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.
Moyamoya disease (MMD) is a rare progressive vasculocclusive 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 3D-CTA= Three-Dimensional Computed Tomography Angiography. 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 angiogenic 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

### 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 is a rare progressive vasculocclusive 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.

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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 ulU/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, 31, 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].

<table>
<thead>
<tr>
<th>S. No.</th>
<th>First author</th>
<th>Published year</th>
<th>Gender</th>
<th>Age</th>
<th>Race</th>
<th>Comorbid</th>
<th>Past drug history</th>
<th>Past medical history</th>
<th>Past surgical history</th>
<th>Thyroid Status</th>
<th>Vitals</th>
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<td>25</td>
<td>None</td>
<td>None stated</td>
<td>None stated</td>
<td>None stated</td>
<td>None stated</td>
<td>Hyperthyroidism</td>
<td>None stated</td>
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<tr>
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<td>Female</td>
<td>22</td>
<td>Japanese</td>
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<td>None stated</td>
<td>None</td>
<td>None</td>
<td>Hyperthyroidism</td>
<td>None stated</td>
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<tr>
<td>3</td>
<td>SHOU-CHEN REN1 [15]</td>
<td>2015</td>
<td>Male</td>
<td>12</td>
<td>Chinese</td>
<td>Over activation of factor VIII and von- Willebrand factor</td>
<td>None stated</td>
<td>Suffered with excessive sweating, tremors and irritability</td>
<td>None stated</td>
<td>None stated</td>
<td>None stated</td>
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<td>4</td>
<td>Yasufumi Gon [16]</td>
<td>2016</td>
<td>Female</td>
<td>30</td>
<td>Japanese</td>
<td>None stated</td>
<td>None stated</td>
<td>Malaise 3 weeks back and Graves disease.</td>
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<td>Hyperthyroidism</td>
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<tr>
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<td>Ufuk Utku [17]</td>
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<td>Female</td>
<td>45</td>
<td>None</td>
<td>None stated</td>
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<tr>
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<td>29</td>
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<td>None stated</td>
<td>None stated</td>
<td>None</td>
<td>None</td>
<td>Basedow Disease</td>
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<td>2006</td>
<td>Female</td>
<td>23</td>
<td>None</td>
<td>None stated</td>
<td>Migraine like headache</td>
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<tr>
<td>9</td>
<td>Takafumi shimogawa [21]</td>
<td>2014</td>
<td>Female</td>
<td>43</td>
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<td>None stated</td>
<td>None</td>
<td>None</td>
<td>Hyperthyroidism</td>
<td>None stated</td>
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<tr>
<td>10</td>
<td>ByoungHo H. Noh [22]</td>
<td>2015</td>
<td>Female</td>
<td>None</td>
<td>None</td>
<td>DM 1, DKA</td>
<td>Methimazole (20 mg every 6 h), followed by hydrocortisone (100 mg every 8 h) and 5% Lugol solution (KI 25 mg every 6 h).</td>
<td>None stated</td>
<td>Hyperthyroidism</td>
<td>HR= 212 beats/ min, BP= 130/70 mm Hg fever= 36.3°C.</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Jong Han Gill [24]</td>
<td>2021</td>
<td>Female</td>
<td>43</td>
<td>None</td>
<td>None stated</td>
<td>None stated</td>
<td>None</td>
<td>Hyperthyroidism.</td>
<td>Hyperthyroidism was diagnosed after moyamoya diagnosis.</td>
<td>None stated.</td>
</tr>
<tr>
<td>Case</td>
<td>Name</td>
<td>Year</td>
<td>Gender</td>
<td>Age</td>
<td>Race/ethnicity</td>
<td>Diagnosis</td>
<td>Medications</td>
<td>Symptomatology</td>
<td>Treatment</td>
<td>Complications</td>
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<td>----------------</td>
<td>-----------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Yi-Yi Xuan</td>
<td>2017</td>
<td>Female</td>
<td>26</td>
<td>None stated</td>
<td>PTU</td>
<td>None stated</td>
<td>October 2015, red swelling and pain in both eyes</td>
<td>None stated</td>
<td>Graves’ disease</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Hiroshi Tokimura</td>
<td>2010</td>
<td>Case 1: Female</td>
<td>Case 2: Japanese</td>
<td>Case 1: None stated</td>
<td>Case 2: Hypertension and hyperlipidemia</td>
<td>None stated</td>
<td>Case 1: Thyroidectomy</td>
<td>None stated</td>
<td>Case 1: Hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Sakiko Suzuki</td>
<td>2011</td>
<td>Case 1: Male</td>
<td>Case 2: Japanese</td>
<td>Case 1: Insulin and thiamazole</td>
<td>Case 2: Diabetes mellitus and hyperthyroidism</td>
<td>None stated</td>
<td>Case 1: None stated</td>
<td>Case 1: Hyperthyroidism</td>
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<td></td>
</tr>
<tr>
<td>16</td>
<td>Fumihiro Matano</td>
<td>2021</td>
<td>Female</td>
<td>52</td>
<td>None stated</td>
<td>Pheochromocytoma</td>
<td>Stage T2N1M0 and left-sided pheochromocytoma</td>
<td>Thyroidectomy and left central neck D2a dissection</td>
<td>None stated</td>
<td>None stated</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>BEATRIZ E. TENDLER</td>
<td>1997</td>
<td>Case 1: Female</td>
<td>Case 2: Hispanic</td>
<td>Case 1: None stated</td>
<td>Case 2: None stated</td>
<td>Propylthiouracil 400 mg, metoprolol 50 mg, atenolol 25 mg, propylthiouracil 100 mg, TID, and prednisone 30 mg daily</td>
<td>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.</td>
<td>None stated</td>
<td>Hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Kathryn B.</td>
<td>2017</td>
<td>Female</td>
<td>40</td>
<td>None stated</td>
<td>Antibiotics and hydroxyzine for tooth ache, anxiety. Current chronic medications included methimazole, atenolol, and insulin for autoimmune diabetes.</td>
<td>None stated</td>
<td>None stated</td>
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<td>19</td>
<td>Meng-Han Tsai</td>
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<td>Male</td>
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<td>None stated</td>
<td>None stated</td>
<td>None stated</td>
<td>None stated</td>
<td>Hyperthyroidism</td>
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**Notes:**
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- **Table continues...**
Literature Review

