Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol. 5 No. 3 (2024): March2024 Issue
https://doi.org/10.51168/sjhrafrica.v4i3.1006
Original Article

A RETROSPECTIVE STUDY ON NEUROPSYCHOLOGICAL AND AUTONOMIC OBSERVATIONS OF CASPR2-RELATED MORVAN SYNDROME.

Rashmi Singh[1], Nikhil Kumar[2]*
PG, Department of General Medicine, I.G.I.M.S., Patna, Bihar, India.[1]
Junior Resident, Department of Neuro Medicine, I.G.I.M.S., Patna, Bihar, India.[2]

ABSTRACT.

Introduction:
The defining feature of Morvan syndrome is cerebral, autonomic, and peripheral hyperexcitability; this is caused by the antibody against contactin-associated protein 2 (CASPR2). The study aimed to examine the cognitive, autonomic, electrophysiologic, polysomnographic, and clinical spectrum of Morvan syndrome patients associated with CASPR2.

Methods:
A retrospective study was conducted. Samples of serum and CSF positive for CASPR2 antibodies for three years were evaluated. Those with Morvan syndrome, identified by clinical and electrophysiologic basis, were among them.

Results:
Among the patients with Morvan syndrome, 28 (M: F = 10:4) had an onset of 37.1 ± 17.5 years. Clinical characteristics included spastic speech (4), dysphagia (4), behavioral abnormalities (4), seizures (2), cold intolerance (2), muscular twitching (24), sleeplessness (24), pain (22), paresthesias (18), hyperhidrosis (14), hypersalivation (12), double incontinence (6). Myokymia (24), hyperactive tendon reflexes (20), and tremor (12) were found during the neurologic examination. Neuromyotonia (24) and higher spontaneous activity (14) were seen on the EMG. Six cases of insomnia, two cases of absentee deep sleep, two instances of high-frequency beta activity, one point of REM behavior disorder, and one case of periodic leg movements were found in the polysomnography results of twelve patients.
Neuropsychological testing showed slight temporal and left frontal involvement. No cancers were identified during the workup. Each patient received steroids. Ten neuropathic pain patients had complete neurologic remission at follow-up.

Conclusion:
This work has advanced the understanding of Morvan syndrome linked to CASPR2. It is critical for greater awareness and early detection because immunotherapy may be able to treat it.

Recommendation:
Regularly get evaluated for the majority of common investigations, including brain MRIs, EEGs, PET scans, and CSF analyses. Individuals who should undergo regular evaluations are those presenting characteristic symptoms such as spastic speech, dysphagia, behavioral abnormalities, seizures, and neuromuscular issues.

Keywords: *Morvan Syndrome, Autoimmune encephalitis, Autonomic dysfunction, CASPR2*
Submitted: 2024-01-24 Accepted: 2024-01-30

Corresponding author: *Rashmi Singh[*]*
Email: *rashmijune02@gmail.com*
PG, Department of General Medicine, I.G.I.M.S., Patna, Bihar, India.

INTRODUCTION.

In 1890, Augustine Marie Morvan wrote about a rare condition known as la choree fibrillary, or Morvan syndrome, which was linked to chronic sleeplessness and autonomic dysfunction [1]. Antibodies against contactin-associated protein 2 (CASPR2) create hyperexcitability in the peripheral, autonomic, and central nervous systems [2, 3].

Very few cases of Morvan syndrome have been connected to heavy metal exposure and local drug usage. Roughly 40% of instances of this Morvan syndrome are linked to prostate, lung, or thymus cancer [1-3].
CASPR2, an axonal transmembrane protein belonging to the neurexin superfamily and generated in both the central and peripheral nervous systems, binds to contactin-2. The Kv1 potassium channel clustering in the adjacent paranodal area, which promotes axon myelination,

depends on its cytoplasmic domain [4]. The CASPR2 gene, CNTNAPD2 polymorphisms, and mutations have been linked to peripheral nerve hyperexcitability, epilepsy, and schizophrenia [5].

The neurologic illness related to CASPR2 antibody exhibits a broad range of clinical manifestations, including pain, limbic encephalitis, epilepsy, Morvan syndrome, and anterior horn cell disorder [6]. The following trio of clinical characteristics is used to diagnose Morvan syndrome: Brain disorientation, impaired cognitive function, delusions, and sleeplessness. Myoclonus, peripheral nerve hyperexcitability, autonomic symptoms, hyperhidrosis, changes in blood pressure, and clinical or electrophysiologic evidence of spontaneous muscular overactivity in the form of severe cramps, fasciculations, myokymia, and neuromyotonia [2, 3].

