Biological and Clinical Sciences Research Journal
eISSN: 2708-2261; pISSN: 2958-4728
www.bcsrj.com
DOI: https://doi.org/10.54112/bcsrj.v2024i1.1070
*Biol. Clin. Sci. Res. J., Volume, **2024**: 1070*
Original Research Article

PROSPECTIVE STUDY OF NEUROLOGICAL COMPLICATIONS OF DIPHTHERIA

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(Received, 28th May 2024, Revised 29th August 2024, Published 30th September 2024)

Abstract: *Diphtheria remains a significant infectious disease, particularly in unimmunised and partially immunised populations. Neurological complications of diphtheria, though less commonly recognised, can have serious consequences if not promptly identified and treated.* ***Objective:*** *To examine the neurological complications associated with diphtheria, focusing on their onset, relationship with respiratory illness, and recovery patterns.* ***Methods:*** *This cross-sectional study was conducted at Nishtar Hospital Multan between January 2023 and January 2024. Thirty patients, aged 3 to 18 years, who were hospitalised with confirmed diphtheria and associated neurological complications, were included in the study. Demographic data, including age, gender, and vaccination status, were recorded, along with details of respiratory illness severity and symptoms of diphtheria-related complications. Comprehensive clinical and neurological evaluations were performed, supported by relevant investigations. Statistical analysis was conducted using [statistical software], with results presented as frequencies, percentages, and means where appropriate.* ***Results:*** *A total of 25 cases of diphtheria in which some sort of neurological complications developed were involved in this research. The mean age of the study population was 6.6 ±5.5 years, range 3-18 years. A latent interval of 4-49 days between the development of membranous tonsillitis and neurological problems was found. Isolated palatal paralysis was seen in 15 children (60%). All children(100%) showed nasal twang, regurgitation, and difficulty in swallowing as bulbar symptoms. Three children (12%) showed signs of third cranial nerve involvement, exhibiting ptosis and diplopia. Two children (8%) experienced unilateral lower motor neuron facial palsy. All 25 patients recovered completely. Recovery time they were ranged from 1-6 weeks for isolated bulbar palsy to 10-16 weeks for quadriparesis and 6 weeks for DP.* ***Conclusion:*** *Diphtheritic polyneuropathy should be recognised promptly by paediatricians and neurologists. Early identification and differentiation of various neuropathies are critical for effective treatment and contact tracing, with a generally favourable prognosis.*

Keywords: Bulbar Palsy, Diphtheria, Motor Weakness, Neurological Complications, Polyneuropathy

Introduction

Diphtheria is a prevalent infectious illness in both unimmunised and partially immunised groups. (1). Between 2007 and 2011, the World Health Organisation recorded 20,000 cases of diphtheria, with Asia accounting for 17,926 cases (89.6%), surpassing all other continents in reporting. (2). Diphtheria has resurfaced in kids, teens, and adults throughout many states. (3). Toxigenic strains of C. diphtheriae produce a toxin that causes pseudomembrane development in the pharynx, larynx, and nasal passages. (4). Diphtheria persists primarily due to low immunisation rates. (5). According to the National Health Survey, just 43.5% of children aged 12 to 23 months were immunised across the country, with coverage as low as 30% in Baluchistan, Pakistan. (6)The country's immunisation rates vary significantly among states and districts. Doctors often overlook diphtheria and its associated neurological consequences due to its underestimation in areas with inadequate immunisation coverage.

Diphtheria has a high risk of neurological consequences. (7). Neurological consequences are multiphasic in development and reflect the severity of the initial illness. (8). Corynebacterium diphtheriae produces an exotoxin that causes neurological symptoms. There is limited literature on diphtheria-related neurological problems. The primary problems are low suspicion, overlooked, and under-reporting. Therefore, this study was conducted to investigate the neurological problems associated with diphtheria, focusing on their onset, link to respiratory disease, and recovery patterns.

