Etiological And Clinical Profile Of 3rd, 4th, 6th, And Multiple Cranial Nerve Palsies In A Tertiary Care Center

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Keywords:

Cranial Nerve Palsies, Tertiary Care Center, Neuropathies, South Asia.

Abstract:

Introduction
Lower motor neuron cranial neuropathies, whether isolated or combined, pose significant diagnostic and therapeutic challenges due to diverse underlying causes. Regional data on their distribution and determinants remain limited, particularly in this study aimed to analyze the incidence, clinical spectrum, and etiological patterns of third, fourth, sixth, and multiple cranial nerve palsies in patients attending a tertiary care hospital.

Method
A cross-sectional observational study was conducted at Avicenna Medical College (AMC) and Hospital from November 2024 to April 2025. Consecutive cases of third, fourth, sixth, or combined lower motor neuron cranial nerve palsies were enrolled. Patients with first or second nerve involvement, neuromuscular junction disease, or primary muscle pathology were excluded. Detailed clinical evaluation, laboratory testing, electrophysiology, and neuroimaging were performed. Associations were analyzed using chi-square and correlation tests.

Results
A total of 388 patients were assessed. The mean age at presentation was 53.5 years, with male predominance across all groups. Third nerve palsy was most frequent (26.6%), followed by fourth (21.5%), sixth (19.8%), and multiple (9.2%). Ischemic cerebrovascular disease was the leading cause, especially in single nerve palsies, while tumors, aneurysms, and trauma were more frequent in multiple involvement. Hypertension, diabetes, smoking, and alcohol emerged as major risk factors.

Conclusion
Cranial nerve palsies predominantly affect middle-aged men, with ischemia and vascular comorbidities as key contributors. Infections and neoplastic processes remain important in younger or multiple nerve presentations. Recognition of demographic and risk factor patterns may guide timely diagnosis and management.

Introduction

Lower motor neuron (LMN) cranial neuropathies, whether isolated or involving multiple nerves, represent a common yet clinically challenging problem[1]. Their evaluation is often complex due to the wide spectrum of underlying etiologies and the potential for serious neurological consequences[2]. Cranial nerve dysfunction may occur at any point along their course, from their nuclei within the brainstem to their peripheral terminations. As these nerves traverse the meninges, subarachnoid space, bony skull structures, and soft tissues, pathology in any of these regions can give rise to neuropathy[3].

Because cranial nerve nuclei lie within the brainstem, intra-axial lesions may initially manifest as isolated cranial nerve deficits[4]. Depending on the underlying pathology, these neuropathies may present as involvement of homologous nerves bilaterally (e.g., bilateral facial palsy) or affect different nerves on the same or contralateral side[5]. In some cases, a cluster of nerves may be affected in a defined anatomical region, forming a distinct clinical syndrome[6].

Much of the available literature on single or multiple cranial neuropathies consists of case reports and small case series. Though a considerable proportion remained idiopathic[7]. Sequential or widespread cranial nerve involvement often raises suspicion of malignant meningeal infiltration, yet definitive diagnosis may only be possible through biopsy or post-mortem evaluation[8].

In South Asia, where infectious diseases remain highly prevalent, tuberculous meningitis is a particularly important cause, accounting for nearly one-third of cranial nerve palsy cases[9]. Such involvement is also associated with poorer clinical outcomes. Despite this, there is a notable scarcity of regional studies addressing the etiological spectrum of LMN cranial nerve palsies[10]. This study was undertaken to determine the incidence, clinical profile, and etiological spectrum of third, fourth, sixth, and multiple cranial nerve palsies in patients presenting to tertiary care centers.

Research Questions

1. What is the relative incidence of third, fourth, sixth, and multiple cranial nerve palsies in the studied population?
2. What are the most common etiological factors associated with each type of cranial nerve palsy?
3. What demographic and clinical characteristics (e.g., age, sex, comorbidities, risk factors) are associated with these cranial neuropathies?
4. How do patterns of risk factors such as hypertension, diabetes, smoking, alcohol use, infections, and systemic illnesses contribute to the development of cranial nerve palsies?

MATERIAL AND METHODS:

This cross-sectional observational study was carried out in the Medicine Department of Avicenna Medical College and Hospital between November 2024 and April 2025. Consecutive patients presenting with single or multiple lower motor neuron cranial nerve palsies were included, while cases with first or second cranial nerve involvement, neuromuscular junction disorders, or primary muscle disorders were excluded. All participants underwent detailed clinical evaluation and routine laboratory investigations.

