

Moyamoya Disease and its Association with Thyroid Disorders; a Pakistani Case Report and a Review of Case Reports

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Abstract

Objective: We aimed to report the case of a Pakistani female who presented with MMD and hyperthyroidism, and the worldwide literature review of the case reports on MMD associated with hyperthyroidism.

Methods: The study was carried out using PRISMA's recommendations. An electronic search on PubMed, Cochrane Library, and Google Scholar was carried out. Articles explaining the association between Moyamoya disease and thyroid-related diseases were included.

Results: A total of 31 studies were included in the review, with the preponderance of Japanese females. The review has systematically compiled in detail all the aspects of moyamoya syndrome and thyroid disorders- from detailed histories of the included patients to the treatment interventions used and their outcomes.

Conclusion: The authors are with the suggestion that more cases of MMD and its association with other major factors should be presented in Pakistan as well as in all parts of the world.

Keywords: Moyamoya Disease, Thyroid Disorders, Hyperthyroidism, Graves' Disease.

Abbreviations

TSH= Thyroid-Stimulating Hormone

FT4= Free Thyroxine

FT3= Free Tri-Iodothyronine

T4= Thyroxine

T3= Tri-Iodothyronine

TR-Ab= Thyrotropin Receptor Antibody

TPO-Ab= Thyroid Peroxidase Antibody

TG-Ab= Thyroglobulin Antibody

ATG= Anti-Thymocyte Globulin

US= Ultrasound

CT= Computed Tomography

3D-CTA= Three-Dimensional Computed Tomography Angiography

MRI= Magnetic Resonance Imaging

MRA= Magnetic Resonance Angiography

DWI= Diffusion-Weighted Imaging

ICA= Internal Carotid Artery

MCA= Middle Cerebral Artery

ACA= Anterior Cerebral Artery

PCA= Posterior Cerebral Artery

CTX=Cefotaxime

STA-MCA bypass= Superficial Temporal Artery- Middle Cerebral Artery bypass

EDAS= Encephalo-Duro-Arterio-Synangiosis

EMS= Encephalo-Myo-Synangiosis

EDMS= Encephalo-Duro-Myo-Synangiosis

Key Summary

- Moyamoya disease (MMD) is a rare progressive vaso-occlusive disorder, characterized by progressive stenosis of terminal portions of internal carotid arteries, anterior portions of the circle of Willis especially, the anterior and middle cerebral arteries.
- We aimed to report the case of a Pakistani female who presented with MMD and hyperthyroidism, and the worldwide literature review of the case reports on MMD associated with hyperthyroidism. The purpose was to compare the MMD management in Pakistan and throughout the world.
- The study was carried out using PRISMA's recommendations. An electronic search on PubMed, Cochrane Library, and Google Scholar was done. The search results were screened according to the study title and abstracts and then according to the full texts.
- Case
- Twenty case reports and eleven literature reviews were selected to add to our study. The review has systematically compiled in detail all the aspects of moyamoya syndrome and thyroid disorders- from detailed histories of the included patients to the treatment interventions used and their outcomes.

1. Introduction

Moyamoya disease is a rare developing cerebrovascular disorder that involves cerebral arteries which are occluded due to ongoing stenosis [1]. The word Moya-Moya means a “puff of smoke” in Japanese which was seen during an angiography that is made by the collateral circulation developed to compensate for the blockage in this disease [2]. The defect can be found in any artery but in some cases, they were found in the median or anterior cerebral artery. It makes an abnormal net-like or fibrous dim-like picture when visualized [3]. This disease can be found in both adults as well as children and may lead to headaches, seizures, ischemic stroke, intracranial hemorrhage, and transient ischemia attack [4]. This disease was first described by two renowned scientists named Takeuchi and Shimizu in 1957 [5].

The etiology of this disease is unknown but due early age of onset and the incidence rate found in certain ethnic groups indicate

hereditary relation of this disease. The gene of RNF213 was shown to be strongly associated with Moyamoya disease in the population of east Asia [6]. The factor of finding less prevalence of Moyamoya disease in the white population which carries less common non-Arg4810Lys variants of RNF213 has opened many new avenues of investigation [7]. Some studies also suggest that circulating angiogenetic factors, such as growth factors, vascular progenitor cells, and cytokines could cause neovascularization by damaging the structures and forming excessive collateral routes and promoting intimal hyperplasia [8].

The Moyamoya disease is common in many different races but was first discovered in Japan. Later, China, Korea, and southeastern Asia also reported this disease. An incidence rate of 0.35/100,000 and a prevalence rate of 3.16/100,000 was recorded in Japan in 1995. The prevalence was found more in males comparing it with females with a ratio of 1.8:1. The prevalence of this disease found in China was 3.92/100,000 as reported. No data had clearly shown the incidence of Moyamoya in Europe and the United States, but literature analysis shows that white people have low incidence than Asians, especially Japanese or South Koreans [9]. It can be said that this disease is familial especially in Japanese as they have a 10.5 higher prevalence rate suggesting genetic factors to be assessed [10].

Moyamoya disease has been underreported in Pakistan. In the limited literature on Moyamoya disease, only two case series and a few case reports have been reported [11-14]. Many studies have reported similar presentations as stroke in a younger population, which raises the question that whether this is underdiagnosed in Pakistan [15]. Additionally, no reports have been found from Pakistan on Moyamoya disease associated with any other disease especially autoimmune, like thyroid abnormalities.

Moyamoya disease has no specific way of treatment but many surgical options such as indirect bypass, and direct bypass and their combination to increase cerebral blood flow have been found to treat ischemic problems [16]. Surgical Revascularization is considered to prevent further strokes, but it is still controversial to be used to prevent future hemorrhagic stroke in MMD [17]. MMD is a disease that could have an improved prognosis if

diagnosed and assessed accurately. The imaging modalities such as conventional computed tomography (CT) and magnetic resonance imaging (MRI), digital subtraction angiography, CT angiography (CTA), and magnetic resonance angiography can be used for diagnosis and help to treat this disease. The cerebral hemodynamics could be evaluated by single-photon emission CT, positron emission tomography, xenon-enhanced CT, perfusion CT, dynamic susceptibility contrast MRI, and arterial spin labeling MRI that could help to measure the parameters hemodynamically [18].

All over the literature, MMD has been described to relate to several systemic diseases for example atherosclerosis, autoimmune diseases, meningitis, brain tumors, and Down syndrome (DS). We aimed to report the case of a Pakistani female who presented with MMD and hyperthyroidism, and the worldwide literature review of the case reports on MMD associated with hyperthyroidism. The purpose was to compare the MMD management in Pakistan and throughout the world.

2. Methods

The study was carried out using PRISMA's recommendations, a comprehensive overview of the main results from the studies performed to evaluate the association between the Moyamoya disease and hyperthyroidism, Graves' disease, and thyrotoxicosis [19, 20].

2.1. Literature Search

An electronic search on PubMed, Cochrane Library, and Google Scholar was done to identify the studies that were published from the inception of the databases. A broad search strategy was deployed, consisting of "Moyamoya, quasi-Moyamoya, Graves' disease, thyrotoxicosis and thyroid function or thyroid autoantibodies". All the articles from 1990-2022 were reviewed thoroughly. The same search strategy was used on all the databases.

2.2. Inclusion-Exclusion Criteria

A comprehensive inclusion-exclusion criterion was designed to omit any sort of confusion for the authors as well as readers. It included

1. Only the published reports were included in the study.
2. Articles published only in the English language were included.
3. Articles explaining the association between the Moyamoya disease and thyroid-related diseases like hyperthyroidism, Grave's disease, and thyrotoxicosis were included. Those reports which explained other associations of the Moyamoya disease as well were not excluded.

2.3. Data Extraction

Initially, the search results were screened according to the study title and abstracts and then according to the full texts. The selected studies were then scanned according to the inclusion criteria, and the finalized articles were included in this review. Reference lists of relevant articles were also scanned to identify further relevant studies. All the duplicates were removed. Two authors independently screened and extracted the relevant data from the

finalized articles. Google spreadsheets were used for the data extraction purpose and tables were made on Microsoft Word.