Over the past 20 years, many suitcase series and single case reports of Morvan syndrome have been recorded. The earliest occurrences of Morvan syndrome were associated with antibodies against voltage-gated potassium channels (VGKCs), notably, CASPR2 and leucine-rich glioma-inactivated 1 (LGI-1) antibodies. Eventually, though, the association between Morvan syndrome and CASPR2 antibody involvement is more common [7, 8].

Aim of the Study: The current investigation was carried out to provide a more comprehensive understanding of Morvan syndrome, focusing on its imaging, autonomic, electrophysiologic, polysomnography (PSG), and neuropsychological manifestations.

Objectives of the study.

The study's objectives encompass a comprehensive investigation of Morvan syndrome, with a focus on multiple facets of the condition. These objectives include the examination of imaging characteristics associated with Morvan syndrome, analysis of autonomic dysfunction and its clinical manifestations, assessment of electrophysiological findings for diagnostic insights, evaluation of polysomnography (PSG) results to identify sleep-related abnormalities, and an exploration of neuropsychological manifestations and cognitive involvement in individuals diagnosed with Morvan syndrome.

METHODS.

Study Design.

A retrospective study was conducted.

Study Setting.

The research was conducted at the Indira Gandhi Institute of Medical Science (I.G.I.M.S.), Patna, Bihar, India for three years.

Participants.

The study consisted of 52 patients with Morvan syndrome who tested positive for CASPR2.

Inclusion criteria.

Individuals exhibiting diverse neurologic symptoms and having elevated serum levels of CASPR2 antibodies were evaluated.

Exclusion criteria.

Individuals were excluded from the study if they did not meet the inclusion criteria, which required the presence of diverse neurologic symptoms and elevated serum levels of CASPR2 antibodies. Additionally, patients with incomplete medical records or missing essential clinical information were excluded from the analysis. Those who did not undergo the Euroimmun cell-based immunoassay for neuropil antibodies or had inconclusive test results were also excluded from the study to ensure a cohesive and reliable dataset for analysis.

Data collection.

All the participant's medical records were reviewed. The case records contained the patient's clinical characteristics, investigations, and demographic profile information.

Procedure.

Euroimmun cell-based immunoassay, a commercially available indirect immunofluorescence test, was used to screen patient CSF and serum samples of neuropil antibodies for a panel linked to autoimmune encephalitis. Substrates are coated and treated with either an unadulterated CSF sample or the patient's serum at a 1:10 dilution on microtiter plates. Fluorescence-labeled anti-human antibodies recognize the antigen-antibody complexes and subsequently appear under a fluorescence microscope.

Bias.

There was a chance that bias would arise when the study first started, but it was avoided by giving all participants

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol. 5 No. 3 (2024): March2024 Issue
https://doi.org/10.51168/sjhrafrica.v4i3.1006
Original Article

identical information and hiding the group allocation from the nurses who collected the data.

Statistical analysis.

The data obtained from the study was arranged in a tabulated manner in an Excel sheet, and the data was then subjected to statistical analysis (frequency, percentage, mean, standard deviation, etc.). Statistical analysis is accomplished using an appropriate software program (e.g., SPSS). A $p< 0.05$ change is considered to be statistically significant.

Ethical Consideration.

The patient gave written informed consent before data collection, and the study was authorized by the institutional ethical committee of I.G.I.M.S., Patna, Bihar, India. Every patient whose personal information (pictures, videos, and PSG) was available gave written informed consent.

RESULTS.