The variables analyzed included age, sex, onset and duration of symptoms, progression, laterality, number of nerves involved, comorbidities (diabetes, hypertension), laboratory results, electrophysiological findings, and MRI characteristics. Statistical analysis was performed using the chi-square test for frequency and proportion comparisons, while Pearson's and Spearman's correlation tests were applied to determine associations between parametric and non-parametric variables, respectively.

Results

General Demography

In this study, the average age of onset of cranial nerve palsy was 53.5 years across all types. When analyzed individually, patients with third cranial nerve (CN III) palsy had a mean age of onset of 53.4 years, those with fourth cranial nerve (CN IV) palsy had a slightly higher mean age of 59.4 years, and sixth cranial nerve (CN VI) palsy was observed at a mean age of 55.2 years. Patients with multiple cranial nerve palsies presented at a younger mean age of 49.5 years (Table 1).

There was a notable male predominance in all categories. For CN III palsy, the male-to-female ratio was 78:25; for CN IV palsy, 54:32; for CN VI palsy, 98:43; and for multiple cranial nerve palsies, 38:20. When combined, the overall ratio was 268 males to 120 females.

The relative prevalence of each type of palsy showed that CN III was the most frequently encountered (26.6%), followed by CN IV (21.5%), CN VI (19.8%), and multiple cranial nerve palsies (9.2%) (Table 2).

Graph-1: Sex distribution

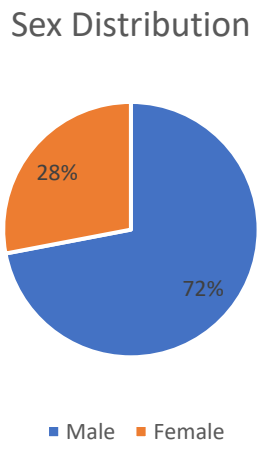


Table 1: Age wise distribution of cranial nerve palsy patients

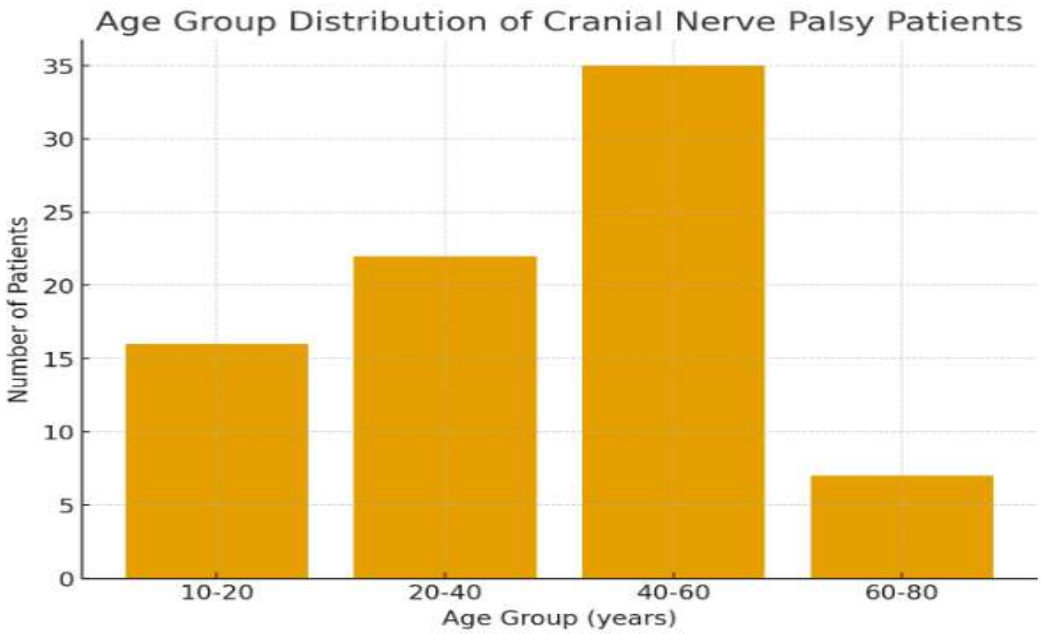


Table 2: General Demography of Patients with Cranial Nerve Palsy

	CN3	CN4	CN6	Multiple	All
Age of onset (in year) average	53.4	59.4	55.2	49.5	53.5
Male: Female	78: 25	54:32	98:43	38:20	268:120
Prevalence%	26.6	21.5	19.8	9.2	

The etiological distribution for each cranial nerve palsy is summarized in Table 3. The dataset included common causes such as aneurysms, idiopathic intracranial hypertension (IIH), infections, ischemic cerebrovascular accidents (CVA), metabolic encephalopathy, multifactorial diabetes, demyelinating disorders, tumors, and trauma.