3. Results

3.1. Case

A 45-year-old, Pakistani female patient, a known case of poorly controlled hypertension presented with an altered level of consciousness, slurring of speech, vomiting, headache along with decreased vision in both eyes. A primary health care center referred her to Holy Family Hospital/Rawalpindi Medical University. Her family revealed having a cerebrovascular accident a week ago. CT angiography of the brain was performed showing marked luminal narrowing of the supra-clinoid segment of the left internal carotid artery, A1 and M1 segments of anterior and middle cerebral arteries with associated extensive serpiginous collateral vessels formation. 2D echo appeared normal having an EF of 60%. The radiographic findings and the neurological symptoms led to a diagnosis of moyamoya disease. Further investigations were carried out to assess any associated Thyroid disorders, as many studies suggested the common association of moyamoya disease and Thyroid disorders. Standard lab tests were done to understand the picture of the thyroid gland.

Blood tests showed Anti Thyroglobulin <20 IU/mL, Anti Thyroid Peroxidase 185 IU/mL, T3 levels 1.29, T4 levels 10.47 & TSH levels 0.96 uIU/ml. Her blood Cp revealed HB 11.1g/dL, WBC 5.1 x 10⁹/uL, PLT 273 x 10⁹/uL, Lymphocytes 37.5% & Granulocytes 53.4%.

She was started on Anti-thyroid drugs, Steroid injections, Antiplatelet, Nymalize (Calcium Channel blocker), Amlodipine Besylate, and Rosuvastatin (Lipid-lowering drug). She was then planned for surgical revascularization.

3.2. Study Selection

We performed a literature search of different databases (1991-2022) that showed us a result of 1899 articles, after reviewing the titles and abstracts of the articles we were able to seek out 51 articles. We further had to remove 19 articles after a full-length review. Finally, 20 case reports and 11 literature reviews were selected to add to our study.

3.3. Baseline Characteristics

The total cases presented in this review are 31 (case reports 20, literature reviews 11), with the preponderance of Japanese females, however, Chinese 15, Korean 22, Caucasian 29, Hispanic 29,39 and Asian 33 races were in minority. Overall, the patients' ages ranged from 12-55 years, although, most of them were in their 20s. We considered different characteristics in our study that are summarized in table no.1. Comorbidities were assessed in which we found commonly headaches, Diabetes, DKA, hyperlipidemia, and Grave disease [29, 30, 35, 30, 34, 44, 47]. Some other comorbidities such as Down syndrome was also seen [38, 39]. The patients that have hyperthyroidism are mostly treated with some famous drugs such as propylthiouracil and methimazole which were also used by our patients in this study [31, 33, 50, 51]. They were also found with a combination of drugs named hydrocortisone

or insulin in some studies, but the above-mentioned two drugs were common in all [30, 51, 37, 38, 40]. While one study had a history of brompheniramine, and pseudoephedrine used by the patient [40]. When evaluating surgical history, Thyroidectomy was the most common surgery found in most patients in many cases [34, 36, 37, 40, 46]. The vitals were mostly normal where temperature, heart rate, and blood pressure were assessed. The analysis of heart rate showed a range between 90-150 bpm, but one study exceeded

200 bpm [30]. The blood pressure and temperature were mostly normal except in one study where the blood pressure was quite low for both the patients i.e. 32/64 & 50/80 [42]. Medical histories mostly manifested hyperthyroidism, grave disease, diabetes mellitus, and Down syndrome, however, some unique disorders such as pheochromocytoma were also observed [36]. The thyroid status in most patients was found to be hyperthyroidism, with only three studies that had hypothyroidism [34, 37, 40].

S. No.	First author	Published year	Gender	Age	Race	Comorbid	Past drug history	Past medical history	Past surgical history	Thyroid Status	Vitals
Case Reports											
1	Cai Gao-Rui [13]	2022	Female	25	None stated	None stated	None stated	Diffuse goiter 3 years back	None stated	Hyperthyroidism	None stated
2	Akiko Ishigami [14]	2013	Female	22	Japanese	None stated	None stated	None	None stated	Hyperthyroidism	None stated
3	SHOU-CHEN REN1 [15]	2015	Male	12	Chinese	Over activation of factor VIII and von-Willebrand factor	None stated	Suffered with excessive sweating, tremors and irritability	None stated	None stated	None stated
4	Yasufumi Gon [16]	2016	Female	30	Japanese	None stated	None stated	Malaise 3 weeks back and Graves disease.	None stated	Hyperthyroidism	None stated
5	Ufuk Utku [17]	2004	Female	45	None stated	None stated	None stated	None stated	None stated	Hyperthyroidism	None stated
6	Kenji Kushima [18]	1991	Case 1: female. Case 2: female.	Case 1: 26. Case 2: 22.	Case 1: Japanese. Case 2: Japanese.	Case 1: None stated. Case 2: none stated.	Case 1: Anti-thyroid drugs for hyperthyroidism. Case 2: anti-thyroid drug therapy.	Case 1: Hyperthyroidism 5 years ago, resolved after taking anti-thyroid drug therapy, Graves' disease just before moyamoya diagnosis. Case 2: Neck swelling 5 years back, exophthalmos, hyper-hidrosis, and weight loss. Left hemiparesis and motor aphasia at 22 years.	Case 1: none stated. Case 2: none stated.	Case 1: Graves' disease Case 2: Graves' disease	Case 1: fever (38-39°C) Case 2: None stated
7	Shiro Yamas [19]	2005	Female	29	None stated	None stated	None stated	None stated	None stated	Basedow Disease	None stated
8	Ai-Ling Shen1 [20]	2006	Female	23	None stated	Migraine like headache	None stated	None stated	None stated	Hyperthyroidism	None stated
9	Takafumi shimogawa [21]	2014	Female	43	Japanese	None stated	None stated	None stated	None stated	Hyperthyroidism	None stated
10	ByoungHo H. Noh [22]	2015	Female	None stated	None stated	DM 1, DKA	Methimazole (20 mg every 6 h), followed by hydrocortisone (100 mg every 8 h) and 5% Lugol solution (KI 25 mg every 6 h).	None stated	None stated	Hyperthyroidism	HR= 212 beats/min, BP= 130/70 mm Hg fever= 36.3°C.
11	Chong Kun Cheon [23]	2014	Case 1: female. Case 2: female.	Case 1: 12. Case 2: 15.	Case 1: None. Case 2: None.	Case 1: None stated Case 2: None stated.	Case 1: methimazole 20 mg daily. Case 2: 10 mg of methimazole daily.	Case 1: Graves' disease for 10 months. Case 2: Graves' disease for past 7 years.	Case 1: None stated. Case 2: None stated.	Case 1: Graves' disease Case 2: None stated.	Case 1: None stated Case 2: None stated
12	Jong Han Gill [24]	2021	Female	43	None stated.	None stated.	None stated.	Hyperthyroidism.	None stated.	hyperthyroidism was diagnosed after moyamoya diagnosis.	BP= 175/80 mm/Hg HR= 150 beats/min, fever= 38.5°C.