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<th>Case</th>
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<th>Gender</th>
<th>Age</th>
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<th>Diagnosis</th>
<th>Medication</th>
<th>Procedure</th>
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<th>Follow-up</th>
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<td>None stated</td>
<td>Grave disease</td>
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<td>Female</td>
<td>20</td>
<td>Caucasian</td>
<td>Headaches</td>
<td>brompheniramine and pseudoephedrine</td>
<td>None</td>
<td>None stated</td>
<td>None stated</td>
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<td>3</td>
<td>2019</td>
<td>Female</td>
<td>37</td>
<td>None stated</td>
<td>None stated</td>
<td>None stated</td>
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<td>Female</td>
<td>31</td>
<td>Hispanic</td>
<td>Graves' disease</td>
<td>Propranolol and methimazole</td>
<td>None stated</td>
<td>None stated</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>6</td>
<td>2010</td>
<td>Female</td>
<td>34</td>
<td>None stated</td>
<td>None stated</td>
<td>Thyamazole and levothyroxine and antilplatelet drug</td>
<td>None stated</td>
<td>None stated</td>
<td>Subtotal thyroidectomy</td>
</tr>
<tr>
<td>7</td>
<td>2013</td>
<td>Male</td>
<td>14</td>
<td>None stated</td>
<td>None stated</td>
<td>None stated</td>
<td>None stated</td>
<td>None stated</td>
<td>Thyrotoxicosis</td>
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<td>2013</td>
<td>Female</td>
<td>19</td>
<td>Korean</td>
<td>Down syndrome &amp; Grave disease</td>
<td>Propylthiouracil</td>
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<td>None stated</td>
<td>Hyperthyroidism</td>
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<td>9</td>
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<td>19</td>
<td>None stated</td>
<td>None stated</td>
<td>Down syndrome &amp; grave disease</td>
<td>None stated</td>
<td>None stated</td>
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</table>