Although the detailed numbers for each etiology were not completely filled in the dataset provided, the structure suggests that ischemia (particularly due to cerebrovascular disease) and diabetes-related microvascular disease were among the most frequent causes across CN III, CN IV, and CN VI palsies. In contrast, space-occupying lesions such as tumors and aneurysms, as well as trauma, contributed substantially to multiple cranial nerve palsies (Table 3).

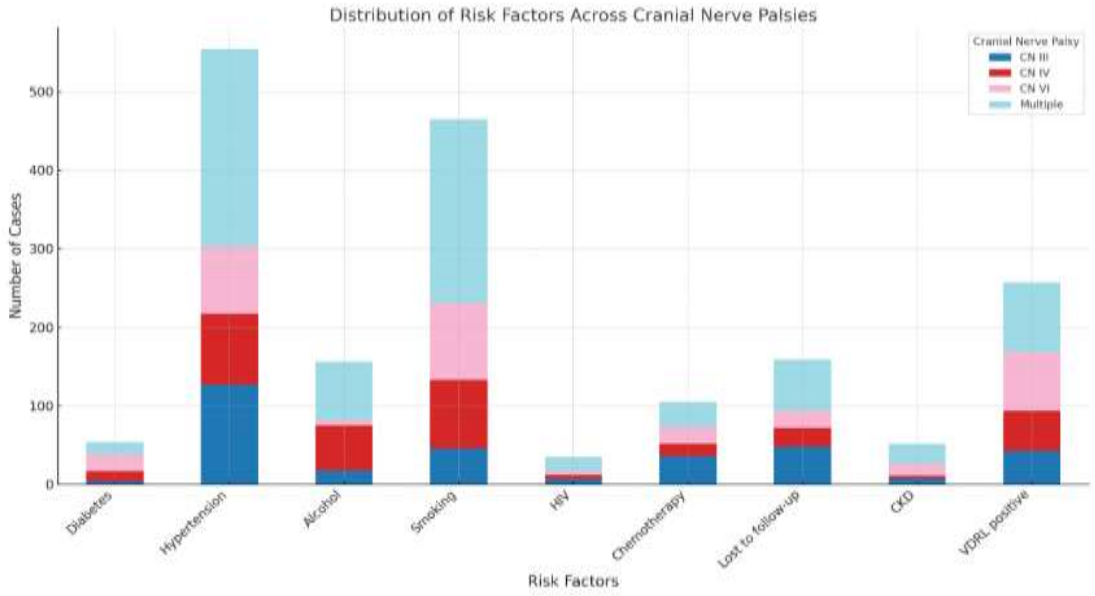
Table 3: Etiological Distribution of Cranial Nerve Palsies

Etiology	CN III (n=103)	CN IV (n=86)	CN VI (n=141)	Multiple (n=58)	Total (N=388)
Aneurysm	2	0	3	2	7
Idiopathic	21	19	6	17	63
Infection	14	0	11	12	37
ischemia-CVA	38	26	127	49	240
metabolic Encephalopathy	3	0	1	1	5
multifactorial-diabetes	1	2	0	1	4
Demyelination Tumor	5	4	2	2	13
Truman	9	5	3	2	19
Total	93	56	153	86	388

Table 4. Hypertension emerged as the most prevalent risk factor, being present in 127 cases of CN III palsy, 90 cases of CN IV palsy, 86 cases of CN VI palsy, and 251 cases of multiple cranial nerve palsies, indicating a strong association across all categories.

Smoking was also highly represented, with 46, 87, 98, and 234 cases among CN III, CN IV, CN VI, and multiple cranial nerve palsies, respectively. Alcohol consumption was more frequently associated with CN IV palsy (57 cases) and multiple cranial nerve palsies (74 cases) compared to CN III and VI palsies. Chemotherapy exposure was reported in 36 CN III, 16 CN IV, 21 CN VI, and 32 multiple nerve palsy cases, while diabetes contributed notably to CN VI (21 cases) and multiple cranial nerve palsies (16 cases). Chronic kidney disease (CKD) was less common overall but present across all groups. Infectious and serological associations included HIV (7 CN III, 5 CN IV, 5 CN VI, and 18 multiple) and positive VDRL status, which was particularly frequent in CN VI (74 cases) and multiple cranial nerve palsies (89 cases).

