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EDITORIAL STAFF

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(Examples): Enzensberger W, Fischer PA. Metronome in Parkinson's disease [Letter]. Lancet 1996;347:1337. Clement J, De Bock R. Hematological complications of hantavirus nephropathy (HVN) [abstract]. Kidney Int 1992;42:1285.

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h. Doctoral Dissertation

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Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis [serial online] 1995 Jan-Mar [accessed 1996 Jun 5];1(1):24 screens. Available from:

URL: http://www.cdc.gov / ncidod/ EID/eid.htm

b. Electronic Medium: CD-ROM Monograph

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reeves JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0 San

Diego: CMEA; 1995.

c. Electronic Medium: Computer File

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EDITORIAL

Turning a New Leaf

A new year, new beginnings, and a brand new start.

Having been tasked to head the official publication of the organization, I not only felt the pressure of maintaining the quality of scientific papers published, but as I read through the editorial box of past editors-in-chief with the very first being ATO (Artemio T. Ordinario), the burden of carrying on the tradition felt heavy on my shoulders. But I will not let this pressure intimidate me but on the other hand encourage me to do my best.

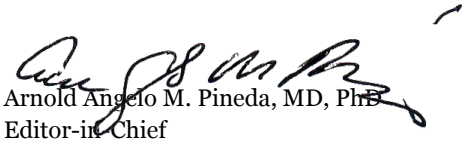
My plans for the PJN include revitalizing interest in publication not only for our training residents, but also for our Fellows. Online submissions will facilitate faster peer review and decreased turnaround time. This is a work in progress and is being updated regularly until our submission process will be solely online only.

Another source of original material are the proceedings from both our midyear and annual meetings. A lot of very interesting topics may have been missed out so this will offer the chance to get a second look of clinically relevant material in print version.

The councils have also come up with their own research as well as our outreach, and hopefully, this will be the foundation of finally establishing a comprehensive database for common neurological diseases in the country.

Lastly, the PJN will be sporting a new look on the outside, with a brighter hue of yellow and more vibrant fonts to signal changes for our beloved PJN.

As we turn a new leaf, both for the organization and publication, we hold on to the PNA vision of conducting innovative and translational research and the mission of advancing expertise in the neurological sciences by upholding the PNA values of commitment, drive for excellence, collegiality and social responsibility.



Arnold Angelo M. Pineda, MD, PhD
Editor-in-Chief

ORIGINAL SCIENTIFIC ARTICLES

Use of Cannabis in the Improvement in the Unified Parkinson's Disease Rating Scale Score of Parkinson's Disease: A Meta Analysis

Jose Gil C. Guillermo Jr., MD, Diane Charlene T. Gochioco, MD, John Isaac G. Merin, MD, Viktoria Ines P. Matibag, MD, and Ma. Katrina Margarita A. Zialcita, MD, FPNA

BACKGROUND
Cannabis, the source of Δ9-tetrahydrocannabinol (THC), the primary psychotropic compound, and cannabidiol (CBD), a nonpsychoactive chemical with potential therapeutic properties, has been widely used as a psychoactive drug, medicinal drug, or industrial hemp. Cannabinoids exert their effect in the brain mainly by interacting with two types of receptors: CB1 and CB2 receptors, which are currently being studied for its possible therapeutic effects for the symptomatic treatment of Parkinson's Disease.

METHODOLOGY
Databases searched were PubMed via National Center for biotechnology Information, CINAHL, Medline, Academic Search, Biomedical Reference collection, via EBSCOhost, and Cochrane Library. Queries were sent to local institutions for unpublished studies compatible with the criteria for study eligibility. Participants' characteristics, study design, intervention features, outcome variables, reported effects, and study quality were retrieved. Random effects model was used because heterogeneity was significant.

RESULTS
The analysis of the four clinical trials included in the study showed that *Cannabis* and its derivatives' effects on the mean motor UPDRS showed statistically significant decrease.

CONCLUSION
Cannabis and its derivatives may have an effect in the short-term symptomatic treatment of Parkinson's Disease, although controlled studies with larger samples must be done before any conclusions may be made.

INTRODUCTION

Cannabis is a plant that is the source of over 60 pharmacologically active compounds or phytocannabinoids, including Δ9-tetrahydrocannabinol (THC), the primary psychotropic compound, and cannabidiol (CBD), a nonpsychoactive chemical with potential therapeutic properties.[1] Cannabis has three recognized species, *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. Cannabis has been widely used as a psychoactive drug, medicinal drug, or industrial hemp. Its legality for use still varies from country to country as a result of the agreement about Indian hemp in the International Opium Convention back in 1925[1], as well as its supposed addictive effect as a psychoactive drug on its users.

The future of Cannabis as a medical drug appear promising as the number of scientific studies has expanded notably over the past few decades. Currently, there is still no large-scale human trial which would unequivocally confirm that medical *Cannabis* is effective for medicinal purposes, or more effective than other medicines on the market.[2] While the most popular fields of research focus on cannabinoids as a treatment for pain control, cancer, Post-traumatic Stress Disorder, and

From the University of the East Ramon Magsaysay Memorial Medical Center, Department of Clinical Neurosciences

pediatric epilepsy, an emerging possible indication for Cannabis may be for movement disorders.

Cannabidiol (CBD) is one of the main components of Cannabis sativa, but is not involved in its psychomimetic effects. Pharmacological studies on CBD have shown that the substance has a wide spectrum of action with different effects on different systems.[3] Cannabinoids exert their effect mainly by interacting with two types of receptors: CB1 and CB2 receptors. CB1 receptors are located mainly on neurons and glial cells in the brain and in several other organs in the body, while CB2 receptors are found mainly on immune cells, and are less common in the brain than CB1 receptors.[4] CBD acts on other brain signaling systems (e.g., serotonin receptors), and it is these actions that are thought to be important to its therapeutic effects.[5]

The neuroprotective properties of CBD have been under increasing scientific scrutiny in the context of neurodegenerative diseases, including Huntington's disease, Alzheimer's disease, and Parkinson's disease.[6] Cannabinoids, through the brain's endocannabinoid receptors, can decrease the activity of the output system of dopaminergic neurons downstream from the striatum through the stimulation of gamma-aminobutyric acid (GABA)ergic receptors localized on striatopallidal neurons.[7] This study aims to determine whether the use of Cannabis or its derivatives, along with the standard of care, will result in a reduction of the total motor UPDRS score of patients with Parkinson's Disease.

RATIONALE

The treatment of Parkinson disease (PD), which is characterized by the selective degeneration of mesostriatal dopaminergic neurons, is based on the administration of levodopa and related compounds, allowing normal brain dopaminergic transmission to be re-established. Available pharmacologic treatments offer only temporary improvement of the symptoms with varying effectiveness among individuals, making it a challenge for a physician to individualize treatment and adjust it necessarily throughout the course of the disease. Long-term treatment of PD patients with levodopa eventually leads to the appearance of motor complications, which result from both the severity of the loss of nigrostriatal dopaminergic neurons and the pulsatile administration of the drug.[8]

The motor manifestations of PD result from reduced dopaminergic inputs to the striatum. This leads to enhanced corticostriate glutamatergic drive and overactivity of the indirect pathway, resulting in hypoactivity of the globus pallidus externa. As a consequence, there is disinhibition of the subthalamic nucleus and increased excitatory drive to the globus pallidus interna and substantia nigra. The final result is excessive inhibition of the motor thalamus and brainstem locomotor regions and abnormal synchronization of oscillatory activity in the basal ganglia circuits.