Fifty-two patients with various neurologic disorders- some of which were previously listed- were discovered to have positive serum CASPR2 antibodies. The study population (53.8%) consisted of patients with Morvan syndrome who were assessed over three years. None of the patients had taken any native drugs or been exposed to any poisons. There was a 10:4 male majority; the median age was 33.5 years, and the mean was 37.1 ± 17.5 years.
The presented symptoms have been observed within a range of two to six weeks in the patient cohort. Within the central nervous system (CNS) category, dysphagia was reported in four individuals, insomnia in 24, behavioral disturbances in four, spastic speech in four, and seizures in two patients. In terms of peripheral nerve hyperexcitability, muscle twitching was noted in 24 cases, while pain was reported in 22, and paresthesias in 18 patients. Within the autonomic nervous system, 14 individuals experienced hyperhidrosis, 12 had hypersalivation, six exhibited double incontinence, and two reported cold intolerance. Notably, twenty cases had a history of prior infectious diseases. During neurological examinations, myokymia was detected in 24 patients, hyperactive tendon reflexes in 20, and postural tremor in 12. Four patients displayed signs of polyminimyoclonus, ataxic gait, bifacial weakness, and spastic speech.
Parameters related to hematocrit and biochemistry were within normal ranges. Four individuals had increased CSF protein, but the CSF study revealed an average cell count. One patient's autoimmune antinuclear profile showed that they were positive for AMA-M2. Every patient's autoimmune profile showed CASPR2 positive. Furthermore, two patients had positive results for LGI1, while another had borderline positive results for Zic-4 and anti-PNMA2 (Ma2/Ta).
Sixteen patients underwent tests of their autonomic function. Eight had clear-cut autonomic dysfunction, two had early dysfunction (determined by the test involvement or by two tests with borderline findings by heart rate-based autonomic function), and six showed normal autonomic functioning using traditional autonomic function testing. The patients' lower HRV, root mean square of SD, total low-frequency and high-frequency powers, and the SD of normal-to-normal intervals indicated reduced parasympathetic activity and increased sympathovagal balance.
Eight individuals had resting tachycardia (heart rate more than 100 beats per minute), two had postural tachycardia syndrome (higher heart rate while standing, with little change in blood pressure), and four had orthostatic hypotension (lower systolic/diastolic blood pressure by more than 20/10 mm Hg) (Table 1).

Table 1: Autonomic Variables in Patients with Morvan Syndrome Compared with Laboratory Normative Values.

S. no	Autonomic Variable	Patients with Morvan Syndrome (n=16)	Laboratory Normative Value
1	Deep breathing difference, bpm	13.1± 5.3	>15
2	Orthostatic test, max: min ratio	1.06± 0.08	>1.04
3	Valsalva ratio	1.3± 0.1	>1.21
4	Orthostatic test	13± 13.2	<10
5	Isometric hand grip test	9± 5.6	>15
6	SDNN	23± 14.6	141± 39

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol. 5 No. 3 (2024): March2024 Issue
https://doi.org/10.51168/sjhrafrica.v4i3.1006
Original Article

7	RMSSD	13.2± 10.6	27± 12
8	Total power	648.6± 305.6	3466± 1018
9	Low-frequency power	199± 105	1170± 416
10	High-frequency power	122.7± 75.7	975± 203
11	Low-frequency, normalized units	59± 14.3	54± 4
12	High-frequency, normalized units	29± 14.3	29± 3
13	LF/HF ratio	2.56± 1.39	0.5-1.5

Following confirmation of the diagnosis, steroids were administered to all patients, and 22 individuals also underwent plasmapheresis. The duration of the steroids was three to six months. Follow-up periods varied from three and a half to six months. Over two to three months, all patients showed complete neurologic and autonomic remission; ten patients nevertheless experienced neuropathic pain, and two patients experienced fatigue. It's interesting to note that neither autoimmune diseases nor cancer were discovered in any of the patients at the time of admission or follow-up. They all responded exceptionally well to first-line immunotherapy.

DISCUSSION.

The study included 52 patients, with 53.8% diagnosed with Morvan syndrome over three years, primarily male (M: F-10:4) with a mean age of 37.1 ± 17.5 years. They presented a range of CNS, peripheral nerve, and autonomic symptoms, without prior drug use or toxin exposure. Hematocrit and biochemistry were normal, but some had increased CSF protein. Autonomic function tests revealed various dysfunction levels, including reduced parasympathetic activity. Resting tachycardia, postural tachycardia syndrome, or orthostatic hypotension were present in some patients. Following diagnosis, all received steroids, with some undergoing plasmapheresis, showing significant improvement during a two to three-month follow-up. Notably, no autoimmune diseases or cancer were detected, underscoring the effectiveness of first-line immunotherapy in managing Morvan syndrome.

The study provides insights into the clinical presentation, diagnostic findings, and treatment response of patients with Morvan syndrome and CASPR2 antibodies. The majority of patients exhibited significant improvement following immunotherapy, highlighting the importance of early detection and treatment in managing this condition.
The symptoms of Morvan syndrome are a combination of many irregular muscle contractions, cramps, weakness, hyperhidrosis, sleeplessness, and delirium [9]. Thymoma, malignancies (prostate adenoma and sigmoid colon cancer), two autoimmune illnesses, and myasthenia gravis have all been linked to it, pointing to an autoimmune or paraneoplastic genesis [10, 11]. Additionally, gold, mercury, and manganese heavy metal toxicity have been linked to Morvan syndrome [2, 12]. Later research revealed that VGKC complex antibodies, mainly directed against CASPR2, are present in Morvan syndrome patients [13].