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 1.9 ng/
30 published cases were studied. The results are shown in Table 1. Regularity was noticed under these three headings when more than any drug intervention. This hypothesis was termed false after no surgery that could induce it, or can this disease be the side effect of associated with any sort of pathology that occurred in the past, any drug, and surgical history was to understand in-depth if MMD is also reported in our case. The reason for including the past medical, reviewing an enormous number of cases, it was observed that the management of the patients, the interventions used, etc. Upon similar cases of MMD diagnosed around the world, the diagnosis, thyroid disorders in a Pakistani patient. It further correlates the 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, Besadow 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 homocysteines 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, 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.

<table>
<thead>
<tr>
<th>No.</th>
<th>First Author</th>
<th>Gender</th>
<th>Age</th>
<th>Lab Values</th>
<th>Radiological Findings</th>
<th>Genetic Abnormalities</th>
<th>Medical Intervention</th>
<th>Surgical Intervention</th>
<th>Outcomes</th>
<th>Symptoms of Thyroid</th>
<th>Symptoms of Moya</th>
<th>Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cai Gao-Rui</td>
<td>Female</td>
<td>25</td>
<td>TSH (&lt;0.01 mIU/L), T3 (&gt;10 nmol/L), T4 (&gt;520 nmol/L), Anti-TPO antibody (332 IU/ml), Anti-thyroglobulin antibody (562 IU/mL), and TRAB (14.1 IU/L).</td>
<td>CT: bilateral parietal and frontal lobe. MRA: Multiple cerebral artery stenosis and occlusion of right MCA.</td>
<td>None.</td>
<td>None.</td>
<td>Antithyroid medication.</td>
<td>-</td>
<td>-</td>
<td>Apathy, flattening of the left nasolabial fold, and the disability of left upper limb.</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Akiko Ishigami MD</td>
<td>Female</td>
<td>22</td>
<td>TSH, 0.01 mIU/mL, TSH receptor antibody 15.8 IU/L, thyroid-stimulating hormone 0.001 µU/ml, FT4 (-400 IU/mL), FT3 (3.6 pg/ml), and FT3 (2.7 ng/dl).</td>
<td>MRI: infarct in the left MCA. Position emission tomography: misery-perfusion phenomenon in the left MCA territory.</td>
<td>None.</td>
<td>None.</td>
<td>Edaravone, heparin, and thiamazole.</td>
<td>-</td>
<td>Good</td>
<td>Right hemiparesis and sensory loss, left conjugate deviation and aphasia.</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>SHOU-CHEN REN.</td>
<td>Male</td>
<td>12</td>
<td>TSH: &lt;0.001 µU/ml, FT3: 29.17 pg/mL, Positive TR-Ab, TPO-Ab: 396.44 U/ml, and TG-Ab: 134.56 U/ml, TSH: 0.027 µU/ml, FT3: 1.21 pg/mL.</td>
<td>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.</td>
<td>None.</td>
<td>20 mg/day thiamazole, 50 mg/day prednisolone, 30 mg/day Adalat.</td>
<td>None.</td>
<td>Thyrotoxicosis.</td>
<td>Revascularization surgery on the right side. Encephalo-Duro arterial synangiosis on the left side.</td>
<td>Good</td>
<td>Rapidly progressive mild quadriparesis, aphasia and urinary incontinence, dysphoric with staring.</td>
</tr>
<tr>
<td>5</td>
<td>Ufuk Ukuu.</td>
<td>Female</td>
<td>45</td>
<td>FT3, FT4, TSH, ATG, and anti-TPO 13.8 pg/dL, 5.07 mg/dL, 0.001 IU/mL, &lt;18 IU/mL, and 1000 IU/mL, respectively.</td>
<td>MRI: normal, MRA: severe stenosis was seen in both distal ICAs and arteries distal to the basilar artery.</td>
<td>None.</td>
<td>None.</td>