METHODS

Eligibility Criteria

Studies deemed eligible were the clinical trials whose study population includes patients with PD. All of the studies are in the English language. The studies must compare patients who received Cannabinoids, in addition to the usual or accepted level of care, versus controls who received the usual or accepted level of care for Parkinson's Disease. The UPDRS score pre- and post-treatment must be documented in each study.

Exclusion Criteria

The studies excluded in the analysis are studies that did not use UPDRS as an outcome measure, studies that used animal models, and studies aside from clinical trials.

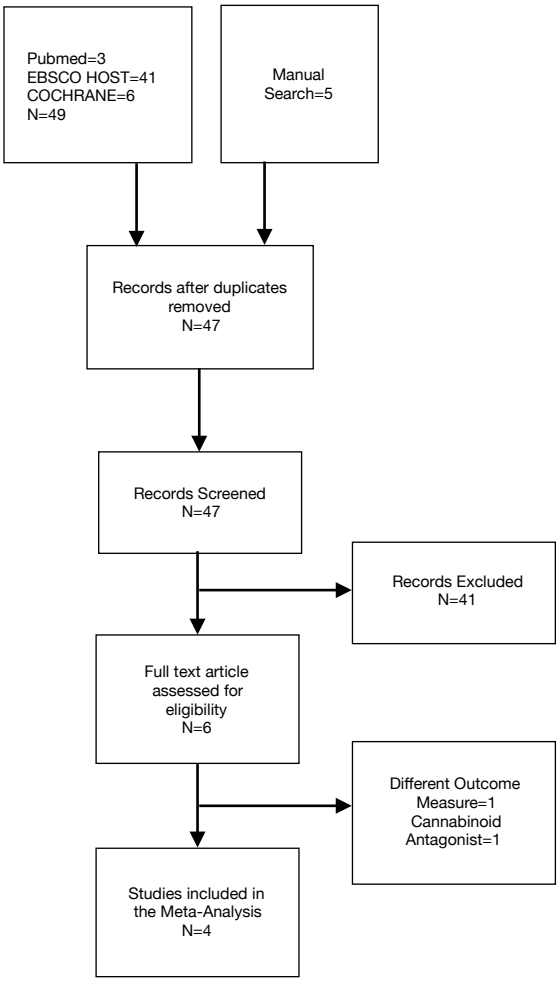
Information sources

The following databases were used to search for relevant publications dated 1990 up to October 10, 2017. PubMed via National Center for biotechnology Information, CINAHL, Medline, Academic Search, Biomedical Reference collection, via EBSCOhost, and Cochrane Library. Queries were sent to local institutions for unpublished studies compatible with the criteria for study eligibility. References were searched from citations in prior publications and reviews on the subject of study.

SEARCH STRATEGIES

Search terms that were used included (((cannabis OR cannabidiol OR marijuana OR tetrahydrocannabinol[MeSH Terms])) AND (treatment[MeSH Subheading] OR therapy[MeSH Subheading])) AND (parkinson's OR parkinsons[MeSH Terms]). (Cannabis OR Cannabidiol OR Tetrahydrocannabinol) AND UPDRS. A manual search of the reference lists of retrieved articles was also done.

Figure 1. Flowchart of Articles Selection



Study Selection

Data collection process

Data from included studies were extracted using a standardized data extraction form. Extracted data included identifying information for each study, such as author, publisher, and year published, as well as the relevant outcome in the form of UPDRS pre- and post-treatment. Baseline characteristics of treatment groups were extracted if available.

Risk of Bias (quality) assessment

Studies included for qualitative analysis were independently reviewed by three authors for compatibility with eligibility criteria, and for methodological quality in accordance to recommendations outlined in the Cochrane Handbook for Systematic Reviews.

Adherence to each criterion were scored as 'yes' (y), 'no' (n), 'unclear' (?), or 'not applicable' (n/a). Items with "n/a" were excluded from calculation for quality assessment. Based on the percentage of risk of poor methodology and/or bias, each study was assigned to the following categories: good description (80—100%), poor description (50—79%), or very poor description (0—49%).

Any conflict in the appraisal of a criterion between representative authors was settled by discussion. Studies of adequate methodological quality were subsequently included in the meta-analysis.

OUTCOME MEASURES

The primary outcome measure examined in the analysis is the UPDRS before and after treatment with cannabinoids.

Study Selection

A literature search based on databases and a manual reference search revealed 47 potentially relevant articles. Studies were chosen based on: (1) randomized or non-randomized trials, (2) The intervention therapy utilized the use of *Cannabis* or Cannabinoids in through oral consumption or smoking. 41 articles were excluded in the screening, leaving 6 articles screened for eligibility. From the 6 articles, 4 studies met the eligibility criteria, and thus were included in the meta-analysis.

Study Characteristics

Risk of Bias within studies

Methodological quality was good for the controlled trials included in the analysis, with no conspicuous anomalies in methodological quality observed. It was noted, however, that there was a disparity in follow-up times at one week and four weeks, respectively. One study also utilized a crossover design, while others randomly matched individuals to treatment groups.[12] The methodological quality of the two open label studies included was deemed to be fair to poor, as may be expected due to the nature of treatment delivery used. Smoking of *Cannabis* precludes blinding of the patient with regards to choice of treatment, thus, these studies falter in this category.[13,14] Notably, one of the two studies was unable to implement blinding of outcome assessment, raising the risk for reporting bias for this study.[13]

Synthesis of the Results

Data analysis was conducted in Review Manager 5.3 using the generic inverse variance method with mean difference as effect measure.

Table 1. Study characteristics

Author	Study Design	Sample Size	Intervention	Outcome
Chagas et. al (2014)	Randomized, double-blind, placebo-controlled study.	Control=7 Cannabidiol 75mg/day=7 Cannabidiol 300mg/day=7	Cannabidiol 75mg/day or 300mg/day for 6 weeks.	UPDRS Total UPDRS Total Motor Parkinson's Disease Questionnaire-39 UKU Side effect rating scale Assessment done after 6 weeks.
Carroll et. al (2004)	Randomized, double blind, crossover study	17 PD patients were randomized to receive oral *Cannabis* extract followed by placebo or vice versa.	*Cannabis* extract (2.5 mg of ^{9}-THC and 1.25 mg of cannabidiol per capsule) or Placebo Each treatment phase lasted for 4 weeks with an intervening 2-week washout phase.	UPDRS (32-34) dyskinesia Scale UPDRS Total UPDRS Total Motor Rush Scale Bain Scale Tablet Arm Drawing Task Assessment done after 4 weeks.
Lotan et. al (2014)	Open-Label Observational Study	22 patients	Smoking 1 dose of *Cannabis* (0.5g)	UPDRS 20-29 UPDRS Total motor Assessment done after 30minutes
Shohet et. al (2016)	Open-Label Observational Study	20 patients	Smoking 1 dose of *Cannabis* (1g)	UPDRS Total Motor Visual Analog Scale Present pain intensity scale Short form McGill Pain Questionnaire Medical Cannabis Survey National Drug and Alcohol Research Center Questionnaire Assessment Done after 30 minutes

Figure 2. Forest Plot of Comparison: Total UPDRS (fixed-effects model)

