.56	74.96	69.07	0.657
Female	50 (51%)	8 (32%)	30 (65%)	88	0.027*
Male	47 (48%)	17 (68%)	16 (35%)	80	
Hypertension	50 (51%)	20 (80%)	40 (87%)	110	0.000*
Hypercholesterolemia	23 (24%)	15 (60%)	40 (87%)	78	0.000*
Smoking	21 (22%)	2 (8%)	3 (6.6%)	26	0.002*
Diabetes	16 (16%)	15 (60%)	14 (30%)	45	0.000*
Ischemic heart disease	8 (8%)	8 (32%)	4 (8.7%)	20	0.003*
Prior stroke	5 (5%)	9 (36%)	14 (30%)	24	0.000*
Atrial fibrillation	37 (38%)	12 (48%)	26 (56%)	75	0.111
Malignancy	13 (13%)	22 (88%)	41 (89%)	76	0.910

Demographics	No Statin (n=97)	HIS (n=25)	LIS (n=46)	Total (n=168)	*P*-value
Antiplatelets	12 (12%)	13 (52%)	19 (41%)	34	0.000*
Oral anticoagulants	5 (5%)	2 (8%)	2 (4.3%)	9	0.073
Fibrate	2 (2%)	2 (8%)	0 (0%)	4	0.102
Ezetimibe	2 (2%)	1 (4%)	2 (4.3%)	5	0.715
Baseline mRS					
0	90 (92%)	20 (80%)	39 (85%)	149	
1	5 (5%)	5 (20%)	3 (6.5%)	13	
2	0 (0%)	0 (0%)	3 (6.5%)	3	0.048*
4	1 (1%)	0 (0%)	1 (2.2%)	2	
5	1 (1%)	0 (0%)	0 (0%)	1	
Initial systolic BP,mean (SD)	152.64	155.39	153.89	146.74	0.309
Initial diastolic BP,mean (SD)	83.36	85.46	83.46	80.38	0.564
Glycemia, mean (SD)	135.32	167.63	134.89	132.11	0.076
Hemoglobin A1c	5.78	6.73	6.01	5.83	0.180
LDL level (mean)	123.33	82.54	94.41	106.84	0.393
NIHSS (mean)	15	13.32	17.98	15.51	0.024*
ASPECTS (mean)	7.99	8.48	8.39	8.16	0.876
Collateral score	3.92	3.76	4.09	3.92	0.334
Cardioembolic, etiology (yes), n(%)	52 (53%)	15 (60%)	34 (74%)	101	0.068
Occlusion site					
Right MCA					
M1	30 (31%)	8 (32%)	14 (30%)	52	0.990
M2	12 (12%)	0 (0%)	2 (4%)	14	0.071
Left MCA					
M1	25 (26%)	9 (36%)	13 (28%)	47	0.596
M2	7 (7%)	1 (4%)	8 (17%)	16	0.091
Right ICA	8 (8%)	3 (12%)	9 (19.5%)	20	0.149
Left ICA	16 (16%)	3 (12%)	2 (4.3%)	21	0.121
Basilar artery	7 (7%)	2 (8%)	3 (6.5%)	12	0.973
Right VA	0 (0%)	0 (0%)	0	0	0
Left VA	1 (1%)	0 (0%)	0	1	0.699
Procedural data					
Thrombolytic agents	37 (38%)	7 (28%)	17 (37%)	61	0.639
General anesthesia	62 (64%)	14 (56%)	20 (43%)	96	0.048*
First line thrombectomy strategy					
Stent retriever	49 (51%)	7 (28%)	30 (65%)	86	0.011*
Aspiration	59 (61%)	20 (80%)	26 (56%)	105	0.299
Stent retriever and aspiration	11 (11%)	0 (0)	2 (4.3%)	13	0.100

Demographics	No Statin (n=97)	HIS (n=25)	LIS (n=46)	Total (n=168)	*P*-value
Other	13 (13%)	2 (8%)	2 (4.3%)	17	0.228
Stenting					
No stenting	93 (96%)	25 (100%)	43	43	0.422
Cervical	1 (1%)	0 (0%)	2	2	0.288
Intracranial	2 (2.1%)	0 (0%)	1	1	0.765
Time from onset to puncture, min, median (IQR)	504.44	416.52	429.73	469.43	0.358
Time from puncture to recanalization, min, median (IQR)	56.12	44.5	53.62	53.39	0.064
Time from onset to recanalization, min, median (IQR)	574.41	452.54	480.52	526.42	0.140

HIS indicates High intensity statin; LIS indicated Low to moderate intensity statin; ASPECT, Alberta Stroke Program Early CT Score; BP, blood pressure; ICA, intracranial carotid artery; IQR, interquartile range; M1, M1 segment of the middle cerebral artery; M2, M2 segment of the middle cerebral artery; VA, vertebral artery