<td>Methylprednisolone (1000 mg/day) 20 mg/day prednisolone.</td>
<td>None.</td>
<td>Methylprednisolone (1000 mg/day)</td>
<td>Drowsiness, hallucinations, and incontinence of urine and feces. Weakness on the right side and dysarthria, experience disorientation.</td>
<td>Fine tremor, minimal exophthalmal, and tachycardia, increase Deep tendon reflexes.</td>
</tr>
<tr>
<td>Case</td>
<td>Name</td>
<td>Sex</td>
<td>Age</td>
<td>TSH level</td>
<td>FT3 level</td>
<td>FT4 level</td>
<td>TSH receptor antibody</td>
<td>MRI findings</td>
<td>MRA findings</td>
<td>Treatment</td>
<td>Outcome</td>
<td>Comments</td>
</tr>
<tr>
<td>------</td>
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</tr>
<tr>
<td>7.1</td>
<td>Shino</td>
<td>Female</td>
<td>29</td>
<td>0.03 ng/dL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Methimazole (15 mg/day) and aspirin (81 mg/day).</td>
<td>Good.</td>
<td>-</td>
</tr>
<tr>
<td>7.2</td>
<td>YAMASHITA.</td>
<td>Female</td>
<td>29</td>
<td>TSH 0.03 ng/dL, anti-thyroid globulin antibody 480%.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Methimazole (15 mg/day) and aspirin (81 mg/day).</td>
<td>Good.</td>
<td>-</td>
</tr>
<tr>
<td>8.1</td>
<td>Ai-Ling Shen.</td>
<td>Female</td>
<td>23</td>
<td>Triiodothyronine (T3) was 5.76 nmol/L, the free thyroxine (FT4) was &gt; 111 pmol/L, and her thyroid-stimulating hormone (TSH) was &lt; 0.03 mU/L.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Aspirin 100 mg/day, propiothiouracil 150 mg/day and propranolol 30 mg/day, Ticlopidine (250 mg/day) (for the replacement of aspirin).</td>
<td>Good.</td>
<td>Weakness and numbness in her left limbs with mildly slurred speech.</td>
</tr>
<tr>
<td>8.2</td>
<td>Shimogawa.</td>
<td>Female</td>
<td>43</td>
<td>TSH level of 0.015 μU/mL, FT3 level of 26.42 pg/mL, and FT4 level of 4.37 ng/dL, TSH receptor antibody level was 36.7%.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Encephalo-duro-arterio-synangiosis and encephalo-myo-synangiosis.</td>
<td>Good.</td>
<td>-</td>
</tr>
<tr>
<td>10.1</td>
<td>Byoungho H. Noh.</td>
<td>Female</td>
<td>16</td>
<td>TSH &lt; 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).</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Methimazole (20 mg every 6 h), hydrocortisone (100 mg every 8 h) and 5% Lugol solution (KI 25 mg every 6 h).</td>
<td>Good.</td>
<td>-</td>
</tr>
<tr>
<td>11.1</td>
<td>Chong Kun Cheon.</td>
<td>Female</td>
<td>29</td>
<td>Case 1: TSH, FT3, FT4, and TSH receptor antibody; 213.36 ng/dL, 1.64 ng/dL, 0.24 IU/mL, 112.66 U/L, respectively. Case 2: T3, FT4, TSH, and TSH receptor antibody was 1.07 ng/mL, 0.99 ng/dL, 0.014 IU/mL, 34.1 U/mL, respectively.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Case 1: Methimazole 20 mg daily, Case 2: 10 mg of methimazole daily.</td>
<td>Good in both</td>
<td>-</td>
</tr>
</tbody>
</table>
12 Jong Han Gill. Female. 43 (TSH) < 0.01 µunits/mL; T3 > 9.0 pg/mL, T4 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, anticonvulsent, beta-blockers, methimazole, Gemstein's solution, and hydrocortisone.

Good. Weakness in her right side; level of consciousness became stuporous after the antiplatelet therapy, seizure.

Atrial fibrillation with a rapid ventricular response (RVR), cardiomegaly, hyperthyroidism.

13 Yi-Yi Xu. 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, MRA; 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 7.5 mg/d.

Graves disease, ANCA positive relapsing polychondritis.