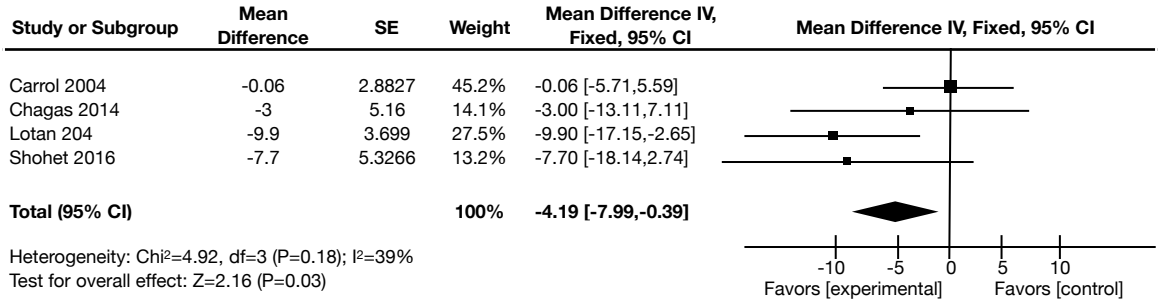
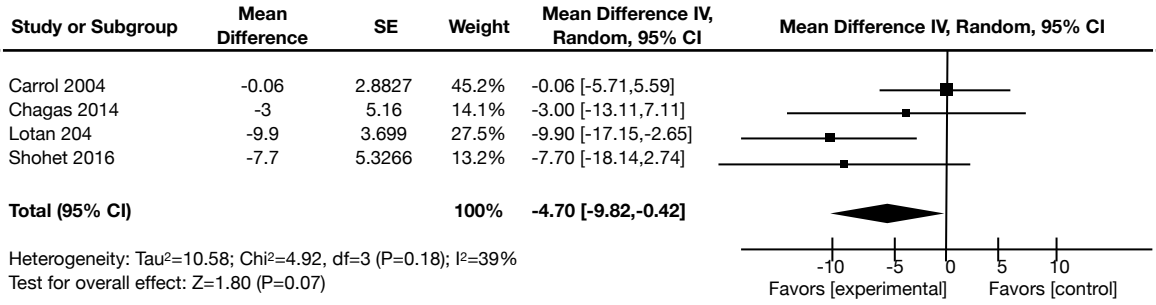


Figure 3. Forest Plot of Comparison: Total UPDRS (random-effects model)



Using the fixed effects model, the estimate of mean difference showed a significant decrease In UPDRS score. -4.19 [-7.99, -0.39] (P=0.03). Analysis using a random effects model did not result in a change in the direction of the treatment effect, however the observed treatment effect was not seen to be significant -4.70 [-9.82, 0.42] (P=0.07). In light of the similarity of fixed and random effects estimates, it may be presumed that the magnitude and direction of treatment effect is not considerably affected by study size.

Heterogeneity was not seen to be significant in both fixed- effects [Chi^2 = 4.92, df = 3 (P = 0.18); I^2 = 39%;] and random-effects analyses [Tau^2 = 10.58; Chi^2 = 4.92, df = 3 (P = 0.18); I^2 = 39%].

DISCUSSION

Alleviating symptoms of PD is truly a big challenge for a physician. Effective long-term treatment that benefit patients continue to elude us. Novel therapeutics such as *Cannabis* seem promising, but its current label as a prohibited drug in several countries has prevented it from being used for medicinal or research purposes, slowing down the progress of gathering data that may serve as groundwork for larger scale studies.

After a thorough review of the four studies, there seems to be a beneficial effect of *Cannabis* and its derivatives on the UPDRS score. A decrease was seen in the mean UPDRS using the fixed effects model, although it showed no statistical significance in the random effects model. This may be of use as a springboard for future studies of medical *Cannabis* for movement disorders.

Currently as of writing, the use of medical marijuana has been approved in the lower house of the Philippines as House Bill 180, but is still being reviewed by the Senate of the Philippines, after which must be approved by the President of the Philippines. [15] Hence, the use of medical *Cannabis* in the Philippines may be soon be seen in the horizon.

RECOMMENDATIONS

It is recommended that large-scale studies be done to increase validity of the outcome measure. Standardizing the measure of cannabinoid levels in the serum should be developed in future studies to assure that the effects of the cannabinoid result from the same amount regardless of route given (through smoking or per orem) or strain used. We expect a rise in the studies with larger samples and studies with better designs as *Cannabis* gains more credibility for its medicinal purposes among researchers, physicians, and the common public.

LIMITATIONS

The limitations of this study are: the small sample size of the studies analyzed, the time frame to which measurements were taken (short-term vs long-term), legality of the substance, and different types of vehicles and doses utilized for the administration of *Cannabis*.

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Clinical Profile and Outcome of Patients with Cerebrovascular Disease After Myocardial Infarction in A Tertiary Hospital: A Case Series

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BACKGROUND
Stroke in patients with myocardial infarction result in worse patient outcomes, greater cost and higher risk of mortality. Currently, there has been no published data regarding patients who develop stroke post MI in the Philippines.

OBJECTIVE
To describe the occurrence, clinical profile and outcome of patients who had stroke within one year of acute myocardial infarction.

METHODOLOGY
Records of patients with acute myocardial infarction (MI) from January 1, 2013 - January 31, 2016 who had a stroke within one year follow up were reviewed to describe the clinical profile of these patients, the mortality rate and functional outcomes at one year post MI.

RESULTS
Among patients enrolled in the AMI Program with one year follow up, 11 patients (1.94%) had stroke. Most were males (9/11, 81.82%) with mean age of 60 years. Common findings in these patients were: hypertension (8/11, 72.73%), diabetes mellitus (7/11, 63.64%), smoking (6/11, 54.55%), STEMI (6/11, 54.55%), anterior wall hypo-/akinesia (7/11, 63.64%), concentric left ventricular hypertrophy (7/11, 63.64%) and LAD involvement (7/8 patients, 87.5%). Atrial fibrillation was uncommon (3/11, 27.27%) but was observed in those with earlier (<14 days) strokes, dependence and mortality. Stroke occurrence was highest in the first 2 weeks (7/11, 63.64%) with mean GCS 13+2 and mild in severity (4/11, 36.36%). Cerebrovascular infarction (90.91%) was the most common stroke type, usually due to large artery atherothrombosis (5/10, 50%) and usually with involvement of the MCA (10/10). Hemorrhagic conversion was infrequent (3/10, 30%). Dependence (MRS >3) was seen in 7/11 (54.55%) and mortality (2/11, 18.18%) was slightly higher than non-stroke patients (10/303, 10.23%) at one year-post MI.

CONCLUSION
Stroke occurrence was higher in the first two weeks post MI. Most were males, mean ages of 60 years; with hypertension, diabetes and history of smoking; STEMI, anterior wall hypo-/akinesia, concentric LVH, and LAD involvement. Atrial fibrillation was infrequent but was observed in patients with earlier strokes (<14days), more severe disability on discharge and mortality at one year follow up. Dependence (MRS >3) was common at discharge and mortality was higher than those without stroke at one year post MI.

KEYWORDS
cerebrovascular disease; myocardial infarction; outcome; stroke

BACKGROUND

The Philippines is burdened by chronic diseases, with diseases of the heart and the vascular system as the foremost cause of mortality.[1] Individually, myocardial infarction (MI) and cerebrovascular disease (stroke) confer disability and socio-economic burden among patients and their caregivers.