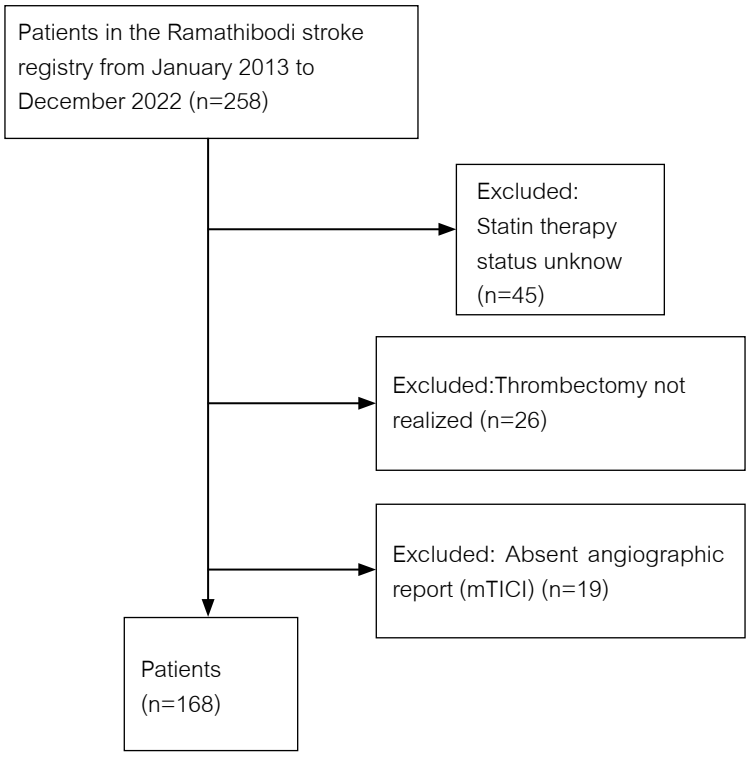

Figure 1 Flow chart

Angiographic Outcomes

As shown in Table 2, on multivariate analysis no significant difference in recanalization rates, number of passes and periprocedural complication was found between patients with high intensity statin and without statin. No difference in reperfusion rates was observed in the Endovascular treatment group. Prior statin therapy was not associated with complete recanalization.

Table 2 Comparison of outcome between patients treated with no statin and high intensity statin

	No Statin (n=97)	HIS (n=25)	OR (95% CI)	*P*-value	OR (95% CI) after adjustment†	*P*-value
Angiographic outcomes						
First-pass recanalization	17 (18%)	11 (44%)	3.395	0.005*	0.500	0.125
mTICI score 0	15 (15%)	1 (4%)	0.241	0.141	0.887	0.466
mTICI score 1	2 (2%)	0	0.980	0.474	0.955	0.404
mTICI score 2a	10 (10%)	0	0.919	0.141	0.889	0.725
mTICI score 2b	35 (36%)	6 (24%)	0.665	0.389	0.750	0.386
mTICI score 3	37 (38%)	17 (68%)	3.334	0.007*	0.500	0.083
Total pass >1	50 (51%)	13 (52%)	1.013	0.976	0.750	0.386
Complication	13 (13%)	3 (12%)	0.777	0.747	0.333	0.248
Clinical outcomes						
END	20 (21%)	6 (24%)	1.202	0.718	0.778	0.598
PH	25 (26%)	7 (28%)	0.950	0.914	0.667	0.386
	No Statin (n=97)	HIS (n=25)	OR (95% CI)	*P*-value	OR (95% CI) after adjustment†	*P*-value
sICH	3 (3%)	2 (8%)	1.752	0.496	1.752	0.003*
mRS score after discharge						
score 0-2	23 (24%)	5 (20%)	0.992	0.988	0.556	0.083
score 3-5	48 (49%)	10 (40%)	0.575	0.205	0.778	0.386
score 6	11 (11%)	1 (4%)	0.346	0.294	0.833	0.157
mRS score after 90 days						
score 0-2	39 (40%)	12 (48%)	1.561	0.304	0.333	0.248
score 3-5	31 (32%)	8 (32%)	0.869	0.761	0.500	0.386
score 6	9 (9%)	1 (4%)	0.399	0.37	0.800	0.524

END ,early neurological deterioration;

†Calculated using the no antithrombotic group as reference after adjustment for center, age, hypertension, hypercholesterolemia, diabetes, previous stroke, ischemic heart disease, glycemia, admission NIHSS score, admission ASPECT score, intravenous thrombolysis, stroke etiology, time from symptom onset to puncture

Clinical Outcomes

On fully adjusted shift analysis and multivariate analysis of binary outcome variables after imputation, patients without statin therapy, HIS and LIS had similar discharge mRS and 90 days mRS, parenchymal hematoma (Table 2). Symptomatic ICH occurred significantly more in the high intensity statin group than in the no statin group [OR 1.725 (95% CI, 3.5-11);P value = 0.003].

Discussion

This retrospective cohort study assessing the effect of prior statin treatment with endovascular thrombectomy. Emphasized 3 main results: (1) there are major baseline differences in the population of patients with prior statin therapy versus no prior statin therapy, (2) after adjusting for those differences, the apparent difference in rates of recanalization, and 30-day functional outcomes becomes nonsignificant and (3) Symptomatic ICH occurred significantly more in the high intensity statin group than in the no statin group.

Previous studies demonstrated the effectiveness of statins on functional outcomes and reduced ICH incidence after catheterization. the study had a large number of people participating in the study. This makes the effect of treatment clearly visible[13].

The limitations of this study are multifactorial. (1) There were fewer people in the statin group who did not see the clear results of this study. (2). There was a clear confounding factor in the statin population, such as DM and HT hypercholesterolemia, than in the population who did not receive statins and (3) We cannot concluded that statin exposure causes symptomatic ICH because the event is low and the population is small. However, univariated analysis showed tha High intensity statin has an effect on first pass effect and good angiographic outcome.

Conclusion

In conclusion, this study demonstrates the neutral effect of statin treatment with angiographic outcomes and clinical outcomes with endovascular thrombectomy. Due to such limitation, future studies on the effects of statins and vascular catheterization should have a larger population or have randomized controlled trials.