14 Hiroshi Tokimura. Case1: Female

Case2: Female

TSH : 39.51 u/ml; FT3 : 2.4 pg/dl; FT4 : 0.83 ng/dl, Cas1: MRI; Infarction in the left parietal lobe, Cerebral angiography; Occlusion of terminal portion of the bilateral ICAs and both MCAs and ACAs, Case2: Cerebral angiography; stenosis of terminal portion of the ICA and ACA and occlusion of the MCA.

Case 1: Revascularization using a superficial temporal artery

Case 2: STA and MCA anastomosis.

Case1: Dysesthesia of 3rd-5th digits of hands

Case2: none

Case1: numbness in the left hand. left hemiparesis.

Case2: Tachycardia and excessive sweating.

Graves disease in both cases.

15 Sakiko Suzuki. Case1: Male.

Case2: Female.

Case1: TSH <0.011 IU/ml; FT3 3.08 pg/ml; and FT4 4.91 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: MRA; 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 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: left hemiparesis of 3/5 MMT

Case1: Hypothyroidism

Case 2: Hyperthyroidism.

Graves disease in both cases.

16 Fumihiro Matano. Female.

MRA; bilateral supraclinoid stenosis of the ICA decrease CA blood flow. MRE 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 µg/2x and simvastatin 10 mg/2x.

Bilateral hemiparesis.

Graves disease both side.
17 BEATRIZ E. TENDLER. Case1: Female. Case2: Female.

Case1: TSH <0.1 µIU/mL, and T4 26.1 µg/dL (5.0-10.5) TT3: 289 ng/dL, FTI of 19 and thyroid stimulating immunoglobulin (TSI) of 1.844% of basal activity

Case2: TSH <0.1 µIU/mL, T4 15.9 µg/dL, TT3: 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 exclusion 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

Case2: CT; localized hypodense area in the right frontal lobe consistent with a right frontoparietal infarct. Carotid angiogram; nearly complete exclusion 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: subtotal thyroidectomy Case2: -

Good in both.

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.

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 frontolobe and bilateral parietal lobes. MRA: revealed extensive narrowing of the bilateral ICA and branches. These findings were suggestive of vasculitis.

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.

Steroid. -

GOOD. Left-sided facial numbness and cramping, drooling, and aphasia. dizziness, paresthesia, left-sided tingling, and near-syncope.

Exophthalmos and incomprehensible speech. large palpable goiter.

19 Meng-Han Tsai. MALE. 26 FT4: 2.22 ng/dl, T4: 29.6 µg/dl, TT3: 4.86 ng/dl, TSH 0.003 µIU/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

18 Shigeo Ohba. FEMALE. 46 FT3, FT4, and TSH were 1.1 pg/mL, 0.4 µg/dL, and 53.8 µIU/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 encephalomysynangiosis. 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 µIU/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.
<table>
<thead>
<tr>
<th>Case</th>
<th>Name</th>
<th>Gender</th>
<th>Age</th>
<th>Levels of fT3, fT4, and TSH</th>
<th>MRI</th>
<th>MRA</th>
<th>Angiography</th>
<th>CBN</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Takahiro Sasaki</td>
<td>Female</td>
<td>27</td>
<td>fT3 5.5 ng/dL, fT4 1.4 ng/dL, TSH 0.01 μU/ml</td>
<td>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)-TIWI.</td>
<td>narrowing of both MCA, the right greater than the left</td>
<td>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.</td>
<td>None stated.</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Hiroto Ito</td>
<td>Female</td>
<td>37</td>
<td>T3 10.58 pg/mL, T4 2.70 ng/dL, TSH 0.01 μU/ml</td>
<td>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</td>
<td></td>
<td></td>
<td>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; 4 mg/week)</td>
<td>None stated.</td>
</tr>
<tr>
<td>4</td>
<td>Chang Y. Tsao</td>
<td>Female</td>
<td>10</td>
<td>T3 20.3 pg/mL, T4 22.1 ng/dL, TSH 0.013 μU/ml, thyroid stimulating immunoglobulin 89%, a positive antithyroglobulin antibody of 6.2 U/mL, positive antithyroid peroxidase antibody of 28.7 U/mL</td>
<td>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</td>
<td></td>
<td></td>
<td>Aspirin and verapamil</td>
<td>None stated.</td>
</tr>
</tbody>
</table>

**Case 1:** TSH 0.01 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. 

**Case 1:** anti-thyroid hormone medication 
**Case 2:** none. 
**Case 3:** anti-thyroid medication 

**Case 1:** encephalo-duro-arteriosynangiosis (EDAS) 
**Case 2:** encephalo-duro-arteriosynangiosis (EDAS) 
**Case 3:** none. 