According to WHO, stroke is a syndrome of rapidly developing clinical signs of focal (or global)

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disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.[2] Stroke may be classified as either infarction or hemorrhage. Focal neurologic deficits that are present transiently without evidence of infarction is called transient ischemic attack.[2] Meanwhile, myocardial infarction (MI) implies necrosis of myocardial cells from prolonged ischemia and may be recognised by clinical features, including electrocardiographic findings, elevated biomarkers of myocardial necrosis and imaging.[3] Where there is evidence of cardiac injury, as in ST elevation MI or non-ST elevation MI, cardiac arrhythmias or cardiac dysfunction may occur which in turn increase the long-term stroke risk.[4] When stroke occurs after MI, patient outcomes are worse and cost is greater.[5, 6]

In the Philippines, stroke is the second leading cause of mortality with a prevalence rate of 0.9% in the general population and with ischemic stroke (70%) seen more frequently than hemorrhagic stroke (30%).[7] After thorough review of local online data and a hand search of published data, there are currently no published studies regarding the incidence of stroke after MI. Determining the clinical profile of patients who have stroke post MI may be beneficial in individualising treatment and follow up for patients with multiple risk factors.

OBJECTIVES

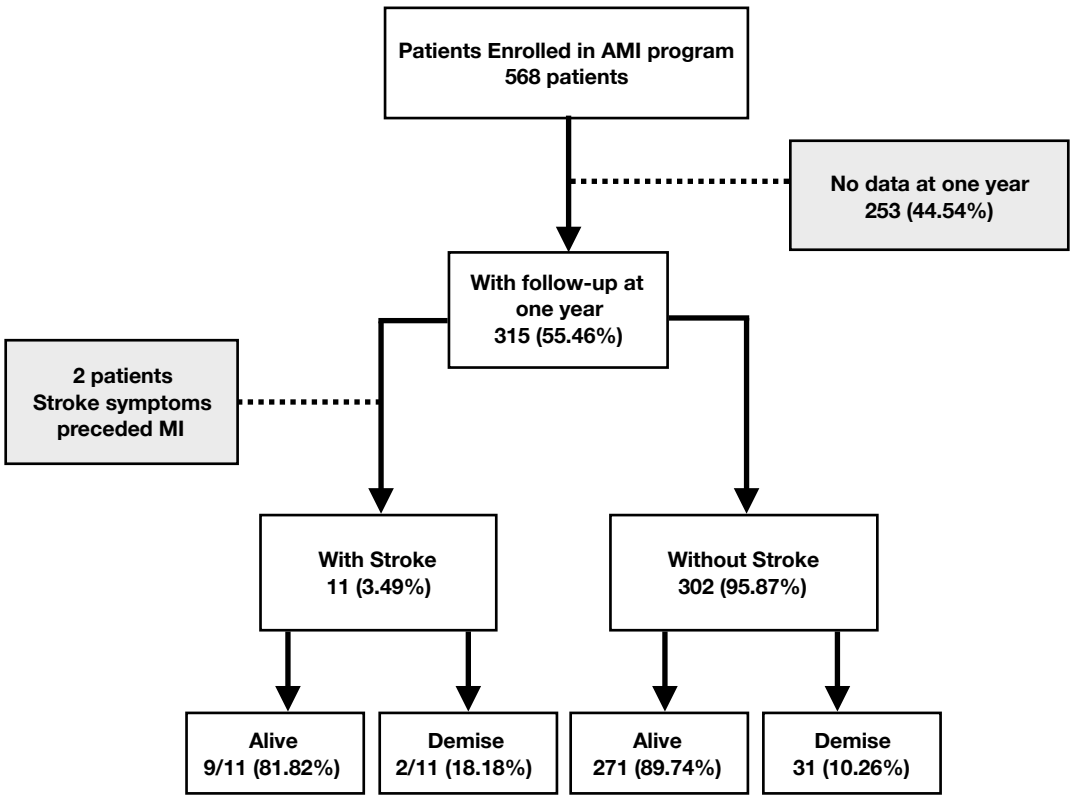
General

This study aimed to determine the clinical profile of patients with stroke within one year post myocardial infarction.

Specific Objectives:

1. To describe the clinical profile of patients with stroke within one year post myocardial infarction as to:
   a. Demographic profile: Age, Sex, Nationality
   b. Past medical history: co-morbidities (hypertension, diabetes mellitus, dyslipidemia; chronic kidney disease, coronary artery disease and previous myocardial infarction; previous stroke; chronic obstructive pulmonary disease

Figure 1. Patients enrolled in the AMI Program from January 1, 2013 - January 31, 2016 with one year follow up data



and obstructive sleep apnea) and modifiable risk factors like smoking and excessive alcohol use.

c. Cardiologic profile: type of AMI; echocardiographic findings of left ventricular systolic dysfunction (EF <40%), wall hypokinesia, chamber enlargement (left atrial enlargement, concentric ventricular hypertrophy) and the presence of thrombus; the presence of congestive heart failure and atrial fibrillation; aspirin use within 24 hours; vessel involvement in angiography; and the use of additional interventions like PCI with or without stenting; and/or thrombolysis

d. Neurologic profile: type of stroke; TOAST classification, arterial distribution and presence of hemorrhagic conversion; GCS and NIHSS scores; and medical or surgical decompression if provided

2. To describe patient outcomes at one year post MI as to survival and functional outcome using the Modified Rankin Scale.

METHODOLOGY

Acute Myocardial Infarction Program

The Acute Myocardial Infarction (AMI) Program caters to patients with acute myocardial infarction; and is the first program in the country accredited by the Joint Commission International in 2015. It targets a door-to-balloon time and provides long-term care for patients post MI in coordination with allied health professionals. AMI cases were diagnosed by the cardiologist when there was a rise and/or fall of cardiac biomarker values, preferably cardiac troponin, with at least one of the following: symptoms of ischemia, new or presumed new significant ST-segment - T wave (ST-T) changes or new left bundle branch block (LBBB), development of pathological Q waves in ECG, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or identification of an intracoronary thrombus by angiography or autopsy.[8,9]

Population and Sample

Patients enrolled in the AMI Program from January 1, 2013 to January 31, 2016 with follow up one year post MI were identified. Patients who had stroke during the follow up period (see Figure 1) were included in the study. Stroke was diagnosed by the neurologist based on clinical findings supported by neuroimaging. Only those who were admitted in the institution at the time of stroke were included. Among those diagnosed with stroke within 24 hours post MI, patients were excluded if stroke symptoms preceded the symptoms or diagnosis of MI.

Table 1. Patient Characteristics

Characteristics	Frequency (Percentage) n=11 (1.94%)
Age (mean, standard deviation)	60 ± 10.71
<50 years	2 (18.18%)
51 - 60	5 (45.45%)
61 - 70	2 (18.18%)
>70	2 (18.18%)
Sex (Males)	9 (81.82%)
Nationality (Filipino)	11 (100%)
Presence of Co-morbidites	
Hypertension	8 (72.73%)
Diabetes Mellitus	7 (63.64%)
Dyslipidemia	3 (27.27%)
Chronic Kidney Disease	1 (9.09%)
Chronic Obstructive Disease	0
Obstructive Sleep Apnea	0
Previous MI	0
Atrial Fibrillation	1 (9.09%)
Documented CAD	0
Previous Stroke	3 (27.27%)
History of Smoking	6 (54.55%)
Pack Years [a]	17.6 years ± 5.26
Excessive Alcoholic Beverage	0
Cardiovascular Risk Factors	
Type of MI (STEMI)	6 (54.55%)
Type of MI (NSTEMI)	5 (45.45%)
Atrial fibrillation	3 (27.27%)
Heart Failure on admission	2 (18.18%)
Post arrest	1 (9.09%)
Anterior wall involvement (hypo-/akinesia in echo)	7 (63.64%)
Depressed systolic function (EF <40%)	4 (36.36%)
Concentric left ventricular hypertrophy	7 (63.64%)
LA enlargement	0
Intracardiac thrombus	0
Thrombus on repeat echo during occurrence of stroke	2/4 (50%)
Aspirin given within 24hours of admission for MI	11 (100%)
Coronary Angiography (n=8)	8 (72.73%)
LAD involvement	7/8 (87.50%)
Additional intervention done (n=8)	
PCI	6 (54.55%)
Thrombolysis for MI (streptokinase)	2 (18.18%)
CABG	0