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A Man with Worsening Legs Instability

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A 40-year-old Thai man residing in Nakhon Ratchasima Province, Thailand.
Occupation: general employee

Chief Complaint

Worsening legs instability for 2 months

History of Present Illness

5 months ago: He began to experience gradually onset of muscle instability in both legs. He reported that he had a limp along with difficulty with balance. The severity of the instability in both legs was symmetrical without abnormal sensation and pain in any muscles. Difficulty in balance, constant during the day and night. He is still able to do his normal daily activities. He denied fever, headache, dizziness and visual disturbance. Urinary and bowel functions were normal.

2 months ago: His difficulty with balance has worsened, affecting his mobility. He has never had muscle aches and both arms can function normally. He denied dysphagia, diplopia, dyspnea and aspiration symptoms.

Past and Personal History

- Occasional smoking and drinking
- Refused to use vasoconstrictive drugs compound

Family History

- No reported history of muscle weakness or stroke-like symptoms in any family members

Physical Examinations

General appearances: A Thai aged man, normosthenic build, alert and active

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Vital signs: BT 36 C, HR 70 bpm, RR20 tpm, BP104/72 mmHg

HEENT: pink conjunctivae, anicteric sclerae, no parotid and thyroid gland enlargement, no carotid bruit

Heart and lungs : unremarkable

Abdomen: soft, not tender, no hepatosplenomegaly

Extremities: pruritic papular eruption on both legs, no edema, radial and pedal pulses are symmetric

DRE: normal sphincter tone

Neurological examinations

Consciousness: Alert and active, follows commands, oriented to time, place, and person

Cranial nerves:

CN I: equally sense of smell, **CN II**: pupil 2mm RTLBE, pupil direct and consensual light reflex were normal with negative RAPD, no visual field defect, **CN III, IV, VI**: extraocular muscle movements were intact, **CN V**: normal facial sensation, intact corneal reflex, normal mastication muscles, **CN VII**: no facial palsy, **CN VIII**: intact, **CN IX, X**: equally palatal movement, positive gag reflex, centrally positioned uvula, **CN XI**: head turning and shoulder shrugging were intact, **CN XII**: normal tongue movement, no tongue atrophy

Motor: mild atrophy both legs without spasticity, normal muscle tone, motor power grade V in upper extremities and grade IV+ both proximal and distal parts in lower extremities

Sensory: intact pinprick, fine touch and proprioception

DTR: 2+ for all extremities

Cerebellar signs: spontaneous horizontal nystagmus with increased amplitude while moving EOM in both eyes, minimally bilateral impaired FTNF test, dysdiadokokinesia, impaired Tandem gait and HTK test, No truncal ataxia, No slurred speech

Babinski and clonus: negative

Meningeal signs: no stiffness in the neck

Cortical signs: normal motor speech, comprehension and repetition, no hemineglect

Problem lists

1. Progressive paraparesis without bowel and bladder involvement
2. Bilateral cerebellar hemispheric dysfunction
3. Suspected HIV infection

Discussion

A young male patient presented with gradually onset progressive leg weakness accompanied by an unsteady gait. Upon examination, decreased motor power in the legs was observed equally, without sensory and bulbar involvements. Characteristics of weakness are a loss of muscle coordination rather than a loss of power to exert effort. The anatomical lesion is likely to be in cerebellar regions or its connections. And the pathology of the disease is likely to be a diffuse inflammatory process rather than a mass-like because the lesions appear to recur with the duration of the disease progression. Important objective evidence that allows the neurological lesion to be considered further is the detection of a pruritic papular eruption rash on both legs that the patient was not concerned. The appearance of the rash suggests that the patient may be immunocompromised. The mechanism behind the progressive paraparesis is most likely secondary to an opportunistic CNS infection. The possible differential diagnosis includes JC virus infection, herpes viral encephalitis, toxoplasmic

encephalitis, neurosyphilis, primary CNS lymphoma, and autoimmune encephalitis.

Investigations

Complete blood count: Hb 13.2 g/dL Hct 40.1% WBC 3600 10*3/uL (N48% L38%) Plt 264 10*3/uL

Syphilis test: RPR non-reactive, **HIV antibody: Reactive****

Liver function test: TP 8.5 g/dL, Glo 4.2 g/dL, Alb4.3 g/dL, TB 0.6 mg/dL, DB 0.3 mg/dL, AST 53 U/L, ALT 60 U/L, ALP 71 U/L

Electrolyte: Na 137.2 mmol/L, K4.34 mmol/L, Cl 104 mmol/L, HCO3 22 mmol/L

Creatinine 1.03 mg/dL, eGFR 90.4 ml/min/ 1.73m^2

Thyroid function test: FT3 1.77 pg/mL, FT4 0.86 ng/dL, TSH 1.013 mIU/L

HBs Ag, Anti-HBs, Anti-HCV: non reactive

CSF profile: opened pressure 12 cmH_2O, Closed pressure 11 cmH2O, Colorless and clear, pH 8.0, Specific Gravity 1.005, RBC 0 cell/uL, WBC 7 cell/uL, (L 99%, N1 %), protein 58.2 mg/dL, sugar ratio 60%, Gram, AFB and India ink were negative. Culture was negative

CSF PCR for the JC virus: detectable**

CSF PCR for HSV: undetected, **CSF-VDRL**: non-reactive

EKG: normal sinus rhythm, rate 85 /min regular, no ischemic pattern, no chamber enlargement