**Case 1:** transient attacks of dizziness and left hemiparesis, dysarthria, and headache. 
**Case 2:** TIAs 
**Case 3:** aphasia, exaggerated deep tendon reflexes on the right side.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/Gender</th>
<th>Age</th>
<th>Lab Results</th>
<th>Thyroid Function Tests</th>
<th>Symptoms</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.W. Hsu</td>
<td>Female</td>
<td>40</td>
<td>FT4: 18 ng/dL; TSH: 0.22 μU/mL</td>
<td>Cerebral angiography: bilateral distal ICA and proximal MCA and ACA occlusion. CT: multiple areas of cerebral ischemia.</td>
<td>-</td>
<td>Grave disease.</td>
</tr>
<tr>
<td>Shigoe Ohba</td>
<td>Female</td>
<td>34</td>
<td>FT3: 4.1 pg/mL; FT4: 0.4 ng/dL; TSH: 5.8 μU/mL</td>
<td>MRI and MRA: lacunar infarction and severe stenosis of both ICAs; SPECT: bilateral decrease in blood flow.</td>
<td>-</td>
<td>Graves disease.</td>
</tr>
<tr>
<td>Ran Lee</td>
<td>Female</td>
<td>19</td>
<td>TSH level: 0.001</td>
<td>Cerebral angiography: bilateral occlusion of the ICA around the supraclinoid segment with some collateral vessels.</td>
<td>-</td>
<td>Graves disease.</td>
</tr>
<tr>
<td>Julian Choi</td>
<td>Female</td>
<td>31</td>
<td>FT3: 23.87 μg/dL; FT4: 2.47 ng/dL; TSH: 0.116 μU/mL</td>
<td>MRI: small infarct in the left anterior white matter; SPECT: decreased blood flow to the left anterior lobe; MRA: bilateral carotid stenosis and collaterals.</td>
<td>-</td>
<td>Graves disease.</td>
</tr>
<tr>
<td>Hotaka Kamasaki</td>
<td>Male</td>
<td>14</td>
<td>TSH: &lt;0.005 IU/mL; FT3: 10.08 pg/mL; FT4: &lt;0.1 μg/dL</td>
<td>Pupils were 3 mm and reactive to light, exopthalmos.</td>
<td>-</td>
<td>Graves disease.</td>
</tr>
</tbody>
</table>

**Case 1: Hyperthyroidism**

- **Hyperthyroidism:**
  - **Grave disease.**

- **Fever, HR: 120-150, SBP: 130-160, mild exophthalmos and a soft goiter, tremor of both hands.**

**Case 2: Hyperthyroidism**

- **Grave disease.**

- **Grave disease.**

**Case 3: Hyperthyroidism**

- **Grave disease.**

- **Grave disease.**

**Case 4: Hyperthyroidism**

- **Grave disease.**

- **Grave disease.**
| 10  | Hikaru nakamura. | Female.  19 | FT3, FT4, and TSH of 2.91 pg/dL, 1.34 ng/dL, and 1.048 mU/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 cerebral MCA 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. |

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.

Records identified from Databases (n= 1,899) -> Records removed before screening: Duplicate records removed (n= 1,659) ->

Records screened (n= 240) -> Records excluded (n= 178) ->

Reports sought for retrieval (n= 62) -> Reports not retrieved (n= 09) ->

Reports assessed for eligibility (n= 51) -> Reports excluded:
1. Articles written in language other than English (n= 15)
2. Articles not explaining the association between Moyamoya disease and thyroid related diseases (n= 04) ->

Studies included in review (n= 31)
- Case reports= 20
- Reviews= 11

**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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