13	Yi-Yi Xuan [25]	2017	Female	26	None stated.	None stated.	PTU.	October 2015, red swelling and pain in both eyes. Several episodes of redness and pain of auricles and eyes bilaterally for 9 months. History of hyperthyroidism, treated with PTU for 8 years.	None stated.	Graves' disease.	None stated.
14	Hiroshi Tokimura [26]	2010	Case 1: female. Case 2: Female.	Case 1: 19. Case 2: 52.	Case 1: Japanese. Case 2: None stated.	Case 1: None stated. Case2: Hypertension and hyperlipidemia.	Case 1: None stated. Case 2: None stated.	Case 1: None stated. Case 2: Hypertension, hyperlipidemia, and hyperthyroidism.	Case 1: Thyroidectomy. Case 2: None.	Case 1: hypothyroidism. Case 2: Hyperthyroidism.	Case 1: None stated. Case 2: None stated.
15	Sakiko Suzuki [27]	2011	Case 1: Male. Case 2: Female.	Case 1: 38. Case 2: 43	Case 1: Japanese. Case 2 : Japanese.	Case 1: Diabetes mellitus and Autoimmune disease. Case 2 : Diabetes mellitus and Grave disease.	Case 1: Insulin and thiamazole. Case 2: Insulin and thiamazole.	Case 1: Diabetes mellitus and hyperthyroidism. Case 2: Diabetes mellitus and hyperthyroidism.	Case 1: None stated. Case 2: None stated.	Case 1: Hyperthyroidism. Case 2: Hyperthyroidism.	Case 1: None stated Case 2: None stated
16	Fumihiro Matano [28]	2021	Female.	52.	None stated	Stage T2N1M0 MTC and left-sided pheochromocytoma.	None stated	Pheochromocytoma and stage T2N1M0 MTC.	Thyroidectomy and left central neck D2a dissection	None stated	None stated
17	BEATRIZ E. TENDLER, [29]	1997	Case 1: Female. Case2 : Female.	Case 1: 37. Case 2: 47	Case 1: Hispanic. Case2 : Caucasian.	Case 1: None stated. Case 2: None stated.	Case 1: Propylthiouracil 400 mg, and metoprolol 50 mg, later, atenolol 25 mg, propylthiouracil 100 mg, TID and prednisone 30 mg daily. Case 2: atenolol 75 mg, and propylthiouracil 450 mg. Later, propylthiouracil 700 mg/day and preoperative treatment with 5 drops of saturated solution of iodine/ day for 7 days, and hydrocortisone 200 mg IV 2 hours.	Case 1: Mild episodes of reactive airway disease. Case 2: Dysarthria and accelerated hypertension and episodic reactive airway disease thought to be asthmatic bronchitis with exacerbations.	Case1: None Stated. Case 2: Thyroidectomy and angioplasty.	Case 1: Hypothyroidism. Case 2: Hypothyroidism.	Case 1: BP= 140/90 mm Hg HR= 120 beats per minute . Case 2: None stated.
18	Kathryn B. [30]	2017	Female.	40.	None stated.	None stated.	Antibiotics and hydroxyzine for tooth ache, anxiety. Current chronic medications included methimazole, atenolol, and insulin for autoimmune diabetes.	One week before, the patient complained of anxiety, light headedness, and tooth pain. The following day she complained of difficulty speaking, vision. Also diagnosed with auto-immune diabetes changes, tongue numbness, and anxiety, the symptoms attributed to a possible drug reaction from either of the 2 newly prescribed medications.	None stated.	Hyperthyroidism.	HR= 127 beats/ min, BP= 160/81 mmHg, and fever= 97.7°F.
19	Meng-Han Tsai, [31]	2006	Male.	26	None stated.	None stated.	None stated.	None stated.	None stated.	Hyperthyroidism.	BP= 160/90 mmHg HR= 112 beats/minute.

20	Shigeo ohba [32]	2011	Female.	46	None stated.	None stated.	Thiamazole and levothyroxine antiplatelet therapy.	Graves' disease and a thyroid tumor.	Subtotal thyroidectomy.	Hypothyroidism.	None stated.
Literature Review											
1	Shaneela Malik [33]	2020	Female.	23	Asian.	Hyperthyroidism.	None stated.	Grave disease.	None stated.	Hyperthyroidism.	None stated.
2	Takahiro Sasaki [34]	2006	Case 1: Female. Case 2: Female. Case 3: Female.	Case 1: 27 Case 2: 16 Case 3: 37	Case 1: Japanese Case 2: Japanese Case 3: Japanese	Case 1: Hypertension. Case 2: None stated. Case 3: None stated.	Case 1: Anti-thyroid therapy. Case 2: None stated. Case 3: Anti-thyroid therapy.	Case 1: Graves disease with goiter, bilateral exophthalmos. Case 2: Transient Ischemic Attacks with left hemiparesis and faintness several times for 6 months. Case 3: None stated	Case 1: None stated. Case 2: None stated. Case 3: None stated.	Case 1: Hyperthyroidism. Case 2: Hyperthyroidism. Case 3: Graves Disease.	Case 1: BP=150/80, HR=116 beats/min. Case 2: BP=132/64, HR=80 beats/min. Case 3: None stated.
3	Hiroto Ito, [35]	2019	Female.	37	None stated.	None stated.	None stated.	Asthma.	None stated.	Hyperthyroidism.	None stated.
4	Chang Y. Tsao [36]	2004	Female.	20	Caucasian.	Headaches.	brompheniramine and pseudoephedrine.	Increased fatigability, loose stools, episodes of feeling warm over the previous two years, allergies and headaches	None.	Hyperthyroidism.	BP= 134/80 mm/hg, HR= 120 beats/min.
5	S.W. Hsu [37]	2006	Female.	40	None stated.	None stated.	None stated.	Grave disease.	None stated.	Hyperthyroidism.	BP= 210/110 mm/Hg, HR= 97 baets/min.
6	Shigeo Ohba [38]	2010	Female.	34	None stated.	None stated.	Thiamazole and levothyroxine and antiplatelet drug.	None stated.	Subtotal thyroidectomy.	Hyperthyroidism.	None stated.
7	Julian Choi [39]	2016	Female.	31	Hispanic.	Graves' disease.	Propranolol and methimazole.	None stated.	None stated.	Hyperthyroidism.	BP= 179/83 mm/Hg, HR= 115 beats/min.
8	Hotaka Kamasaki [40]	2013	Male.	14	None stated.	None stated.	None stated.	None stated.	None stated.	Thyrotoxicosis with no specific diagnosis of hyperthyroidism or graves disease.	undocumented slight fever, SBP= 130-160 mm/Hg, HR=120-150 beats/min.
9	Fumihiro Matano [41]	2013	Case 1: female. Case 3: female. Case 4: male.	Case 1: 32. Case 3: 55. Case 4: 53.	Case 1: none stated. Case 3: None stated. Case 4: None stated.	Case 1: None stated. Case 3: None stated. Case 4: Hypertension, diabetes, and hyperlipidemia.	Case 1: None stated. Case 3: None stated. Case 4: None stated.	Case 1: None stated. Case 3: None stated. Case 4: None stated.	Case 1: None stated. Case 3: None stated. Case 4: None stated.	Case 1: Hyperthyroidism. Case 3: Hyperthyroidism. Case 4: Hyperthyroidism.	Case 1: BP= 110/60 mmHg. Case 3: 120/70 mm/hg. Case 4: None stated.
10	Ran lee [42]	2009	Female.	19	Korean	Down syndrome & Grave disease.	Propylthiouracil.	Down syndrome and grave disease.	None stated.	Hyperthyroidism.	BP= 135/78 mm/Hg, HR=91 beats/min.
11	Hikaru nakamura [43]	2021	Female.	19	None stated.	Down syndrome & Grave disease.	Thiamazole.	Down syndrome and grave disease.	None stated.	Normal.	None stated.

Abbreviations: DM= Diabetes Mellitus, DKA= Diabetic Keto-Acidosis, BP= Blood Pressure, HR= Heart rate, PTU= Propylthiouracil, MTC= Medullary Thyroid Carcinoma, TID= Three times per Day.

Table 1: Baseline details of the included Case reports and Literature Reviews.

3.4. Presenting complaints

Almost all the patients presented with symptoms that are either related to hyperthyroidism or pointing toward moyamoya disease. Neck swelling (29%) [22, 25, 26, 30, 31, 37-39] was the predominant complaint, although, excessive sweating (12%), [23, 34, 39, 43] tremors (10%) [23, 25, 49], and exophthalmos (23%) [22, 25, 26, 30, 31, 37-39, 50] were also frequently reported which indicate the hyperthyroid state. Among the highlighted symptoms of the moyamoya disease reported on the first visit, paralysis (39%) [21-24, 26, 30, 31, 35, 39, 47, 48] of either the extremity or

either half of the body was on the top of the list along with aphasia (16%), [21-23, 26, 27] weakness (26%) [25, 28, 32, 41, 43, 44, 48, 49] of the face or either of extremity, and sensory symptoms (16%) [23, 25, 27, 38, 40] which include incontinence of urine or feces, numbness in hands were also reported.

4. Lab Values

All the patients underwent common basic thyroid lab tests which included TSH (normal value= 0.5 to 5.0 mIU/L), FT3 (normal value= 2.3 to 4.1 pg/mL), and FT4 (normal value= 0.7 to 1.9ng/

dL), were in a hyperthyroid state at the initial testing. However, some studies also mentioned some other tests which were anti-TPO antibody, [21-25, 30, 38, 43, 44] anti-thyroglobulin antibody [13, 15, 17, 24, 36, 41] thyroid receptor antibody, [21, 22, 24, 29, 31-33, 42, 50] and thyroid-stimulating antibody [22, 50].