Methods

Individual chart review was done for identified cases of stroke post MI. Demographic and past

medical history included co-morbidities, smoking history and heavy alcohol use. The cardiovascular and neurologic profiles were reviewed and described as well. Cardiovascular profile described the type of AMI, whether ST elevation MI (STEMI) or non-ST elevation MI (NSTEMI); echocardiographic findings described the presence of left ventricular systolic dysfunction (EF <40%), wall hypokinesia, chamber enlargement (left atrial enlargement, concentric ventricular hypertrophy), and the presence of thrombus; the presence of congestive heart failure and atrial fibrillation; the use aspirin within 24 hours; vessel involvement on angiography; and the use of additional interventions like PCI with or without stenting; and/or thrombolysis. The neurological profile included GCS and NIHSS score to determine severity of stroke; the type of stroke (whether infarction, hemorrhage or transient ischemic attack); the TOAST criteria10 and type of hemorrhagic conversion (PH1, PH2, HT1, HT2)11 if present; and the type of decompression provided. Outcomes at one year post MI were described according to survival and functional outcome using Modified Rankin Scale. Dependence was described as having an MRS score of >3.

Data Analysis

Data analysis was performed using Stata version 14. Descriptive statistics such as mean, median, range and standard deviation were tabulated for quantitative variables such as age, GCS, NIHSS score and MRS. On the other hand, proportions were tabulated for qualitative variables.

RESULTS

A total of 568 patients were enrolled in the Acute Myocardial Infarction Program (Figure 1) from January 1, 2013-January 31, 2017. Three hundred fifteen patients (55.46%) had one year follow up data while 253 (44.54%) were lost to follow up. Among 303 patients (53.17%) without stroke at one year follow up, 272 patients (89.74%) survived while 31 patients (10.26%) died. There was no sufficient data on the cause of death. There were a total of 13 patients with stroke at one year post MI. Two patients were excluded because the diagnosis of stroke and MI occurred within the first 24hours but the initial presenting symptom was neurological in nature and it was difficult to distinguish if the myocardial infarction preceded the stroke. Only 11 patients (1.94%) with stroke were included in this study. Nine of 11 stroke patients (81.82%) survived at one year post myocardial infarction while 2 of 11 patients (18.18%) died.

The demographic characteristics of stroke patients are in Table 1. Patients were mostly males (9/11, 81.82%) with majority aged 51-60 (5/11, 45.45%) with mean age of 60 (SD +11 years). Common co-morbidities (see Figure 2) included: hypertension (8/11, 72.73%) and diabetes mellitus (7/11, 63.64%), while dyslipidemia (3/11, 27.27%), chronic kidney disease (1/11, 9.09%) and coronary artery disease (1/11, 9.09%) were infrequent. None of the patients had chronic obstructive pulmonary disease, obstructive sleep apnea or prior MI. This may be due to lack of prior work up or poor health seeking behavior. Three of 11 patients (27.27%) had a previous stroke preceding the MI. Among patients with previous stroke, all were males with ages 50-77 years. Strokes were recurrent (>2) in 2 of 3 patients. Mean number of years interval between previous stroke and MI was 7.6 years (range 1-14 years interval from latest stroke to occurrence of MI). Common cardiac findings were concentric left ventricular hypertrophy (3/3), left ventricular systolic dysfunction (EF<40% in 2/3) and anterior wall hypo-/akinesia (2/3) on echocardiography. Left anterior descending artery (LAD) involvement on angiography was seen in all 3 patients with history of stroke prior to MI and re-stroke.

As to modifiable risk factors, smoking was common (6/11, 54.55%) with a mean of 17.6 (+ 5.26) pack years. None of the patients were documented to have heavy alcohol consumption described as >5 alcoholic drinks for males or >4 alcoholic drinks for females on >5 days in the past month according to the National Institute on Alcohol Abuse and Alcoholism. This may have been due to inadequate documentation with regards to the volume taken in by the patients.

Acute Myocardial Infarction (AMI)

Cardiac findings during the acute coronary event are seen in Table 1. Majority of the patients had ST segment selection MI (STEMI) (6/11, 54.55%). Significant echocardiographic findings included the presence of anterior wall hypo-/akinesia on echocardiography (7/11, 63.64%) and concentric left ventricular hypertrophy (7/11, 63.64%). Left ventricular systolic dysfunction (ejection fraction <40%) was seen fewer patients (4/11, 36.36%). None had left atrial enlargement or intracardiac thrombus; however, four patients had a repeat

Table 2. Neurologic Profile and Outcome of Patients with Stroke Post-MI

Characteristics	Frequency (Percentage) n=11
Interval of stroke occurrence post MI (<2 weeks) within the first 24 hours = 3 (27.27%)	7 (63.64%)
Interval of stroke occurrence post MI (2 weeks-3 months)	1 (9.09%)
Interval of stroke occurrence post MI (>3 months)	3 (27.27%)
Mean GCS (standard deviation)	13 ± 2
Mean NIHSS (standard deviation)	11 ± 10
Mean pre-stroke MRS (standard deviation)	0 ±1
Type of Stroke	
Transient Ischemic Attack	1 (9.09%)
Infarction (n = 13)	10 (90.91%)
Type of Infarction (TOAST)	
Cardioembolism	3 (27.27%)
Large Artery Atherosclerosis	5 (45.45%)
Small Artery Occlusion	1 (9.09%)
Undetermined Cause	1 (9.09%)
Malignant infarction	3 (27.27%)
Hemorrhagic Conversion	3 (27.27%)
PH1	1 (9.09%)
PH2	0
HT1	1 (9.09%)
HT2	1 (9.09%)
Intracerebral hemorrhage	0
Infused rTPA	1 (9.09%)
Decompression (n=4)	
Medical + Surgical decompression	3 (27.27%)
Medical decompression only	1 (9.09%)
Outcomes	
Mean MRS at discharge (standard deviation)	3 ± 2
Dependent (MRS ≥3)	7 (63.64%)
Mortality at 1 year	2 (18.18%)

echocardiography at the time of stroke (<14 days post MI) and 2/4 patients (18.18%) developed an apical thrombus compared to baseline echocardiography. Among those who underwent angiography (8/11 patients), LAD involvement was common (7/8 patients, 87.5%) with total occlusion seen in 4/7 patients (57.14%). All patients received aspirin within 24 hours of hospitalization. Only 8 patients received additional intervention: PCI with stenting/IABP placement (6/8, 75%) and thrombolysis (2/8, 25%).

Two of 11 patients (18.18%) had symptoms of heart failure on admission. One of them had cardiopulmonary arrest (4 minutes), was revived and was in shock upon resuscitation requiring vasopressors upon admission. Atrial fibrillation (AF) occurred in 3/11 (27.27%). Two were new-onset and 1 was chronic. In both cases of new-onset AF, stroke occurred within the first two weeks (<14 days) post MI.