CXR: normal cardiothoracic ratio, normal parenchymal of both lungs

MRI brain (figure 1): Asymmetric hypointense signal on T1W (upper row) and hyperintense signal on T2W and T2W/FLAIR (middle and lower rows) in bilateral cerebellar peduncles, bilateral cerebellar hemispheres and brainstem without restricted diffusion of enhancement. No evidence of vasogenic edema or pressure effect. The multiple punctate foci and patchy hyperT2W/FLAIR lesions without restricted diffusion or enhancement at both centrum semiovale and periventricular white matter (not shown)

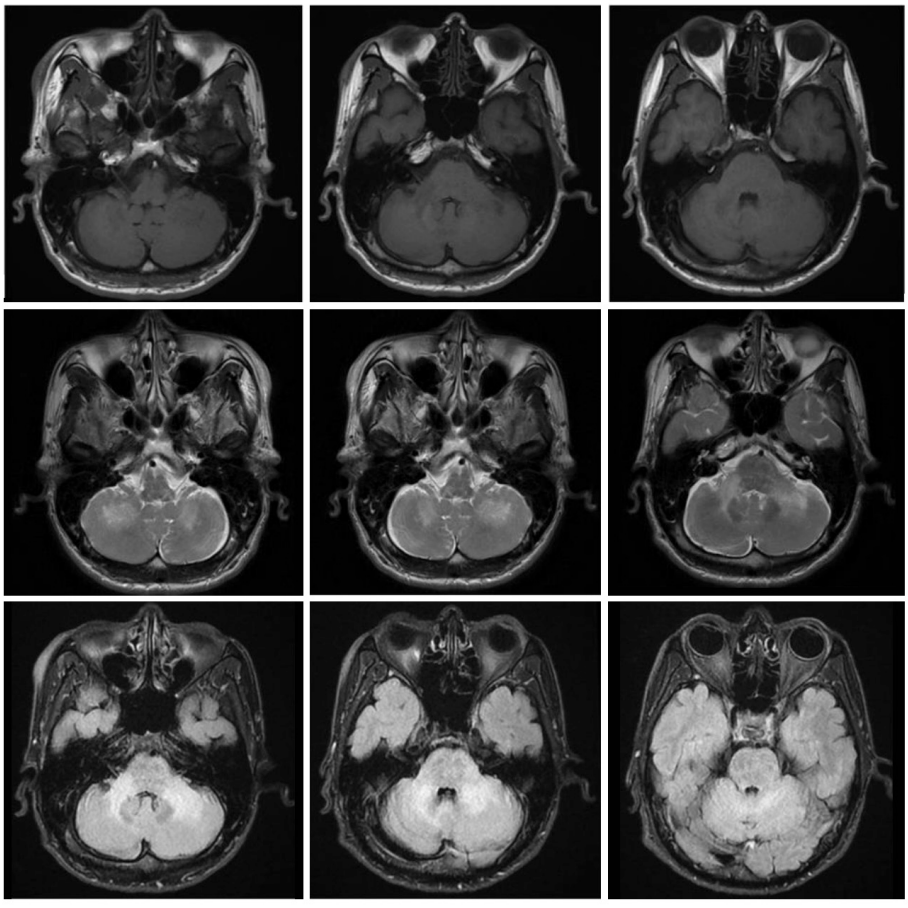

Figure 1 MRI brain (Front cover)

Diagnosis: Progressive multifocal leukoencephalopathy (PML)

Progress note: Based on the medical history, examination, and laboratory results mentioned above, it was revealed that the patient does not have any infection aside from PML. He was promptly and initially treated with Highly Active Antiretroviral Therapy (HAART). His leg weakness gradually improved to the point where he was able to resume walking. During the follow-up treatment, the patient was able to return to normal work, though he still experienced postural tremors and uncoordinated movements. He could walk, and the power of his muscles was graded as V in all extremities.

Conclusion: PML is a neurological disease caused by the JC virus infecting the brain parenchyma. Although PML is rare in general practice, its prevalence has been found to increase, especially in immunocompromised patients.

PML

PML is a rare and frequently fatal demyelinating disease of the CNS, primarily affecting individuals with compromised immune systems. It is caused by the infection of the polyomavirus JC (JCV) in oligodendrocytes.[1,2] Asymptomatic initial infection with JCV happens during childhood, and antibodies can be detected in 86% of adults. [3] In the context of significant cellular immunosuppression, JCV may undergo reactivation, potentially resulting in genomic rearrangement and the emergence of neurotropic variants capable of replicating within glial cells.[3]

This occurs despite the typical latency of the virus in the kidneys and lymphoid organs in the majority of individuals.[4] The virus can subsequently disseminate to the brain, where it initiates a lytic infection of oligodendrocytes, the cells responsible for producing myelin in the central nervous system.[3] Both the subcortical white matter and the cortex are affected by PML-associated demyelination. Infection of cortical neurons by JCV is responsible, and demyelinating lesions of PML often encompass gray matter.[5,6]

Classic PML typically presents with subacute neurological deficits, encompassing altered mental status, motor deficits such as hemiparesis or monoparesis, limb ataxia, gait ataxia, and visual symptoms like hemianopia and diplopia. It is noteworthy that PML may exhibit asymptomatic features during its initial stages.[7,8] PML typically spares the optic nerves and spinal cord. Nevertheless, there was a reported case of PML restricted solely to the spinal cord in one patient, as detected postmortem. Additionally, incidental discovery of PML lesions in the spinal cord was noted during the postmortem examination of another patient with HIV infection who succumbed to hemispheric PML.[9]