5. Brain Imaging Findings

The imaging modalities commonly used were MRI, MRA, ultrasound, and CT, although other techniques like digital subtraction angiography DSA, [28, 29] SPECT, [27, 31, 36, 40, 42, 46, 48-50] and positron emission tomography [22] were also sometimes considered to help substantiate the findings. Almost all the studies documented typical moyamoya vessels (stenosis of ICAs) [21-51], occlusion of MCA, [21, 22, 30, 33, 34, 35, 37, 42, 44] and occlusion of ACA [28, 29, 34, 37, 41]. Infarctions of different areas of the brain like the lobes of cerebral cortex, and basal ganglia were also commonly reported by the majority of patients.

5.1. Medical and Surgical Interventions

All the cases reported in the current study are associated with hyperthyroid states like Graves' disease, Basedow disease, or thyrotoxicosis, so all of them were initially treated with anti-thyroid therapy to normalize the thyroid levels. However, 5 patients were also treated with beta-blockers along with anti-thyroid medication, [23, 28, 37, 41, 48] 2 patients [33, 37] had radioactive therapy, 8 patients [25, 30, 37, 38, 41-43] used steroids, and 8 patients [24, 27, 28, 32, 41, 43, 44, 48] had antiplatelet therapy. 14 patients [23, 29, 31, 34, 35, 40, 42, 44, 46-51] underwent different revascularization surgical procedures like Encephalo-Myo-Synangiosis (EMS) and Encephalo-Duro-Arterio-Synangiosis (EDMS) after the treatment with oral anti-thyroid medication.

5.2. Outcomes

24 studies reported the outcome out of 31. All of them presented good results except 2 patients who died, both patients experienced sudden death, one from the neurologic cause who was found brain dead after electroencephalogram and another had mixed septic cardiogenic shock and new-onset atrial fibrillation which was the culprit of her death [45, 48].

6. Discussion

The current review is the only review that explains the case of MoyaMoya Disease (MMD) and its association with common Thyroid disorders in a Pakistani patient. It further correlates the similar cases of MMD diagnosed around the world, the diagnosis, the management of the patients, the interventions used, etc. Upon reviewing an enormous number of cases, it was observed that the disease is more common in adult females, irrespective of race, as is also reported in our case. The reason for including the past medical, drug, and surgical history was to understand in-depth if MMD is associated with any sort of pathology that occurred in the past, any surgery that could induce it, or can this disease be the side effect of any drug intervention. This hypothesis was termed false after no regularity was noticed under these three headings when more than 30 published cases were studied. The results are shown in Table 1.

The majority of the studies did not report the vitals, likewise, in our case. The few that did, stated increased blood pressure, heart rate, and fever.

Among all the thyroid disorders, graves' disease was the most common association found with MMD in our review, the results were contradictory to an article, which mentioned the rare association between these two disorders [52]. The current article also explained some rare thyroid associations with MMD like hyperthyroidism, Besdow disease, thyroid tumor, thyrotoxicosis, etc. Thyroid hormones can have a direct effect on the vascular smooth muscle and endothelial cells, this theory suggests atherosclerosis is the common pathology in both thyroid disorders and MMD [53]. Surprisingly, none of the included cases has explained atherosclerosis either in the past medical history of the patients or as one of the associations of MMD. However, two reviews, both in their second cases, have stated that hyperlipidemia (a pre- atherosclerotic condition) and transient ischemic attacks a past medical histories of patients [34, 42]. An observational study conducted in 2016 has also expressed the co-existence of MoyaMoya syndrome and atherosclerosis [54]. According to the guidelines on diagnostic criteria of MMD, patients with cerebral atherosclerosis and pathologic net-like intracranial vessels should be categorized as having MoyaMoya syndrome [53].

6.1. MMD and Hyperhomocysteinemia

Considering the fact that increased blood homocysteine levels can lead to atherosclerotic and embolic disorders, [56] hyperhomocysteinemia can be the key to diagnosing MMD. Studies have also explained the positive correlation between thyroid hormone T4 and hyperhomocysteinemia. [57, 58] Although, a test for blood homocysteine level is not suggested as a primary test during any thyroid disorder diagnosis. A prospective study found hyperhomocysteinemia to be the independent risk factor for MMD. According to the study, serum homocysteine levels are found to be increased in patients with moyamoya syndrome than the patients with non-MMD strokes. [59] This finding has also been proven by the 2 case reports (not included in this article) [60, 61]. Abnormal Homocysteine level is also noticed to be the cause of middle cerebral artery stenosis, [62] stenotic pathology of this vessel is also commonly observed in MMD. The mechanism of homocysteine on blood vessels is as follows 63, 64]. Increased serum homocysteine levels lead to endothelial dysfunction, production of NO is reduced due to reduced endothelial Nitric Oxide Synthase (eNOS), induction of smooth muscle cell escalation, increasing foam cell formation, activation of platelets and coagulation cascade, thrombus formation, reduction in blood vessel size. An Article experimented that pathological homocysteine levels cause endothelial dysfunction in cerebral arterioles at a very low concentration as compared to the same effect produced in the aorta, [65] this explains the vulnerability of cerebral vessels to a very slight change in normal homocysteine value.

6.2. MMD and Inflammatory Disease

Our review included the cases that explained the association of MoyaMoya syndrome with other inflammatory diseases such

as polychondritis [33]. Due to insufficient data, the in-depth association between MMD and inflammatory diseases is not understood, however, a published article explained that in a pediatric population, adult-onset autoimmune diseases are linked with MMD [66, 67]. Japanese national survey published in 2014 stated that inflammatory diseases accounted for 17.2% of quasi-MoyaMoya diseases. Among these, hyperthyroidism, auto-immune diseases, and meningitis were in high percentages. Systemic Lupus Erythematosus (SLE), antiphospholipid antibodies syndrome, polyarteritis nodosa, Kawasaki disease, Sjogren's syndrome, Addison's disease, myasthenia gravis, polymyositis, Rheumatoid arthritis, thyroiditis, systemic sclerosis, etc. were mentioned in minority [67-69].

6.3. Surgical and Medical Interventions

Based on the results obtained in table 2, the common medical interventions used for MMD/thyroid disorders were anti-thyroid drug therapy such as Thiamazole (different doses are stated by different studies), anticoagulants like heparin and clopidogrel, NSAIDs- aspirin- to treat inflammation, beta-blockers like metoprolol to control hypertension, glucocorticoids- methylprednisolone- as an anti-inflammation agent. The most common surgical intervention used was indirect revascularization via Encephalo-Duro-Arterial synangiosis, and direct revascularization by superficial temporal artery to middle cerebral artery bypass.