Stroke

The occurrence of stroke was highest in the first 2 weeks post myocardial infarction (7/11, 63.64%) as seen on Table 2. Upon examination by the neurologist, GCS ranged from 9-15 (mean 13+2). NIHSS scores ranged from 0-28 (mean 11+10). Stroke was usually mild (4/11, 36.36%) and had rapidly resolving symptoms clinically. Stroke was moderate in 3/11 (27.27% NIHSS score 8-16) and severe in 3/11 (27.27% NIHSS 22-28). Cerebrovascular infarction (10/11, 90.91%) was the most common stroke type. There were no cases of intracranial haemorrhage; while 1 out of 11 patients (9.09%) had low risk transient ischemic attack (ABCD2=2).

Among those with infarction, large artery atherothrombosis (5/10, 50%) was more frequent compared to cardioembolic infarction (3/10, 30%). Less common were small artery occlusion (1/10, 10%) and stroke of undetermined cause (1/10, 10%) due to refusal of further work up. Three patients (27.27%) had malignant infarction involving the main trunk of the middle cerebral artery. All three patients required both surgical and medical decompression. Three patients (27.27%) had hemorrhagic conversion (HT1 9.09%, PH1 9.09%, PH2 9.09%). The most severe (PH2) type of hemorrhagic conversion was seen in only patient (LAA, MCA) who received rTPA infusion (0.9mg/kg) and required both medical and surgical decompression.

Outcomes

Dependence was common after the stroke, with moderate-severe disability (MRS >3) in most patients (7/11, 63.64%). One patient had a higher baseline MRS score (MRS 4) due to previous stroke. Among patients with MRS >3, common co-morbidities were hypertension (5/7, 71%) and diabetes mellitus (4/7, 57%). STEMI was predominant (5/7, 71%) and common echocardiographic findings were: anterior wall hypo-/akinesia (5/7, 71%) and concentric LVH (4/7, 57%). Left anterior descending artery occlusion was also common (5/6, 83%). In all three patients with AF, MRS scores were higher (MRS 4-6).

Mortality at one year follow up was seen in 2 patients (2/11, 18.18%). This was slightly higher than the mortality among patients who did not have

a stroke (10/303, 10.23%) at one year-post MI. Insufficient data on the causes of mortality may underestimate these values.

For those who did not survive, one case was attributed to brain herniation syndrome from malignant infarction at 19 days post MI while the other occurred at 10 months post MI due to multi-organ failure from sepsis. Common among these two cases were the presence of atrial fibrillation, anterior wall hypo-/akinesia, concentric LVH and LAD involvement on angiography. Also, the patient who died due to brain herniation syndrome was the same patient who had cardiac arrest, in cardiogenic shock upon admission and had atrial fibrillation on the second day of hospitalisation. He eventually recovered and was GCS 14 at the time of referral. He had moderate stroke (NIHSS 18). A repeat echocardiography was done in this patient revealing the presence of thrombus. Despite adequate management, stroke progressed causing malignant infarction. He underwent medical and surgical decompression. The only patient infused with rTPA had severe disability upon discharge (MRS 5) but was alive at one year follow up post MI.

DISCUSSION

The occurrence of stroke within one year post MI (11/568, 1.94%) in the present study was slightly higher compared to the general Filipino population (0.9%)[7]. This was similar to published data; where 1.98% of patients in the United States had a stroke one year after the acute myocardial infarction (AMI)5 or even higher at 4.1% in Sweden.6 Stroke was more common during the first 2 weeks (<14 days) in this study. Hatchet, studying both in-hospital and post discharge events, reported a higher incidence (64%) of stroke in the first 5 days after AMI.14 Ischemic strokes were likewise more common than hemorrhagic stroke[13,14]. The shared risk factors causing thrombosis like hypertension, diabetes and dyslipidemia with additional risk for embolism due to cardiac injury in AMI causes more ischemic events. There were no cases of hemorrhagic stroke in the present study. This may be due to infrequent or absence of the predictors for the occurrence of hemorrhagic stroke such as reperfusion treatment such as thrombolysis,[14] renal failure and previous hemorrhagic strokes.[17]

Independent predictors noted for ischemic stroke after MI were: age, female sex, history of hypertension, diabetes mellitus, previous stroke/TIA, ST-segment elevation myocardial infarction, anterior wall myocardial infarction and heart failure symptoms.[5,14] New-onset atrial fibrillation was also associated in patients with in-hospital strokes.[14]

Most patients were males, as opposed to other studies.[4-6,14] A greater number of risk factors found in men may preclude this finding. Poorer health seeking behaviour contributing to less health prevention strategies seen in males may also be a factor. Increasing age was associated with the risk of stroke as well as AMI, usually over 65 years.13 In this study, majority were aged 51-60 years old (5/11, 45.45%) with a mean age was 60 years. Hypertension, diabetes mellitus and smoking, which are also independent predictors of MI,[4] were common among patients with stroke in the present study. A previous stroke was not common and may have been underestimated due to a small number of patients or insufficient work up or documentation. Further studies must look into the probability that a previous stroke further predicts stroke recurrence after an episode of MI.

In a study by Arboix, factors that enhanced the risk of stroke among those with AMI were severe left ventricular dysfunction with low cardiac output, left ventricular aneurysm, or thrombus and atrial fibrillation.16 The cardiovascular risk factors predominantly observed in this study were ST elevation MI; anterior wall hypo-/akinesia and concentric left ventricular hypertrophy on echocardiography. STEMI can be considered a marker of infarction severity, which explains the increased stroke risk. Despite being present in a minority of patients, the presence of shock and heart failure; and atrial fibrillation were seen in patients with moderate to severe stroke with higher disability on discharge (MRS >3) and in patients who did not survive at one year. Cell injury during AMI leads to cardiac dysfunction and hypo-/akinesia of the cardiac chambers[9-11] which increases the risk for thrombus formation and embolism. This was observed in two of four patients whose echocardiographic studies were repeated at the time of stroke occurrence (<2 weeks). Also, once cardiac injury is present, widespread atherosclerosis is suspected [9,11]. A local study by Fortes (2016), on cardioembolic strokes also noted that atrial fibrillation remains the most common cardiac comorbidity. It may also be seen in athero-thrombotic infarcts as a marker of other conditions that lead to ischemic stroke such as atherosclerosis. Usually, stroke due to atrial fibrillation peaks at 5% in patients aged 65 and older[9]. Despite being

uncommon in the present study (3/11, 27.27%), those with atrial fibrillation were observed to have earlier strokes (<14days in 2/3 patients) post MI, dependence and disability (MRS 4-5 in 2/3 patients) upon discharge and mortality (2/3 patients) during long term follow-up.

STRENGTHS AND LIMITATIONS

This is the first study to be conducted among a large registry of patients with AMI in the Philippines. However, the large number of patients with insufficient one-year follow up data and lack of information on post-discharge, out-of-hospital stroke occurrence may cause the results to be underestimated. Considerations to include these information into the follow up database may be recommended to better evaluate the occurrence of stroke post MI. Classification of stroke using the TOAST criteria was limited to the final diagnosis provided that the patient underwent work up and the diagnosis was agreed upon by the neurologist and cardiologist managing the patient. Improving this classification system may further benefit subsequent studies.