In neuroimaging studies, the typical presentation of PML includes distinct unilateral or bilateral demyelinated foci that do not adhere to cerebrovascular territories. These lesions demonstrate an absence of mass effect or contrast enhancement. Primarily, PML lesions emerge in the subcortical white matter of the parieto-occipital or frontal lobes, though the involvement of additional regions such as the corpus callosum, brainstem, pyramidal tracts, and cerebellum is also observed.[10-12] In up to 17% of cases, deep gray structures such as the basal ganglia and thalamus may be involved, although this manifestation consistently co-occurs with white matter disease.[13] Lumbar puncture coupled with polymerase chain reaction (PCR) analysis serves as the cornerstone for diagnosing PML in individuals manifesting clinical and neuroimaging findings consistent with the condition. The definitive identification of PML is achieved through the detection of JCV DNA within the cerebrospinal fluid via PCR analysis. Thus, PCR represents the optimal modality for validating the diagnosis of PML.[7]

Immune reconstitution is pivotal in managing PML, as there is currently no specific treatment available, and the condition carries a high mortality rate. Therefore, the primary therapeutic approach focuses on restoring the host's adaptive immune response, which has been shown to prolong survival. The implementation of this strategy varies depending on the clinical context:

- For patients with HIV infection: initiating or optimizing effective antiretroviral therapy (ART).
- For patients without HIV infection: withdrawal of immunosuppressive drugs, if feasible.
- For patients with natalizumab-associated PML: discontinuation of natalizumab, a medication used in multiple sclerosis treatment, and initiation of plasma exchange.

Learning point from internship:

As an intern doctor, encountering cases of progressive weakness like the one presented here reinforces the importance of a systematic approach to neurological symptoms. Firstly, it's crucial to conduct a detailed history, paying attention to the onset, progression, associated symptoms, and any underlying medical conditions such as HIV infection in this case. A thorough physical examination focusing on neurological signs, including cranial nerves,

motor, sensory, cerebellar, and reflex assessments, helps localize the lesion and guide differential diagnosis. In cases of progressive weakness, integrating clinical findings with appropriate diagnostic tests such as MRI imaging and cerebrospinal fluid analysis plays a pivotal role in narrowing down potential etiologies. This multidisciplinary approach involving neurology, infectious diseases, and radiology specialists ensures comprehensive evaluation and timely intervention. Furthermore, the experience underscores the significance of maintaining a high index of suspicion for opportunistic infections in immunocompromised patients, emphasizing the need for early initiation of specific therapies tailored to the underlying cause, as seen with the prompt administration of HAART in this instance. Ultimately, this case reinforces the internship learning experience by highlighting the intricate interplay between clinical acumen, diagnostic process, and collaborative patient management in navigating complex neurological conditions such as PML.

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Pseudodementia Revisita: Case Report and Narrative Review

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บทคัดย่อ

ในปัจจุบันที่สังคมกำลังก้าวเข้าสู่สังคมผู้สูงอายุ ภาวะรู้คิดบกพร่อง (cognitive impairment) มักพบได้บ่อยและมีการแย่ลงอย่างต่อเนื่องโดยช้าหรือเร็วขึ้นกับเหตุปัจจัยของแต่ละบุคคล ในการประเมินคนไข้ที่มีภาวะรู้คิดบกพร่องนั้นจำเป็นต้องมีการสืบค้นหาสาเหตุที่สามารถแก้ไขได้ก่อนที่จะสรุปว่าคนไข้นั้นมีสาเหตุจากโรคความเสื่อมของระบบประสาท ซึ่งภาวะซึมเศร้าหรือเดิมทีเรียกว่าภาวะสมองเสื่อมลวง (pseudodementia) ก็ถือเป็นหนึ่งในสาเหตุที่หากแก้ไขก็สามารถทำให้ภาวะรู้คิดบกพร่องกลับมาเป็นปกติได้ ในปัจจุบันเราทราบดีว่าภาวะซึมเศร้านอกจากจะเป็นหนึ่งในสาเหตุที่หากแก้ไขแล้วอาการดีขึ้น ยังอาจเป็นอาการนำอย่างหนึ่งก่อนที่จะมีภาวะสมองเสื่อมหรืออาจเป็นส่วนหนึ่งของอาการพฤติกรรมจิตประสาทของโรคสมองเสื่อม (BPSD) ก็ยังได้ เราจึงได้รายงานกรณีศึกษา เพศชายอายุ 67 ปี มาด้วยอาการภาวะรู้คิดถดถอยลงอย่างต่อเนื่องช้าๆ มา 5 ปี ผู้ป่วยได้รับการประเมินและตรวจสืบค้นต่างๆ ก่อนที่จะส่งมาปรึกษาคลินิคความจำซึ่งได้รับการวินิจฉัยในภายหลังว่าเป็นภาวะซึมเศร้า ภาวะรู้คิดถดถอยของคนไข้ดีขึ้นอย่างมากหลังจากได้รับการรักษาภาวะซึมเศร้าซึ่งเป็นตัวยืนยันที่ดีของการวินิจฉัยภาวะสมองเสื่อมลวง

คำสำคัญ : การตรวจตัวบ่งชี้ทางชีวภาพในน้ำไขสันหลัง, ภาวะซึมเศร้า, FDG เพทสแกน, ภาวะสมองเสื่อมลวง

Abstract

In the geriatric population, cognitive impairment frequently manifests with a progressive decline that varies in severity and rate, contingent upon individual etiological factors. Clinical protocols recommend identifying and addressing reversible factors contributing to cognitive decline prior to ascribing symptoms to irreversible neurodegenerative conditions. Depression, once termed pseudodementia, is recognized as a reversible contributor to cognitive

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dysfunction in older adults. Current perspectives reveal that the interplay between depression and dementia encompasses more than reversible cognitive deficits; it may precede dementia or appear as part of the behavioral and psychological symptoms of dementia. We detail the case of a 67-year-old male with a 5-year history of gradual cognitive decline. Extensive assessments were conducted before his referral to our memory clinic, where a depressive disorder was diagnosed. Remarkable cognitive improvement followed the treatment of his depression, affirming a diagnosis of pseudodementia.