S. No	First Author	Gender	Age	Lab Values	Radiological Findings	Genetic Abnormalities	Medical Intervention	Surgical Intervention	Outcomes	Symptoms of Moyamoya	Symptoms of Thyroid	Associations
Case Reports												
1	Cai Gao-Rui.	Female.	25	TSH (<0.01 mIU/L), T3 (>10 nmol/L), T4 (>320 nmol/L), FT3 (41.1 pmol/L), FT4 (>100 pmol/L), anti-TPO antibody (352 IU/mL), anti-thyroglobulin antibody (3652 IU/mL), and TRAb (14.1 IU/L).	CT; bilateral parietal and frontal lobe. MRA; Multiple cerebral artery stenosis and occlusion of right MCA.	None.	Antithyroid medication.	-	-	Aphasia, flattening of the left nasolabial fold, and the disability of left upper limb.	-	Graves' disease.
2	Akiko Ishigami MD.	Female.	22	TSH, 01 mIU/mL, TSH receptor antibody 15.8 IU/L thyroid-stimulating antibody (TS-Ab) 885%, FT3 30.2 pg/mL, FT4 7.7 ng/dL.	MRI; infarct in the left MCA. Positron emission tomography; misery-perfusion phenomenon in the left MCA territory.	none	Edaravone, heparin, and thiamazole	-	Good	Right hemiparesis and sensory loss, left conjugate deviation and aphasia.	Exophthalmos and thyroid lobe enlargement.	Thyrotoxicosis
3	SHOU-CHEN REN.	Male.	12	TSH, <0.001 µU/ml, FT3, 29.17 pmol/l, Positive TR-Ab, TPO-Ab; 396.44 U/ml, and TG-Ab; 134.56 U/ml, TSH, 0.027 µU/ml; FT3, 3.21 pmol/l.	MRI; multiple regions of cerebral infarcts, MRA; severe stenosis at the bilateral terminal portion of the ICAs, while the bilateral MCAs and ACAs had almost disappeared infarction.	none	20 mg/day thiamazole, 100 mg/day metoprolol, 30 mg/day Adalat.	Revascularization surgery on the right side, Encephalo Duro arterial synangiosis on the left side.	Good	Rapidly progressive mild quadriplegia, aphasia and urinary incontinence, dysphoric with slurred.	Irritability, tremors, excessive sweating, frequent palpitations and enlarged thyroid gland	Graves' disease.
4	Yasufumi Gon MD.,	Female.	30	TSH ≤0.10 µU/mL; FT3 ≥25.0 pg/mL; FT4 ≥8.0 ng/dL; TPO-Ab, 87 IU/mL; TR-Ab, 18.5 IU/L.	US; distal occlusion pattern in the right ICA artery, T1WI; right ICA was thickened, contrast-enhanced (CE) three-dimensional T1WI; indicating vasculitis.	None.	Clopidogrel 75 mg/day.	Right superficial temporal artery to middle cerebral artery bypass.	-	Intermittent transient dysarthria and limb shaking of the left leg, paralytic dysarthria, left central facial nerve palsy and left hemiparesis.	General malaise.	Graves' disease.
5	Ufuk Utku..	Female.	45	FT3, FT4, TSH, ATG, and anti-TPO 13.8 pg/dL, 5.07 ng/dL, 0.001 IU/mL, 418 IU/mL, and 1000 IU/mL, respectively.	MRI; normal, CT; normal, MRA; severe stenosis was seen in both distal ICAs and arteries distal to the basilar artery.	None.	Methylprednisolone (1000 mg/day), 20 mg/day prednisolone.	-	-	Drowsiness, hallucinations, and incontinence of urine and feces. Weakness on the right side and dysarthria, experience disorientation.	Fine tremor, minimal exophthalmia, and tachycardi, increase Deep tendon reflexes.	Graves' disease.
6	Kenji Kushima.	Case 1: female; Case 2: female.	case 1: 26; Case 2: 22	Case 1: T3 7.7 nmol/L, FT4 >66 pmol/L, TSH of <1.0 mIU/L. Case 2: T3 of 5.5 nmol/L, T4 of 265 nmol/L, TSH of 1.0 mIU/L..	Case 1: CT; resemblance with A-V malformation and a low-density area in the right frontoparietal region. Cerebral Angiography; typical net-like vessels at the base of the brain. Case 2: CT; low-density areas in the right frontal, temporal and parietal lobes. Cerebral angiography; narrowing of both ICAs, and net-like vessels at the base of the brain.	None, none.	Case 1: Anti-thyroid drug therapy, Case 2: anti-thyroid drug therapy.	None.	Case 1: Good. Case 2: Good.	Case 1: not mentioned, Case 2: left hemiparesis and motor aphasia.	Case 1: sensory disturbance in the right upper limb, cramp in the right side face and walking disturbance. Case 2: exophthalmos, and a goiter.	Case 1: Graves' disease. Case 2: Graves' disease.

7	Shiro YAMASHITA.	Female.	29	TSH 0.03ng/dl, anti-thyroid globulin antibody 480%.	MRA; stenosis of the bilateral distal ICAs and the bilateral proximal ACA and MCA. CT and MRI; normal, SPECT; slight reduction in the reserve capacity from the left parietal lobe to the occipital lobe.	-	Thiamazole (15mg/day) and aspirin (81mg/day).	-	Good.	Transient aphasia and numbness in extremities.	Vomiting, diarrhea, and fever over 38 C.	Basedow disease.
8	Ai-Ling Shen.	Female.	23	Triiodothyronine (T3) was 5.76 nmol/L, the free thyroxine (FT4) was > 111 pmol/, and her thyroid-stimulating hormone (TSH) was < 0.03 mU/.	Duplex sonography; the smaller caliber of the right ICA with reduced volume flow, MRI; small infarcts in the right centrum semiovale, MRA; segmental narrowing of the right cervical ICA and strictures at the supraclinoid portion of bilateral ICAs, DSA; irregular tubular stenosis of the right cervical ICA and nearly complete occlusion of bilateral supraclinoid ICAs with tortuous collaterals supplying bilateral ACAs and MCAs.	-	Aspirin 100 mg/day, propiothiouracil 150 mg/day and propranolol 30 mg/day, Ticlopidine (250 mg/day) (for the replacement of aspirin).	-	Good.	Weakness and numbness in her left limbs with mildly slurred speech.	Blood pressure was 138/54 mmHg and pulse rate was 113/min, mitral valve prolapse.	Autoimmune thyroid disease.
9	Takafumi Shimogawa.	Female.	43	TSH level of 0.015 μU/mL, FT3 level of 26.42 pg/mL, and FT4 level of 4.37 ng/d., TSH receptor antibody level was 36.7%.	MRI; hyper intense area at the left posterior limb of the internal capsule. MRA and 3D-CTA; bilateral severe stenosis of the distal ICA and proximal MCA and ACA. Digital subtraction angiography; Moyamoya vessels in the left basal ganglia and bilateral stenosis of the distal ICA and proximal MCA and ACA.	-	-	Encephalo-duro-arterio-synangiosis and encephalo-myo-synangiosis.	Good.	Right hemiparesis and dysarthria.	-	-
10	ByoungHo H. Noh.	Female.	16	TSH < 0.001 U/mL, FT4 9.1 ng/dL and T3 7.24 ng/mL, thyroid-stimulating immunoglobulin (16.04 IU/L), anti-TPO-Ab (254.8 U/mL).	DWI; revealed multiple acute infarcts on both hemispheres, MRA; showed stenosis of both distal ICA, and both M1 portions of the MCA,	-	Methimazole (20 mg every 6 h), hydrocortisone (100 mg every 8 h) and 5% Lugol solution (KI 25 mg every 6 h).	-	Good.	Right hemiplegia	Dehydrated tongue and a grade II goiter. increased appetite and polyphagia feeling hot, sweaty, agitated and confused	DKA, hyperthyroidism, auto-immune thyroiditis, DM 1, DIC
11	Chong Kun Cheon.	Case 1: Female; Case 2: Female.	case 1: 12 Case2; 15	Case 1: T3, FT4, TSH, and TSH receptor antibody; 213.36 ng/dL , 1.64 ng/dL , 0.24 uIU/mL , 112.66 U/L , respectively. Case 2: T3, FT4, TSH, and TSH receptor antibody was 1.07 ng/mL , 0.99 ng/dL , 0.01 uIU/mL , 34.1 U/mL , respectively.	Case 1: MRA, cerebral 4-vessel angiography; typical stenosis of the right MCA, SPECT; cerebral hypo perfusion of the right parietal lobe and decreased vascular reserves of both occipital lobes. Case 2: MR; focal hemorrhage at the left insula, basal ganglia, and focal enhancing nodule, with small collateral vessels in basal ganglia and obliteration of both ICA, Cerebral angiography; typical stenosis of the ICA and MCA, SPECT; cerebral hypoperfusion of the left parietal lobe, left thalamus, left basal ganglia, and medial temporal lobe without vascular reserve.	-	Case 1: Methimazole 20 mg daily, Case 2: 10 mg of methimazole daily.	Case 1: cranial revascularization by encephaloduroarterio-synangiosis (EDAS), Case 2: cranial revascularization by EDAS.	Good in both	Case 1: syncope with hyperventilation, Case 2: right-sided hemiparesis, along with the headache of 3 days' duration.	Case 1:-, Case 2: goiter and central type sided facial palsy.	Case 1: graves disease, case 2: graves' disease.