CONCLUSION AND RECOMMENDATIONS

Pertinent observations in the present study include: 1) increased stroke occurrence post MI compared to the general population; and more frequent in the first two weeks post MI; 2) male preponderance, usually 51-60 years; with hypertension, diabetes and history of smoking; 3) possible contributing cardiac risk factors of STEMI, anterior wall hypo-/akinesia, concentric LVH, and LAD involvement; and atrial fibrillation was observed in patients with earlier strokes (<14 days) and had more severe disability on discharge and mortality at one year follow up; 4) strokes were mostly due to large artery atherothrombosis, but usually mild, affecting the middle cerebral artery distribution with infrequent hemorrhagic conversion needing decompression therapy. As to outcomes, stroke post MI resulted in dependence (MRS >3) in most patients and mortality was higher than those without stroke at one year post -MI.

Patients who are admitted for Acute Myocardial Infarction with the aforementioned predisposing factors should be cautioned and closely monitored for signs and symptoms of cerebrovascular disease, especially in the first two weeks. Repeat cardiac work up in high risk patients may be beneficial in the presence of stroke to provide guidance in management.

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PROCEEDINGS FROM THE 2017 ASNA CONVENTION

Movement Disorder Genetics for the Clinician

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ABSTRACT

The contribution of genes to etiology is variable for different movement disorders. Some diseases are by definition genetic, such as Huntington's disease. Other disorders such as Parkinson's disease may have monogenic causes but are largely the result of nongenetic factors. Dystonia and the atypical parkinsonisms have high genetic burdens in their etiologies, with reduced penetrance being a common feature. I review the clinical and molecular features and genotype-phenotype correlations in monogenic causes of autosomal dominant (*SNCA*, *LRRK2*, *VPS35*) and recessive (*PARKIN*, *PINK1*, *DJ-1*) Parkinson disease, and of isolated (*TOR1A*, *THAP1*, *GNAL*) and combined (*GCH1*, *TH*, *ATP1A3*, *PRKRA*, *TAF1*, *SGCE*) dystonia. Because the genetics of movement disorders is complex, genetic testing in aid of clinical diagnosis can only be recommended for genes that are unequivocally disease causing. However, gene panel testing is slowly transitioning into clinical utility, heralding the transition of movement disorder genetics from bench to bedside. This is a shortened version of a book chapter on movement disorder genetics.

INTRODUCTION

Genetics have revolutionized the field of movement disorders in the past 25 years. We now know that Parkinson disease (PD), for example, previously a textbook example of a non-hereditary condition, has a genetic etiology in as much as 3% of cases. Although we are still far from a complete understanding of the disease mechanisms underlying hereditary movement disorders, we have garnered insights into pathophysiology by studying genes, proteins, and pathways.

The degree of genetic contribution to the etiology of movement disorders is highly variable, ranging from fully penetrant causative mutations to low-penetrant mutations and risk factor alleles. Some disorders, such as Huntington disease (HD) are by definition genetic and caused by a mutation in a single gene. Other movement disorders, such as Parkinson disease or the dystonias, can be caused by mutations in several different genes but appear largely sporadic in the overwhelming majority of cases. For common movement disorders with reported frequencies of up to 10% in the general population, such as restless legs syndrome (RLS) and essential tremor (ET), no clearly causative gene has yet been identified and independently confirmed.

An important concept in genetic movement disorders is the phenomenon of reduced penetrance (absence of disease in a mutation carrier, which is found in many dominant disorders) and highly variable disease expression. The latter can sometimes be extreme, with the same gene being involved in distinct phenotypes, referred to as pleiotropy. An illustrative example are mutations in the *ATP1A3* gene – first described to cause rapid-onset dystonia-parkinsonism and now also found as the underlying cause of alternating hemiplegia in childhood and CAPOS (cerebellar ataxia, pes cavus, optic atrophy, sensorineural hearing loss) syndrome.

DISCUSSION

GENETICS OF PARKINSON'S DISEASE AND PARKINSONISM

'Parkinsonism' encompasses the etiologically heterogeneous clinical syndromes that present with bradykinesia, rest tremor, rigidity, and postural instability (Williams & Litvan, 2013). The prototype is idiopathic Parkinson disease, which is typically late-onset and progressive and has a good response to dopamine replacement therapy. Although largely

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not inherited in a Mendelian fashion, in early-onset, familial, and ethnic cases, the probability of an underlying genetic cause is higher (Alcalay et al., 2010).

Genes that are confirmed to be linked with monogenic PD include: *SNCA, LRRK2, VPS35, PARKIN, PINK1,* and *DJ1*. The first three cause dominantly inherited or sporadic disease that closely resembles idiopathic disease; the recessive genes *PARKIN, PINK1,* and *DJ1* meanwhile cause early-onset PD (EOPD).

Dominantly inherited monogenic PD

Single-nucleotide missense mutations and multiplications in the alpha-synuclein (*SNCA*) gene cause monogenic PD that is generally younger at onset (Polymeropoulos et al., 1997). The decline of levodopa-responsive motor symptoms is also faster, and the development of motor fluctuations is typically earlier than in sporadic PD.

LRRK2 (Leucine-rich repeat kinase 2) is the most frequently mutated gene in idiopathic PD. The most common mutation, G2019S, represents 4% of familial and 1% of sporadic PD across all populations (Healy et al., 2008); thus, PARK-*LRRK2* is the most important differential diagnosis when considering genetic PD, given also that the phenotype is often indistinguishable from non-genetic disease (Zimprich et al., 2004).*VPS35* (vacuolar sorting protein 35) was the first PD-causing gene identified via next generation sequencing (Vilariño-Güell et al., 2011; Zimprich et al., 2011). PARK-*VPS35* is dominantly inherited with reduced penetrance, and has a phenotype that is very similar to idiopathic PD (Bonifati, 2014).

Early-onset, recessively inherited monogenic PD

PARKIN mutation carriers have an earlier age at onset but less aggressive disease (Klein & Schlossmacher, 2007). It is the most common form of EOPD across all ethnic groups, representing about 10-20% of cases of PD with age at onset within the fourth decade. Dystonia is a common presenting sign and may even sometimes be seen as an isolated finding (Lohmann et al., 2003; Grünewald et al., 2013).

Mutations in PINK1 were first identified in three EOPD families with homozygous mutations (Valente et al., 2004). It now represents 1-9% of all genetic PD across all ethnicities (Klein & Schlossmacher, 2006). The usual phenotype is indistinguishable from PARK-PARKIN, only with a higher rate of psychiatric symptoms and cognitive impairment (Kasten et al., 2010).

PARK-DJ1 is significantly less common than either PARK-PARKIN or PARK-PINK1, and accounts for only 1-2% of cases (Klein & Schlossmacher, 2006). Clinical and neuroimaging features are similar to the other two recessive PD syndromes (Bonifati et al., 2003).

GENETICS OF DYSTONIA

While Hermann Oppenheim probably described

TABLE 1. Monogenic causes of Parkinson disease

Designation and clinical subgroup	Additional phenotypic notes	Mode of transmission	Previous locus symbol
Typical PD			
PARK-*SNCA*	More aggressive, prominent non-motor features	AD	PARK1 and 4
PARK-*LRRK2*	Sporadic, tremor-dominant PD	AD	PARK8
PARK-*VPS35*	May be sporadic, late-onset PD	AD	PARK17
PARK-*GBA*	Highly reduced penetrance	AD	none
Early-onset PD			
PARK-*PARKIN*	EOPD with dystonia as initial sign	AR	PARK2
PARK-*PINK1*	EOPD with non-motor features	AR	PARK6
PARK-*DJ1*	Rare cause of EOPD	AR	PARK7

AD – autosomal dominant; AR – autosomal recessive

the first cases of genetic dystonia in 1911 (i.e., DYT1), and coined the term 'dystonia musculorum deformans' (Oppenheim, 1911; Klein & Fahn, 2013), the modern history of dystonia genetics dates back to 1994 when mutations in the *GCH1* (GTP cyclohydrolase I) gene were discovered as the cause of dopa-responsive dystonia. Today, confirmed genes for isolated dystonias are *TOR1A*, *THAP1,* and *GNAL*. In the combined forms, dystonia can be accompanied by parkinsonism (*GCH1, TH, ATP1A3, PRKRA, TAF1*) or myoclonus (*SGCE*).