In 2012, the most extensive case series of Morvan syndrome due to CASPR2 was published [14]. The clinical and serologic profiles of 46 of 58 patients discovered through international referral correspondence were observed [18]. Neuromyotonia and neuropsychiatric symptoms, including dysautonomia, disorientation, forgetfulness, hallucinations, and sleeplessness, were found in all the patients. 41.4% of the patients had a tumor association; 22 of the patients had thymomas, and two patients had small-cell lung cancer [14]. There have been 76 instances of CASPR2-associated neurologic diseases described from two neuroimmunology institutions in Barcelona and Rotterdam, eleven of which had Morvan syndrome [5].
Clinical evidence of sleep disruptions has been documented in 31%-48% of cases of Morvan syndrome. 85.7% of participants in the current study reported irregular sleep patterns. Twelve patients in the study attempted PSG. However, only six of them cooperated for the duration of the PSG investigation. Previous research has shown that patients' restlessness, sleeplessness, and behavioral abnormalities made it challenging to do PSG because they prevented their cooperation [15, 9].
While sixteen individuals had average PET scan results, four patients had mild abnormalities, such as hypometabolism in the basal ganglia and high uptake in the leg muscles. It has previously been demonstrated that the left inferior frontal and temporal lobes of four patients with Morvan syndrome had reduced metabolisms [15]. These results are not consistent with other neurologic conditions. Medial temporal lobe hypermetabolism is observed in limbic encephalitis patients [16], and thalamic alterations have been linked to fatal familial insomnia

Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol. 5 No. 3 (2024): March2024 Issue
https://doi.org/10.51168/sjhrafrica.v4i3.1006
Original Article

[17]. A neuropsychological assessment turned up no signs of dementia or cognitive impairment. The left frontal and temporal lobes showed some involvement in three of them.

These complete cardiovascular autonomic functions served as indicators of autonomic dysfunction in the investigation, specifically in individuals with Morvan syndrome. One patient's autonomic functioning showed a decreased quantitative sudomotor axon reflex test response in the foot, associated with compromised cardiovagal and cardiovascular adrenergic function. According to research the CNS and autonomic involvement may originate from peripheral involvement of antibodies on neurohormone secretion or antibodies to VGKC in the CNS [8]. To use that information in the prognostication of this illness, more research is required to examine the disease's progression and the degree of cardiac autonomic involvement.

GENERALIZABILITY.

While the study's single-center, three-year duration limits its broader applicability, it offers valuable insights into Morvan syndrome among CASPR2 antibody-positive patients with diverse neurologic symptoms. Although CASPR2 antibodies are not always present, and clinical presentations can vary, the study's findings contribute to understanding this specific subgroup. The treatment approach involving steroids and plasmapheresis, while not universally applicable, provides important therapeutic insights. To enhance generalizability, future research should expand to larger, diverse cohorts and account for variations in presentations and treatments, building upon the valuable foundation laid by this study.

CONCLUSION.

This work has advanced the understanding of Morvan syndrome linked to CASPR2. The study's key strengths are the efficacy of long-term therapy, the delineation of clinical features, and the comprehensive description of autonomic, neuropsychological, and polysomnographic components. This is a serious restriction that needs to be fixed later on. A follow-up investigation of CASPR2 antibodies, neuropsychology, autonomic nervous system, and polysomnographic examination may have provided more details about the illness.
Understanding better and promptly identifying this uncommon neuroimmunologic illness that may be treated is critical. More research is needed to address the various autonomic, cognitive, and sleep problems that may lead to a more superb quality of life through better management of Morvan syndrome.

LIMITATION.

This study has limitations, including potential recall and selection biases due to its retrospective design and focus on CASPR2 antibody-positive patients with diverse neurologic symptoms. The single-center nature limits generalizability, and the treatment approach may not consider regional variations. The small sample size and retrospective data analysis introduce limitations in statistical power and potential information bias. These limitations affect both the direction and magnitude of potential bias in interpreting the study's results.

RECOMMENDATION.

It is advised to get evaluated regularly for the most common tests, such as brain MRIs, EEGs, PET scans, and CSF studies.

ACKNOWLEDGMENT.