12	Jong Han Gill.,	Female.	43	(TSH) < 0.01 μ units/mL; T3 > 8.0 ng/mL, FT4 of 9.47 pmol/L, and TSH receptor antibody of 37.10 U/L.	MRI= small cerebral infarction in the left frontal lobe. 2nd MRI; infarction markedly increased. Angiography; revealed occlusion of both distal ICAs, with the characteristics of Moyamoya vessels and poor collateral flow in both frontal lobes.	-	Hydration and antiplatelet therapy, anticonvulsant, amiodarone, beta-blockers, methimazole, Gemstein's solution, and hydrocortisone.	-	Good.	Weakness in her right side, level of consciousness became stuporous after the anti platelet therapy, seizure.	-	Atrial fibrillation with a rapid ventricular response (RVR), cardiomegaly, hyperthyroidism.
13	Yi-Yi Xuan.	Female.	26	FT3, FT4, TSH; 5.56 (3.28–6.47) pmol/L, 16.75 (7.9–18.4) pmol/L, and 0.01 (0.34–5.6) uIU/mL, respectively. Thyroid hormone antibody (TRAB) was 5.16 (0–1.75) IU/L.	CT; multiple ischemic foci in the deep white matter in the left frontal lobe, MRA; intracranial segment of the left ICA and the distal segment of the right distal CA were markedly thin, MRI; A near-complete occlusion was found in the M1 segment of the right MCA with sparse distal branches. The left posterior cerebral artery was also thin, with sparse distal branches.	-	Prednisone (30 mg/d) and oral CTX (100 mg/d). Iodine-131 (I131) therapy, CTX was stopped and azathioprine; prednisone was gradually tapered to 7.5mg/d.	-	Good.	-	-	Graves disease, ANCA positive relapsing polyorchondritis.
14	Hiroshi tokimura.	Case1 : Female Case2: Female	Case1 : 19 Case2 :52	TSH : 39.51 u/ml FT3: 2.4 pg/dl FT4 : 0.83 ng/dl,	Case1: MRI; Infarction in the left parietal lobe, Cerebral angiography; Occlusion of terminal portion of the bilateral ICAs and both MCAs and ACAs, Case2 : Carotid angiography; stenosis of terminal portion pf the ICA and ACA and occlusion of the MCA.	-	-	Case1 : Revacularization using a spuercial temporal artery Case 2: STA and MCA anastomosis.	Good.	Case1: Dysesthesia of 3rd-5th digits of hands Case2: none	Case1: Numbness of right hand. Case 2: Tachycardia and excessive sweating.	Case1; Hypothyroidism Case2 : Hyperthyroidism.
15	Sakiko Suzuki.	Case1: Male. Case2: Female.	Case1 : 38 Case2 :43	Case1: TSH <0.01 IU/ml; FT3 13.08 pg/ml; and FT4 4.81 ng/dl Case 2 : TSH <0.010 IU/ml; FT3 20.16 pg/ml; and FT4 7.12 ng/dl.	Case1 : Cerebral angiography; stenosis of the terminal portion of bilateral ICA and the proximal portion of left MCA, MRI and MRA; infarction in the watershed area in the left hemisphere and moyamoya vessels around the circle of Willis Case 2 : MRI; cerebral infarction in the deep white matter of the right frontal region .Cerebral angiography; stenosis in the terminal portion of right ICA with moyamoya vessels around the circle of Willis.	-	Case 1: Insulin and thiomazole Case 2: insulin and thiamazole.	Case 1: Superficial temporal artery (STA)–MCA double bypass on the left side. Case2: STA–MCA double anastomoses on the right side.	-	Case1: left radial nerve palsy Case2: let hemiparesis of 3/5 MMT	Case1: TIA in right upper extremity Case 2 : numbness in the left hand. left hemiparesis.	Graves disease in both cases.
16	Fumihiro Matano.	Female.	52	-	MRA; bilateral supraclinoid stenosis of the ICA decrease CA blood flow. MRI; increase in ischemic lesions in the bilateral hemiparesis DWI; ischemic lesions in the right hemisphere. SPECT; showed new ischemic lesions in the right hemiparesis.	Heterozygous variant of the RNF213.	Levothyroxine sodium 300 μ g/2x and simvastatin 10 mg/2x.	-	-	Bilateral hemiparesis.	-	MEN 2A.

17	BEATRIZ E. TENDLER.	Case1: Female. Case2: Female.	Case1 : 37 Case2 : 47	Case1: TSH <0.1 / iU/mL, and T4 26.1 µg/L [5.0-10.5] TT3; 289 ng/dL. Case2: TSH <0.1 µ /mL, T4 15.9 Ag/ dL, TT3 of 289 ng/ dL, FTI of 19 and thyroid stimulating immunoglobulin (TSI) of 1,844% of basal activity	Case1: CT; localized hypodense area in the right frontal lobe consistent with a right frontoparietal infarct. Carotid angiogram; nearly complete occlusion of the right supraclinoid ICA, and tortuous collaterals supplying the territory of both the right MCAs and, to a lesser degree, the right ACAs Duplex ultrasound; Nothing found	-	Case1 : enteric-coated aspirin, 325 mg/day, propylthiouracil, 100 mg TID, prednisone Case2 : radioactive iodine, prednisone 40 mg/day, cholestyramine 3 g/ day, and atenolol 75 mg/day.	Case1 : subtotal thyroidectomy Case2 : -	Good in both.	Case1 : paresthesias of the left hand and left arm weakness. Case2 : diplopia and weight loss.	Lid retraction. A diffusely enlarged thyroid gland.	Case1; graves disease Case 2; graves disease.
18	Kathryn B.	Female.	40	TSH < 0.05 mIU/L, FT4 6.39 ng/dL, and TPO-Ab level of 687 IU/mL.	CT: bilateral MCA infarcts involving the right frontal lobe and bilateral parietal lobes. MRA: revealed extensive narrowing of the bilateral ICA and branches. These findings were suggestive of vasculitis.	-	Steroid.	-	GOOD.	Left-sided facial numbness and cramping, drooling, and aphasia. dizziness, paresthesias, left-sided tingling, and near-syncope.	Exophthalmos and incomprehensible speech. large palpable goiter.	HYPERTHYROIDISM.
19	Meng-Han Tsai,	MALE.	26	FT4: 2.22 ng/dL, T4: 29.6 ug/dl, T3: 486 ng/dl, TSH 0.003 uIU/ml).	MRI; infarction at posterior limb of right internal capsule. Cerebral angiography; multiple intracranial artery stenosis. Carotid duplex; not significant.	-	propylthiouracil (PTU)	-	GOOD.	Episodic transient left hemiparesis and mild slurred speech lasting for few minutes to 2 hours for one month	Heat intolerance, excessive sweating and palpitation, weight loss and hand tremor. Enlarged thyroid gland	GRAVES AND HYPERTHYROID STATE
20	Shigeo ohba.	FEMALE.	46	FT3, FT4, and TSH were 1.1 pg/ml, 0.4 ng/dl, and 53.8 µU/ml, respectively.	MRI; lacunar infarction and severe stenosis of both ICAs MRA; severe stenosis of the terminal portion of both ICAs. Net-like moyamoya vessels were also detected SPECT; revealed a bilateral decrease in blood flow	-	-	Open surgery with left STA- MCA bypass. Right STA-MCA bypass with encephalomyosynangiosis.	Good	Transient weakness and numbness in her right upper limb, muscle pain, feeling of cold, and weight gain.	-	Graves' disease, thyroid tumor
Literature Reviews												
1	Shaneela Malik.	Female.	23.	TSH level, 0.04 uIU/ mL. TPO-Ab.1300 U/mL; normal, .60 U/mL, FT4; 11.48 ng/dL.	MRI; acute ischemic infarctions in the left hemisphere MRA; tapering occlusive process of the bilateral intracranial ICAs and significant narrowing of the bilateral proximal PCAs, proximal right MCA, and right ACA Catheter angiography; near occlusion of the bilateral carotid arteries distal to the ophthalmic artery.	-	Atenolol, propylthiouracil, methylprednisone, and aspirin and plasmapheresis. Left arteriomyodural synangiosis.	-	Good.	Right arm weakness, fluctuating confusion, facial numbness, and difficulty with speech.	Exophthalmos.	Grave disease.