Monogenic isolated dystonia

In DYT-*TOR1A,* the mean age of onset is at 13 years with twisting of an arm or leg, and progression to involve other limbs and the torso, but usually sparing the face and neck (Bressman et al., 2000). Almost all cases are caused by the same 3-base pair deletion (GAG) in the coding region of the torsin (*TOR1A*) gene, which occurs in 90% of patients of Ashkenazi Jewish origin due to a founder effect (Ozelius et al., 1997). If symptoms do not occur prior to 28 years of age in mutation carriers, they usually remain unaffected for the rest of their life.

THAP1-associated dystonia combines features of focal and generalized primary dystonia and is also inherited in an autosomal dominant manner with penetrance estimated at 40%. The onset is later (mean 19 years) than in *TOR1A*-associated dystonia and there is more prominent cranial involvement with dysphonia being a predominant feature (Fuchs et al., 2009).

Mutations in the *GNAL* gene cause cervical or cranial dystonia with onset most commonly in the thirties (Vemula et al., 2013). *GNAL* mutations probably account for about 1% of all cases of focal or segmental dystonia involving the cranio-cervical region (Kumar et al., 2013).

Monogenic combined dystonias

Dopa-responsive dystonia (DRD) is characterized by childhood onset of dystonia, diurnal fluctuation of symptoms, and a dramatic response to L-dopa therapy (Segawa et al., 1976). Later in the course of the disease, parkinsonian features may occur and may, in rare cases, be the only sign of the condition (Mencacci et al., 2014). The more frequent form of DRD (DYT5a) is caused by dominant mutations in the GTP cyclohydrolase 1 (*GCH1*) gene. Penetrance is lower among men than women.

ATP1A3-associated rapid-onset dystonia has a sudden onset within hours to weeks, typically in adolescence or young adulthood, in response to physical or mental stress. It is inherited in an autosomal dominant fashion with reduced penetrance. Typical features include dystonic spasms predominantly in the upper limbs, orofacial dystonia, dysarthria, and dysphagia, along with symptoms of parkinsonism (de Carvalho Aguiar et al., 2004).

PRKRA-linked dystonia-parkinsonism is a rare, recessively inherited form of early-onset generalized dystonia, which is accompanied by parkinsonism and caused by mutations in the *PRKRA* gene (Camargos et al., 2008).

X-linked dystonia-parkinsonism (XDP) is endemic to the Philippines and inherited in an X-linked recessive fashion (Lee et al., 2012, Domingo et al., 2015). Patients present in adulthood with dystonia, most pronounced in the craniofacial region. The dystonia subsequently generalizes and patients develop parkinsonian features, which predominate in late disease stages. XDP is the only condition among the isolated and combined dystonias with overt neurodegeneration of the striatum. The underlying genetic cause is an in intronic SVA insertion in the *TAF1* gene (Aneichyk et al., 2018), which has been observed in individuals of Filipino descent.

Myoclonus-dystonia (M-D) is characterized by a combination of myoclonus and dystonia with onset

TABLE 2. Selected monogenic causes of atypical parkinsonism

Designation and clinical subgroup	Additional phenotypic notes	Mode of transmission	Previous locus symbol
Kufor-Rakeb Syndrome, PARK-*ATP13A2*	Juvenile parkinsonism with supranuclear gaze palsy, brain iron accumulation	AR	PARK9
Parkinsonian-pyramidal Syndrome, PARK-*FBXO7*	Juvenile parkinsonism with pyramidal signs	AR	PARK15
EOPD with atypical features, PARK-*DNAJC6*	Also with mental retardation and seizures	AR	PARK19
EOPD with atypical features, PARK-*SYNJ1*	With seizures, cognitive decline, dystonia	AR	PARK20

TABLE 3. Monogenic causes of dystonia

Designation and clinical subgroup	Additional phenotypic notes	Mode of transmission	Previous locus symbol
Isolated dystonias			
DYT-*TOR1A*	Early-onset generalized dystonia	AD	DYT1
DYT-*THAP1*	Adolescent-onset dystonia of mixed type	AD	DYT6
DYT-*GNAL*	Adult-onset cranial-cervical dystonia	AD	DYT25
Combined dystonias			
Dystonia plus parkinsonism			
DYT-*GCH1*	Dopa-responsive dystonia	AD	DYT5a
DYT-*TH*	Dopa-responsive dystonia	AR	DYT5b
DYT-*ATP1A3*	Rapid-onset dystonia-parkinsonism	AD	DYT12
DYT-*PRKRA*	Dystonia-parkinsonism	AR	DYT16
DYT-*TAF1*	Dystonia-parkinsonism	X-linked	DYT3
Dystonia plus myoclonus			
DYT-SGCE	Myoclonus-dystonia	AD	*DYT11*

usually in childhood or early adolescence. In most affected individuals, myoclonic jerks are dramatically but transiently ameliorated by intake of alcohol. The disease is inherited as an autosomal dominant trait with reduced penetrance and caused by loss-of-function mutations in the *SGCE* gene (Zimprich et al., 2001).

GENETIC TESTING IN MOVEMENT DISORDERS

This review attempted to simplify the genetic causes of PD and dystonia, however, it is nonetheless obvious that the nuances of inheritable neurologic disorders are complex. Thus, consultation with a geneticist is recommended prior to embarking on "gene hunting" for a suspected case. The decision to undergo genetic testing involves many different factors, including the indication for the test, the implication of the results based on the stage of disease, the feasibility, sensitivity-specificity, and accuracy of the test, and the general lack of neuroprotection in PD and other movement disorders, among others (Klein & Schlossmacher, 2006). Furthermore, several cases of false positive findings exist in the literature (MacArthur et al., 2014), and so a careful assessment of the diagnostic value of any variant discovered by genetic testing cannot be overemphasized.

At least for PD, dystonia, and Huntington's disease, guidelines on molecular diagnosis and clinical genetic testing have been established by the European Federation of Neurological Societies (EFNS) (Harbo et al., 2009). In PD, the guidelines recommend testing for *LRRK2* in familial cases with dominantly inherited PD, and for *PARKIN, PINK1*, and *DJ1* in EOPD and in those suggestive of recessive inheritance, emphasizing the role of history-taking and careful assessment of the family history and inheritance pattern prior to the genetic test. In dystonia, genetic testing for the GAG deletion in *TOR1A*, and for *GCH1* and *SGCE* in clinically compatible cases, is recommended.

Lastly, while genetic etiologies are likely only rare causes of movement disorders such as PD and dystonia, gene panel testing via next generation sequencing technology has recently become available as an option that allows for accurate and final diagnosis in patients facing a long and expensive 'diagnostic odyssey' (Lohmann & Klein, 2014).

ADDITIONAL READING

For a more detailed review of the genetics of movement disorders, Parkinson disease, and dystonia, the following book chapters are recommended reading:

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Domingo A and Klein C. Genetics of Dystonias: Overview. In: Treatment of Dystonia (Eds.: Dressler D, Alternmüller E, Krauss J). 2018 (Cambridge University Press).

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