Keywords: CSF biomarkers; Depression; FDG-PET; Pseudodementia

Introduction

Cognitive impairment has emerged as a prevalent symptom among adults of advanced age, imposing significant impacts on individual health, caregiver burden, and public health infrastructure[1]. In the diagnostic assessment of cognitive impairment, clinicians are urged to consider and exclude various reversible causes before concluding a neurodegenerative origin[2]. Depression, historically referred to as "pseudodementia," stands out among these reversible factors[3]. The decline in the use of the term pseudodementia over the past two decades is attributable to multiple factors, notably, the recognition that depression may not always lead to reversible dementia and may instead serve as a risk factor or a prodromal sign of dementia[4–7]. Another contributing factor to the diminished use of this term is the persistent cognitive impairment observed in at least 24% of patients following remission from depression, despite treatment[8–10]. Additionally, the ineffectiveness of acetylcholinesterase inhibitors and cognitive enhancers in addressing depression-related cognitive impairment, coupled with their adverse effects in nondemented patients, further complicates this issue[11,12]. Although the term pseudodementia has fallen out of favor in contemporary clinical practice, our case report aims to highlight the clinical importance of this condition by demonstrating its presentation and management outcomes.

Case Presentation

We describe a 67-year-old male who consulted a general neurologist due to a slowly progressive cognitive decline observed over a period of 5 years. His educational background included 4 years of formal education, and his professional history involved working as an electrical repairman from the age of 30 to retirement at 60. He was right-handed. His medical history revealed well-controlled essential hypertension that was managed with medications and bilateral sensorineural hearing loss, for which he had been utilizing hearing aids for the last decade.

Approximately 5 years ago, at age 62, the patient began exhibiting pronounced forgetfulness, notably misplacing personal items, neglecting to extinguish lights before retiring, and struggling to remember the next steps while repairing electrical appliances—a task within his expertise for more than 20 years. He reported a perceptible slowdown in cognitive processes, necessitating increased time to formulate and recall intentions. Initially, he was adept at managing his medication regimen. However, over the subsequent 4 years, his condition deteriorated, culminating in the inability to administer medications or perform household appliance repairs—activities previously within his competence. Despite these cognitive setbacks, his basic activi-

ties of daily living remained unaffected. Additionally, the patient experienced sleep disturbances and a diminished appetite, further complicating his clinical picture. His daughter, observing a substantial deterioration in his memory, sought medical evaluation.

During his evaluation, both physical and neurological parameters were found to be within normal ranges. The Thai Mental Status Examination resulted in a score of 22 out of 30, which falls below the normal threshold of 24. Similarly, the Montreal Cognitive Assessment produced a score of 15 out of 30, which is indicative of cognitive impairment, as scores above 25 are typically considered within the normal range. Comprehensive investigations, including blood tests and magnetic resonance imaging with a dementia-specific protocol, were conducted to identify any reversible causes of cognitive decline. These investigations confirmed normal hematological parameters and revealed generalized brain atrophy consistent with the patient's age, without evidence of focal or asymmetrical lobar atrophy. In light of his premature cognitive decline, which occurred before the age of 65, further diagnostic procedures were pursued, including a lumbar puncture for cerebrospinal fluid (CSF) analysis and a fluorodeoxyglucose–positron emission tomography (FDG-PET) scan. CSF analysis revealed that the amyloid beta, total tau, and phosphorylated tau protein levels were within normal limits, and FDG-PET showed no regions of hypometabolism, ruling out many common neurodegenerative conditions.

At our memory clinic, referring patients for an exhaustive neuropsychological evaluation is a cornerstone of our diagnostic approach. This patient's assessment revealed inconsistencies: although he demonstrated adeptness in visual memory tasks (both immediate and delayed recall), he failed to score in auditory memory tasks. Notably, during instances of testing failure, the patient exhibited considerable stress, often digressing into recounting distressing life events, which occasionally necessitated the premature cessation of testing. This significant variance within the cognitive domain of memory, combined with his pronounced stress response, suggested underlying depressive disorder. Application of the Geriatric Depression Scale yielded a score of 13 out of 30, suggesting mild depression.

A deeper investigation of the patient's stress-related history revealed pivotal events. Five years prior, concurrent with the onset of his cognitive decline, he experienced the loss of a cherished pet, leading to significant grief. This period was further complicated by financial pressures stemming from his wife's debts, compelling him to deplete a substantial portion of his savings. These events precipitated a marked deterioration in his marital relationship, characterized by increased conflict. Clinically, he reported insomnia, a diminished appetite, episodes of isolated weeping, and a general lack of motivation. Although there was a slight improvement in his mood over time, his cognitive deficits persisted.