2	Takahiro Sasaki.	Case1: Female. Case2: Female. Case3: Female.	Case1 : 27 Case2 : 16 Case3 : 36	CASE 2; TSH, 0.08 µU/ml; fT3 5.5 ng/dl; fT4 1.4 ng/dl; TSH receptor antibody, TRAb 56.4% CASE 2; TSH 0.01 µU/ml; fT3 9.4 ng/dl; fT4 3.1 ng/dl. CASE 3; TSH<0.1 µU/ml; fT3 4.0 ng/dl; fT4 1.5 ng/dl; TRAb 2.9%, antithyroglobulin antibody, TGAb <0.3 U/ml, anti-thyroid peroxidase antibody, TPO Ab 65.0 U/ml.	CASE1; T2WI and MRI; multiple ischemic lesions in the right upper frontal lobe and in the left paraventricular region, SPECT; decreased regional cerebral blood flow in the right MCA region, Angiography; long narrowed segments at the cervical portions of both ICAs, MRI; hemorrhagic infarction. CASE 2: MRI and MRA; cerebral infarction in the right frontal lobe and stenosis of the distal portion of bilateral ICAs, Angiography = long narrowed segments at the cervical portions of both ICAs, and occlusion of the right anterior cerebral artery. CASE 3: MRI; high-density lesions on T2WI in the deep white matter of the left cerebral hemisphere, SPECT; decreased regional cerebral blood flow in the left ICA region, Angiography; long narrowed segments at the cervical portions of the left ICA and perfusion by superficial temporal artery via a trans-dural anastomosis	-	CASE 1: anti-thyroid hormone CASE 2; none. Case 3: anti-thyroid medication	Case 1: encephalo-duro-arteriosynangiosis (EDAS) Case2: encephalo-duro-arteriosynangiosis (EDAS) Case 3; none.	Case1; Good. Case 2; good. Case 3; good.	CASE1; transient attacks of dizziness and left hemiparesis, dysarthria and headache, exaggerated deep tendon reflexes in the left extremities with a dorsiflexed plantar response on the left CASE 2; TIAs CASE 3; aphasia,exaggerated deep tendon reflexes in the right extremities with a dorsiflexed plantar response on the right side	-	
3	Hiroto Ito,	Female.	37	levels of fT3, fT4, and TSH; 10.58 pg/mL, 2.70 ng/dL, and 0.01 µU/mL, respectively, anti-TPO Ab, 148.0IU/mL, TRAb, 8.3 IU/mL	DWI; cortical and subcortical infarcts in the left MCA territory, MRA; almost-normal cerebral arteries or very mild stenosis of the left ICA, MRI; thick vessel walls in the left ICA than in the right on three-dimensional (3D)-T1WI AFTER 5 MONTH; stenosis of the left ICA from the proximal to distal portion and CBN, MRI; High-intensity lesion on T1 W1 in the distal portion of the left ICA was observed AFTER 2 YEARS; catheter angiography; improved blood flow in the left ACA, MCA, and ICA, as well as mild improvement of stenosis of the terminal portion of the left ICA.	c.14576G>A (rs112735431) in the RNF-213 gene.	Potassium iodide, heparin, warfarin, argatroban, methylprednisolone (IVMP; 1000 mg/day on days 2–6) clopidogrel (300 mg on day 1, and 75 mg/day from day 2), and aspirin (300 mg on day 1, and 100 mg/day from day 2), Methimazole (15 mg/day), prednisolone (PSL; 1 mg/kg/day),methotrexate (MTX; 4mg/week)	None stated.	Good.	Progressing weakness of the right arm, mild paralysis of the right arm.	Felt palpitation and sweating at times.	Felt palpitation and sweating at times.
4	Chang Y. Tsao.	Female.	10	T3 570 ng/dL, a fT3 20.3 pg/mL, T4 22.1 g/dL, fT4 8.8 ng/dL, TSH 0.013 IU/mL, thyroidstimulating immunoglobulin 89% , a positive antithyroglobulin antibody of 6.2 U/mL, positive antithyropoxidase antibody of 28.7 U/mL.	MRI; infarction in the right posterior frontal lobe and right anterior parietal lobe as well as a small infarct in the left frontal lobe MRA; narrowing of both MCA, the right greater than the left		Aspirin and verapamil.	Cranial revascularization by pial synangiosis.	-	Weakness of left side.	Fatigue, loose stools, and episodes of feeling warm.	Grave disease.

5	S.W. Hsu.	Female.	40	F T4, 18 ng/dL; TSH, 0.22 µM/mL.	Cerebral angiography= Bilateral distal ICA and proximal MCA and ACA occlusion. CT; multiple areas of cerebral ischemia.	-	-	-	Bad.	-	Nausea, vomiting, tremors..	Grave disease.
6	Shigeo Ohba.	Female.	34.	FT3, fT4, and TSH were 1.1 pg/ml , 0.4 ng/dl , and 53.8 µU/ml, respectively.	MRI and MRA; lacunar infarction and severe stenosis of both ICAs, SPECT; bilateral decrease in blood flow.	-	Levothyroxine.	left (STA)- MCA bypass. Right STA-MCA bypass with encephalomyosynangiosis	Good.	Transient ischemic attack (TIA).	-	Grave disease.
7	Ran lee.	Female.	19	TSH level 0.001 microunits/mL, T3 level 681 ng/dL, free T4 level 6.0 ng/dL.	Cerebral angiography; bilateral occlusion of the ICA around the supraclinoid segment with some collateral vessels.	-	Propylthiouracil.	Cranial revascularization by EDAS and EMS.	Good.	Central type right facial palsy and episodic transient right-side hemiparesis	Diarrhea and a neck mass.	Grave disease.
8	Julian Choi.	Female.	31	TSH, <0.005 IU/mL; T4, 23.07 µg/dL; Total T3, >651 ng/dL	CT; no acute pathology initially, CTA; complete occlusion of left ICA and severe stenosis of right ICA with stenosis of the M1 and A1 segments with posterior communicating arteries supplying bilateral anterior territories, MRI; restricted diffusion abnormality in the left frontal cortex with associated abnormal T2 and FLAIR signal changes consistent with an acute left frontal cortical infarction.	-	Popranolol 40 mg po Q8 h, and methimazole 10 mg po Q8 h, and antiplatelet therapy, phenytoin, lorazepam levetiracetam and valproate.	Bilateral frontotemporoparietal craniotomy. Bilateral EMS.	Bad.	Progressive right-sided weakness, sluggish and unsteady gait, right facial droop, right arm flaccid paralysis, right leg weakness, absent right shoulder shrug, and right-sided hyperreflexia.	Pupils were 3 mm and reactive to light, exophthalmos.	Graves disease.
8	Hotaka Kamasaki.	Male.	14	TSH= less than 0.1 micro IU/ml, FT4= 3.41ng/dl (elevated), FT4=4.31ng/dl, FT3= 10.08 pg/ml, TSH= less than 0.1, TGAb= 33.6 IU/ml, TPOAB=33.6-positive, TRAB=13.3%-negative, TSAB=135%-negative.	MRI; small infarct in the left anterior white matter. SPECT; decreased blood flow to the left anterior lobe. MRA; bilateral carotid stenosis and collaterals.	-	Anti-thyroid therapy: Thiamazole (MM, 20mg/day), Potassium iodide (KI, 200mg/day), bidoprolol fumerate (5 mg/day).	EDAS.	Good.	Weakness of right arm for 12 months, Soft bruise over the cervical vessels.	Fever, HR 120-150, SBP 130-160, mild exophthalmos and a soft goiter, tremor of both hands.	Graves' disease
9	Fumihiro Matano.	Case 1: female, case 3: female, case 4: male	Case 1: 32, case 3: 55, case 4: 53	Case 1: TSH, 0.116 µU/mL; fT3, 4.98 ng/dL; fT4, 2.47 ng/dL. The TSH receptor antibody 30.7. Case 3: TSH, 0.032 µU/mL; fT3, 5.18 ng/dL; fT4, 2.50 ng/dL. The TSH receptor antibody 15.2 % and TSAb 319 %. Case 4: TSH, 2.07 µU/mL; fT3, 3.96 ng/dL; fT4, 1.88 ng/dL. TSAb was 189 % (>180 %).	Case 1: MRI; cerebral infarction in the right frontal lobe, cerebral angiography; bilateral ICA stenosis, SPECT; perfusion defect in the right frontal region. Case 3; CT; intracerebral hemorrhage in the left frontal lobe, cerebral angiography; bilateral ICA stenosis and right ICA aneurysm. Typical net-like moyamoya vessels were observed. Case 4; MRI; cerebral infarction in the bilateral frontal lobe, cerebral angiography; bilateral ICA stenosis and typical net-like moyamoya vessels.	-	Case 1: Anti-thyroid therapy. Case 3: anti-thyroid therapy, Case 4: Conservative therapy with somatostatin.	Case 1: STA- MCA bypass surgery with encephalogaesyangiosis and EMS. Case 3: none. case 4: none.	Case 1: good. Case3: good. Case 4: good.	Case 1: none stated. Case 3: right hemiparesis, motor aphasia.	Case 1; BP= 110/60, bilateral enlargement of thyroid gland. Case 3: blood pressure was 120/70 mmHg. Case 4: none stated.	Case 1: hyperthyroidism, Case 3: hyperthyroidism Case 4 : hyperthyroidism.