Since the study would not have been possible without the patients, we are grateful to them.

ABBREVIATIONS.

CASPR2- Contactin-associated protein 2
BPM- Beats per minute
CNS - Central Nervous System
CSF - Cerebrospinal Fluid
M: F - Male to Female ratio
EMG - Electromyography
PSG - Polysomnography
EEG - Electroencephalogram
PET - Positron Emission Tomography
VGKC - Voltage-Gated Potassium Channels

SOURCE OF FUNDING.

The study was not funded.

CONFLICT OF INTEREST.

The authors of this research have declared no conflicts of interest.

REFERENCES.

1. Masood W, Sitammagari KK. Morvan syndrome (Morvan fibrillary chorea,

MFC). In: StatPearls (Internet). Treasure Island: StatPearls Publishing; 2020.
2. Haug BA, Schoenle PW, Karch BJ, Bardosi A, Holzgraefe M. Morvan's fibrillary chorea. A case with possible manganese poisoning. Clin Neurol Neurosurgery 1989; 91:53–59.
3. Lotan I, Djaldetti R, Hellman MA, Benninger F. Atypical Morvan syndrome case. J Clin Neurosci 2016; 25:132–134.
4. Poliak S, Gollan L, Salomon D, et al. Localization of Caspr2 in myelinated nerves depends on axon–glia interactions and the generation of barriers along the axon. J Neurosci 2001; 21:7568–7575.
5. van Sonderen A, Schreurs MWJ, Wirtz PW, Sillevis Smitt PAE, Titulaer MJ. From VGKC to LGI1 and CASPR2 encephalitis: the evolution of a disease entity over time. Autoimmun Rev 2016; 15:970–974.
6. van Sonderen A, Ariño H, Petit-Pedrol M, et al. The clinical spectrum of Caspr2 antibody-associated disease. Neurology 2016; 87:521–528.
7. Lee EK, Maselli RA, Ellis WG, Agius MA. Morvan's fibrillary chorea: a paraneoplastic manifestation of thymoma. J Neurol Neurosurg Psychiatry 1998; 65:857–862.
8. Liguori R, Vincent A, Clover L, et al. Morvan's syndrome: peripheral and central nervous system and cardiac involvement with antibodies to voltage-gated potassium channels. Brain 2001;124(pt 12):2417–2426.
9. Morvan AM. De la chorée fibrillaire. Gazette Hebdomadaire de Mèdicine et de Chirurgie 1890; 27:173–200.
10. Halbach M, Hömberg V, Freund HJ. Neuromuscular, autonomic, and central cholinergic hyperactivity associated with thymoma and acetylcholine receptor-binding antibody. J Neurol 1987; 234:433–436.
11. Madrid A, Gil-Peralta A, Gil-Neciga E, Gonzalez JR, Jarrin S. Morvan's fibrillary chorea: remission after plasmapheresis. J Neurol 1996; 243:350–353.
12. Petiot P, Charles N, Vial C, McGregor B, Aimard G. Complications neurologiques des sels d'or: discussion nosologique à propos d'un cas. Rev Neurol 1993; 149:562–565.
13. Vincent A, Bien CG, Irani SR, Waters P. Autoantibodies associated with diseases of the CNS: new developments and future challenges. Lancet Neurol 2011; 10:759–772.
14. Irani SR, Pettingill P, Kleopa KA, et al. Morvan syndrome: clinical and serological observations in 29 cases. Ann Neurol 2012; 72:241–255.
15. Josephs KA, Silber MH, Fealey RD, Nippoldt TB, Auger RG, Vernino S. Neurophysiologic studies in Morvan syndrome. J Clin Neurophysiol 2004; 21:440–445.
16. Fakhoury T, Abou-Khalil B, Kessler RM. Limbic encephalitis and hyperactive foci on PET scan. Seizure 1999; 8:427–431.
17. Perani D, Cortelli P, Lucignani G, et al. [18F] FDG PET in fatal familial insomnia: the functional effects of thalamic lesions. Neurology 1993; 43:2565–2569.

Publisher details:

SJC PUBLISHERS COMPANY LIMITED

SJC Publishers Company Limited

Category: Non-Government & Non-profit Organisation
Contact: +256775434261(WhatsApp)
Email: admin@sjpublisher.org, info@sjpublisher.org or studentsjournal2020@gmail.com
Website: https://sjpublisher.org
Location: Wisdom Centre Annex, P.O. BOX. 113407 Wakiso, Uganda, East Africa.