The therapeutic strategy included the initiation of an antidepressant regimen alongside supportive psychotherapy. At the patient's 3-month follow-up, a discernible improvement was observed in both his mood and cognitive functions. Notably, at the 6-month evaluation, his performance on the Thai Mental Status Examination and the Montreal Cognitive Assessment improved to scores of 25 and 23, respectively, indicating substantial cognitive

recovery. Concurrently, an enhancement in his mood was substantiated by both clinical observation and a decrease in the Geriatric Depression Scale score to 5. Impressively, the patient was able to resume his previous competencies, including the repair of items and the self-management of his medication regimen, mirroring his pretreatment capabilities.

Discussion

In assessing patients with cognitive decline, two fundamental questions arise. The first concerns the etiology of the cognitive impairment, necessitating a comprehensive evaluation for reversible causes. This approach is crucial, as the amelioration of such causes can potentially improve cognitive function, unlike the inevitable progression associated with irreversible, neurodegenerative diseases[2]. The second question distinguishes between dementia and mild cognitive impairment, given that treatment regimens and the resulting caregiver burden and patient prognosis differ markedly between these conditions[13].

Historically, depression was considered a reversible factor, with the expectation that cognitive function would normalize following appropriate treatment, leading to the use of the term "pseudodementia." This term has also been applied to cognitive declines associated with other psychiatric disorders such as mania, schizophrenia, and conversion disorder[3,14]. However, current research has shown that depression may precede dementia as a prodromal symptom or co-occur with it, challenging the notion of its reversibility[7]. Although the treatment of depression does not guarantee a full reversal of cognitive deficits, it is advocated due to the potential for untreated mood disorders to exacerbate cognitive decline[15], as illustrated in our case study. This evolving understanding underscores the complexity of diagnosing and treating cognitive impairment within the context of psychiatric comorbidities

Identifying depression in our patient proved challenging due to time constraints inherent in clinical assessments and the patient's inherent temperament. His daughter revealed that he often concealed his emotional struggles, a tendency attributed to his perceived role and obligations within the family structure. This necessitated multiple consultations to construct a comprehensive clinical picture, with particular emphasis on conducting assessments in a setting isolated from familial influences to encourage candid disclosure of symptoms. Following a detailed explanation of his condition, with an emphasis on the concept of pseudodementia, the patient recognized the extent of his stress and its previously underestimated effect on his cognitive capacities and daily functioning.

Cognitive impairments associated with depression notably affect psychomotor speed, sustained attention, memory, and executive functions[16–18]. The debate regarding the reversibility of these impairments after depression treatment persists within the scientific community. The literature on this topic presents conflicting evidence; certain studies indicate complete cognitive restoration posttreatment [18–20], while others highlight enduring deficits, especially in attention, memory, and executive functions[9,21]. Recent advancements in our understanding suggest that depression not only constitutes a risk factor for dementia[22] but also may present as a prodromal symptom during the preclinical stages or even within the dementia

phase itself[7]. This duality in depression's relationship with cognitive function may explain the observed disparities in cognitive recovery outcomes following the improvement of depressive symptoms. The diagnosis of depression in patients with Alzheimer's disease, the predominant neurodegenerative dementia type, presents significant challenges due to symptom divergence from that in nondemented individuals of advanced age and the insensitivity of conventional diagnostic criteria and scales. In Alzheimer's disease patients, depression is more frequently marked by motivational disturbances, including psychomotor retardation, apathy, and fatigue. These characteristics contrast with the mood-centric symptoms (depressed mood, anxiety, and disturbances in appetite and sleep) observed in nondemented older adults[23,24]. Standard diagnostic instruments—such as the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), the Hamilton Depression Rating Scale, the Cornell Scale for Depression, and the Geriatric Depression Scale—were primarily devised for nondemented individuals, lose validity in dementia patients due to their impaired self-awareness of mood conditions[25–27]. In response to these diagnostic dilemmas, the National Institute of Mental Health introduced the Provisional Diagnostic Criteria for Depression of Alzheimer's Disease (NIMH-dAD) in 2002 (Table 1)[28]. This set of criteria has demonstrated high concordance with DSM-IV diagnoses, exhibiting 94% sensitivity and 85% specificity, thereby offering a reliable tool for identifying depression in Alzheimer's disease patients[29].

Table 1. National Institute of Mental Health Provisional Diagnostic Criteria for Depression of Alzheimer's Disease [Adapted from Reference 28]

A. Three (or more) of the following symptoms must be present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms must either be 1) depressed mood or 2) decreased positive affect or pleasure 1. Clinically significant depressed mood 2. Decreased positive affect or pleasure in response to social contacts and usual activities 3. Social isolation or withdrawal 4. Disruption in appetite 5. Disruption in sleep 6. Psychomotor changes 7. Irritability 8. Fatigue or loss of energy 9. Feelings of worthlessness, hopelessness, or excessive or inappropriate guilt 10. Recurrent thoughts of death, suicidal ideation, plan or attempt
B. All criteria are met for Dementia of the Alzheimer Type (DSM-IV)
C. The symptoms cause clinically significant distress or disruption in functioning
D. The symptoms do not occur exclusively in the course of delirium
E. The symptoms are not due to the direct physiological effects of a substance
F. The symptoms are not better accounted for by other conditions such as major depressive disorder, bipolar disorder, bereavement, schizophrenia, schizoaffective disorder, psychosis of Alzheimer disease, anxiety disorders, or substance-related disorders

Given its ease of use in clinical settings, the Geriatric Depression Scale was employed to assess the severity of depression and to monitor therapeutic response in our patient. Application of the NIMH-dAD revealed that the patient's symptoms, including depressed mood, alterations in appetite and sleep patterns, psychomotor retardation, and diminished energy levels, were indicative of depression. This diagnosis could be established irrespective of the presence of Alzheimer's disease. Notably, these symptoms could also meet the criteria for a depression diagnosis using other standards designed for nondemented patients, such as the DSM-IV. The case underscores the critical nature of comprehensive history-taking: an absence of detailed inquiry into the patient's sleep and dietary habits could have led to an oversight of the underlying mood disorder. Therefore, meticulous history-taking is essential, often providing key insights that may not be as readily apparent through cognitive testing alone.