10	Hikaru nakamura.	Female.	19.	FT3, FT4, and TSH of 2.91 pg/dL, 1.34 ng/ dL, and 1.048 mIU/mL, respectively	MRI; a cerebral infarction extending from the right occipital lobe to the parietal lobe an abnormal vascular network at the cerebral basal area and a champagne bottle-like change of the right cervical ICA SPECT; decreased resting local cerebral blood flow of up to 65% in the territory of the right MCA as compared to the contralateral side.	-	-	STA-MCA anastomosis and EDMS.	Good.	Sudden left-sided hemiparesis.	Fever, diarrhea, and weight loss.	Grave disease.
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Abbreviations: TSH= Thyroid-Stimulating Hormone, FT4= Free Thyroxine, FT3= Free Tri-Iodothyronine, T4= Thyroxine, T3= Tri-Iodothyronine, TR-Ab= Thyrotropin Receptor Antibody, TPO-Ab= Thyroid Peroxidase Antibody, TG-Ab= Thyroglobulin Antibody, ATG= Anti-Thymocyte Globulin, US= Ultrasound, CT= Computed Tomography, 3D-CTA= Three-Dimensional Computed Tomography Angiography, MRI= Magnetic Resonance Imaging, MRA= Magnetic Resonance Angiography, DWI= Diffusion-Weighted Imaging, ICA= Internal Carotid Artery, MCA= Middle Cerebral Artery, ACA= Anterior Cerebral Artery, PCA= Posterior Cerebral Artery, CTX=Cefotaxime, STA-MCA bypass= Superficial Temporal Artery- Middle Cerebral Artery bypass, EDAS= Encephalo-Duro-Arterio-Synangiosis, EMS= Encephalo-Myo-Synangiosis, EDMS= Encephalo-Duro-Myo-Synangiosis.

Table 2: Characteristics of the Case Reports and Literature Reviews.

The review of the databases and other google websites was carried out with the intention of discovering any new surgical method that has been or is being designed to treat MMD with a low post-surgical complications rate, we found no such methods. The after-surgery complications of treating moyamoya syndrome using the direct and indirect revascularization methods are reported by a few articles [70-71]. According to the study, Transient Cheiro-Oral Syndrome (COS) is not rare after surgical revascularization for MMD [71].

6.4. Limitations and Strengths

The current review is able to include all the cases explaining the

correlations between MMD and thyroid disorders present in the major databases. Following point 3 of the inclusion/exclusion criteria, we were not able to present systematically in detail, the other associations of MMD, for instance, with atherosclerosis, inflammatory diseases, high serum homocysteine levels, etc. however, these associations were covered briefly in the discussion section. Another limitation in the review is, that the case that we presented in the review was not documented with all the aspects included, for example, surgical intervention (if applicable) was not present, and the vitals were not taken. Being the first review to present a Pakistani MMD case is the strength of this review.

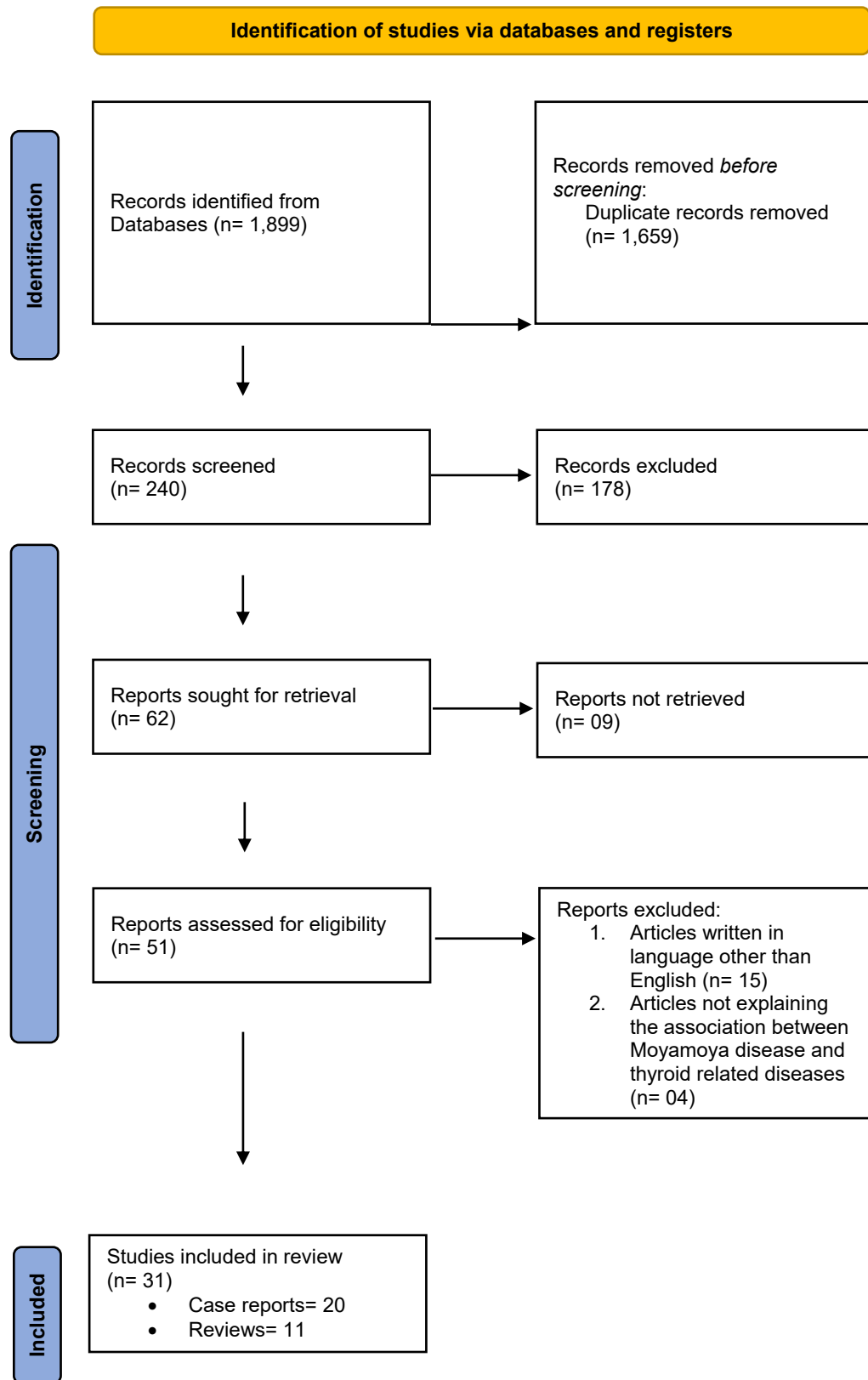


Figure 1: Prisma Flow Diagram.

7. Conclusion

Comparing a Pakistani case with the other cases has proven the hypothesis that the management of MMD is similar in Pakistan as in other countries. However, the authors are with the suggestion that more cases of MMD and its association with other major factors should be presented in Pakistan as well as in all parts of the world. An in-depth understanding of all the associations may be crucial in formulating a new surgical intervention for MMD with a low rate of post-surgical complications.

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