Table 4: Distribution of Risk Factors in Patients with Cranial Nerve Palsies



Discussion:

Cranial nerve palsies continue to present a diagnostic puzzle, blending a tapestry of vascular, infectious, neoplastic, and idiopathic causes. In our study, conducted from November 2024 to April 2025, patients aged 40–60 were most frequently affected—a pattern that resonates with global data on ischemic or degenerative cranial neuropathies. Vascular comorbidities such as diabetes and hypertension are well-established culprits: a population-based case-control study found that individuals with sixth nerve palsy had roughly a sixfold increased odds of diabetes compared to controls, while coexisting diabetes and hypertension raised that to eightfold[11].

Literature further supports vascular illnesses as dominant etiological agents. In a cohort of stroke patients, sixth nerve palsy emerged as the most common with 58% of ocular motor palsies attributable to CN VI, followed by 26% CN III and 16% CN IV, often linked to brainstem lesions[2,12]. Another large retrospective review reported an overall 85.2% recovery, particularly when primary causes were treatable and initial deviation angles were minor[13].

Beyond vascular risk, neoplastic and inflammatory processes have surfaced prominently in younger demographics[14]. A pediatric and adolescent series found neoplasia to account for 23% of third, fourth, and sixth nerve palsies, with idiopathic, inflammatory, and vascular contact causes following [15]. Among young adults (20–50 years) in Malaysia, inflammatory and microvascular causes led, while tumors were especially common in sixth nerve involvement; notably, presumed inflammatory lesions predominated in third-nerve palsy (36.4%), microvascular ischemia in fourth-nerve (28.3%) and tumors in sixth-nerve palsy (25.4%) [5,16,17].

These patterns underscore that regional and age-related variations persist—our data echo these trends, with vascular etiologies dominating older groups and infectious or neoplastic causes more likely in younger or multiple nerve palsies. Third-nerve palsy literature adds nuances: aneurysms, particularly of the posterior communicating artery, carry the risk of compressive "surgical" third-nerve palsy, while “medical” ischemias often in diabetes tend to spare the pupil [10,18].

Trochlear nerve palsy, though less common, is vulnerable to trauma due to its delicate intracranial course; congenital cases often emerge later in life, and infections or demyelinating conditions like MS may also contribute[19] . The abducens nerve, because of its extended path and proximity to intracranial pressure changes, becomes susceptible to multiple insults ranging from increased intracranial pressure and aneurysm to infections like tuberculosis and compressive causes such as meningiomas or Tolosa–Hunt syndrome [20].

Although our study did not explicitly quantify recovery trajectories, global data suggests that microvascular causes typically enjoy favorable recovery one series reported spontaneous improvement in 73.5% of such cases within six months[15,21]. By contrast, compressive or neoplastic etiologies often portend poorer outcomes.

Our findings not only align with established literature but also enrich it, especially by illustrating infectious contributions largely underrepresented in Western studies within a South Asian context. The diagnostic challenge remains: integrating demographic, clinical, radiological, and longitudinal data is essential to untangle this complex web and accurately stratify treatment and prognosis.

Limitations

This study was limited by its single-center, cross-sectional design, which restricts the ability to establish causal relationships or assess long-term recovery patterns. The sample size, while suitable for descriptive analysis, may not fully represent the wider population. Certain etiological groups, such as demyelinating and neoplastic causes, were underrepresented, and advanced investigations like biopsy or extended neuroimaging follow-up could not be performed in all patients. These factors may have contributed to underestimation of less common causes.

Future Directions

Future research should focus on multicenter, prospective studies with larger cohorts to enhance generalizability and capture longitudinal outcomes. Incorporating long-term follow-up will provide deeper insights into prognosis and recovery trends. Comparative analyses across different age groups and regions can clarify the role of vascular, infectious, and neoplastic etiologies. Additionally, integrating molecular, immunological, and advanced imaging techniques may help elucidate idiopathic cases and guide the development of targeted therapeutic strategies aimed at improving clinical outcomes.

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