The diagnosis of depression lacks specific or standardized biomarkers, necessitating reliance on clinical history and anomalous test findings. The pathophysiology of depression is multifaceted, with theories ranging from monoamine depletion[30] and hypothalamic–pituitary–adrenal axis hyperactivity[31] to glutamatergic system imbalances[32] and neuroinflammation[33]. CSF, which is closely associated with brain chemistry, offers a potential avenue for depression diagnosis through analysis, akin to its use in other neurological disorders. Despite the exploration of numerous CSF biomarkers within research settings, the heterogeneity of the underlying mechanisms of depression has led to a proliferation of potential biomarkers. These molecular markers have been studied primarily in small cohorts, complicating the identification of definitive biomarkers for clinical use. A recent meta-analysis of CSF biomarkers in depression reviewed 97 studies that involved 165 biomarkers[34]. Only 42 biomarkers were investigated in more than one study, and of these, only 9 biomarkers (from 48 of the studies) showed significant differences between depressed patients and healthy controls. The small sample sizes associated with these 9 biomarkers currently preclude their utility in enhancing the clinical diagnosis of depression.

In addition to CSF biomarkers, FDG-PET scans and functional magnetic resonance imaging have been instrumental in detecting specific regions of hypometabolism indicative of depression. FDG-PET scans have identified variations ranging from normal to diminished metabolic activity in critical areas, including the frontal, temporal, anterior cingulate, and parietal lobes[35,36]. This imaging technique has also been applied to explore depression within the realms of mild cognitive impairment and Alzheimer's disease, and this approach has consistently detected hypometabolism within the frontal cortex [37,38]. The presence of abnormal hypometabolism in FDG-PET scans, particularly in the context of depression or other neuropsychiatric conditions, is associated with a heightened risk of progressing to mild cognitive impairment[39]. The challenge arises in distinguishing between depression and Alzheimer's disease due to shared hypometabolic regions, such as the parietal and temporal lobes, leading to mixed outcomes in studies attempting differentiation via FDG-PET scans[40]. However, case reports have noted the normalization of hypometabolic areas following depression treatment through antidepressants, electroconvulsive therapy, or a combination thereof, suggesting the potential reversibility of these neuroimaging findings[41–44].

In our reported case, the FDG-PET scan did not reveal any hypometabolic regions typically associated with Alzheimer's disease, presenting a diagnostic conundrum. This absence of hypometabolism might suggest that the patient's depressive symptoms were an early, prodromal indication of Alzheimer's disease, during which FDG-PET scans can still appear normal, or alternatively, that the patient was experiencing late-onset depression accompanied by mild cognitive impairments linked to mood disturbances. Differentiating between these potential diagnoses poses a significant challenge, often necessitating an assessment of a patient's clinical response to mood disorder treatments for a more definitive diagnosis[45]. The marked improvement in mood and cognitive capabilities in our patient following treatment with antidepressants and psychotherapy supports the diagnosis of pseudodementia. Nonetheless, it remains imperative to closely monitor the patient's cognitive functions over time, as there remains a risk for future cognitive decline, possibly due to a resurgence of depressive symptoms or the emergence of a neurodegenerative disorder.

Conclusions

The term pseudodementia has become less prevalent in modern medical discourse, primarily due to its potential to cause diagnostic confusion and its limited contribution to clarifying the complex interplay between dementia and depression. This term historically denoted a reversible form of cognitive decline, often linked to depression or mood disorders, necessitating precise diagnostic labeling rather than the broad use of "pseudodementia." While treatment may not completely reverse cognitive deficits in all cases, it is imperative to rigorously investigate the presence of such reversible conditions. A thorough assessment for treatable causes of cognitive decline is essential before definitively diagnosing a patient with irreversible, neurodegenerative dementia, thereby highlighting the critical need for accurate diagnosis and management in such cases.

Ethics Approval and Consent to Participate

This study received ethical approval from the Siriraj Institutional Review Board at the Faculty of Medicine Siriraj Hospital, Mahidol University in Bangkok, Thailand (reference number: Si 119/2024). Owing to the retrospective design of our study, which inherently preserved the anonymity of the patient, the acquisition of written informed consent from the patient was deemed unnecessary. This exemption was formally granted by the Siriraj Institutional Review Board. The authors affirm that all aspects of this research were performed in strict accordance with the ethical guidelines outlined in the Declaration of Helsinki.

Consent for Publication

Not applicable.

Conflict of Interest Statement

The authors affirm that there are no personal or professional interests that could be construed as conflicts of interest in relation to this study.

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Author Contributions

CD take part in reviewing case and lab test, and manuscript writing. CR take part in review neuropsychological test. LW take part in analysis of

CSF. SC and AR take part in doing neuropsychological test. VS take part in suggestion of case report and manuscript revision.

Data Availability Statement

The datasets generated and analyzed during the course of this study are fully incorporated within the text of this article.

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