Methodology

This cross-sectional study was conducted at the Nishtar Hospital Multan between January 2023 and January 2024 after obtaining authorisation from the hospital's ethics council and institutional review board. Informed consent was taken from all the participants involved in the research. Hospital-based research examined 41 cases of membranous tonsillitis admitted during the study period. Only 37 of these cases were confirmed as diphtheria. Nine patients died during the respiratory illness due to high toxicity. The remaining 28 children received anti-diphtheritic serum (ADS), antimicrobial agents, and supportive care. Four patients had moderate respiratory problems, whereas 24 required a tracheostomy due to severe respiratory distress.

[Citation: Ali, S., Arshad, U., Saddique, A., Zahra, N., Khan, K.A.A., Naqvi, S.Z.H. (2024). Prospective study of neurological complications of diptheria. *Biol. Clin. Sci. Res. J.*, **2024***: 1070*. doi: https://doi.org/10.54112/bcsrj.v2024i1.1070]

These 28 patients were monitored for neurological problems. Only 25 of the 28 cases experienced neurological issues. In all, 25 children were selected for the research.
We documented demographic information such as age, gender, vaccination status, respiratory illness severity, and diphtheria-related sequelae. The authors conducted comprehensive physical and neurological examinations. Investigations included baselines, CSF examination, nerve conduction velocity, and magnetic resonance imaging when needed. All 25 children experienced diphtheria-related neurological sequelae, ranging from moderate to severe and manifesting during different follow-up phases.
All data were analysed with SPSS 21. Quantitative data (e.g., age) was recorded as mean ± SD. Qualitative characteristics, such as gender and kind of neurological complication, were documented using percentages and frequencies.

Results

This research involved 25 cases of diphtheria who developed some sort of neurological complications. The mean age of the study population was 6.6 ±5.5 years, with a range of 3-18 years.

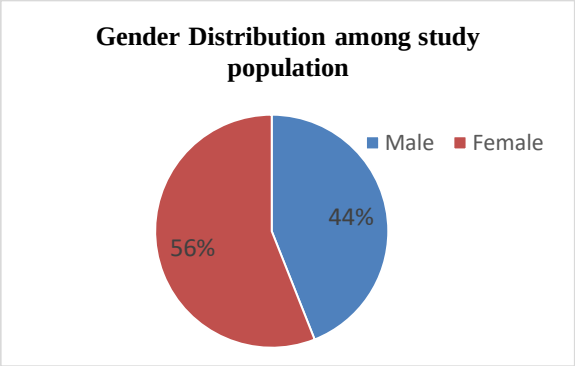

Figure 1 shows the gender distribution among the study population.

Females accounted for 56% of the study population, while males constituted 44%. Twenty patients did not give any vaccination history of diphtheria, while five patients gave a history of at least receiving one shot of the diphtheria vaccine. The majority of the patients belonged to low socioeconomic status (96%) (Table 1).

Table 1: Patient demographics

Variable	Number N=25	%
Mean age in years	6.6 ± 5.5	-
Gender		
Male	11	44
Female	14	56
Vaccination status		
Yes	5	20
No	20	80
Socioeconomic status		
Low	24	96
High	1	4

All participants had a history of membranous tonsillitis and significant respiratory difficulties. A latent interval of 4-49 days between the development of membranous tonsillitis and neurological problems was found. Isolated palatal paralysis was seen in 15 children (60%). All children(100%) showed nasal twang, regurgitation, and difficulty swallowing as bulbar symptoms. Three children (12%) showed signs of third cranial nerve involvement, exhibiting ptosis and diplopia. Two children (8%) experienced unilateral lower motor neuron facial palsy. One child exhibited 6th cranial nerve paralysis symptoms (table 2). 8 children (32%) experienced symmetrical limb weakness. Six patients had ascending paralysis, and two had descending paralysis. A large percentage of patients experienced hyporeflexia or areflexia (88.6%). Sensory symptoms such as paraesthesia and hyperaesthesia were observed in all patients. Two children (8%) developed diaphragmatic palsy (DP) after 2-4 weeks of having pharyngeal diphtheria. One patient required vasopressor medicines due to lost vasomotor tone. Other details of neurological manifestations among the study population are shown in the following table.

Fig 2.Showing the neurological complications in the study population

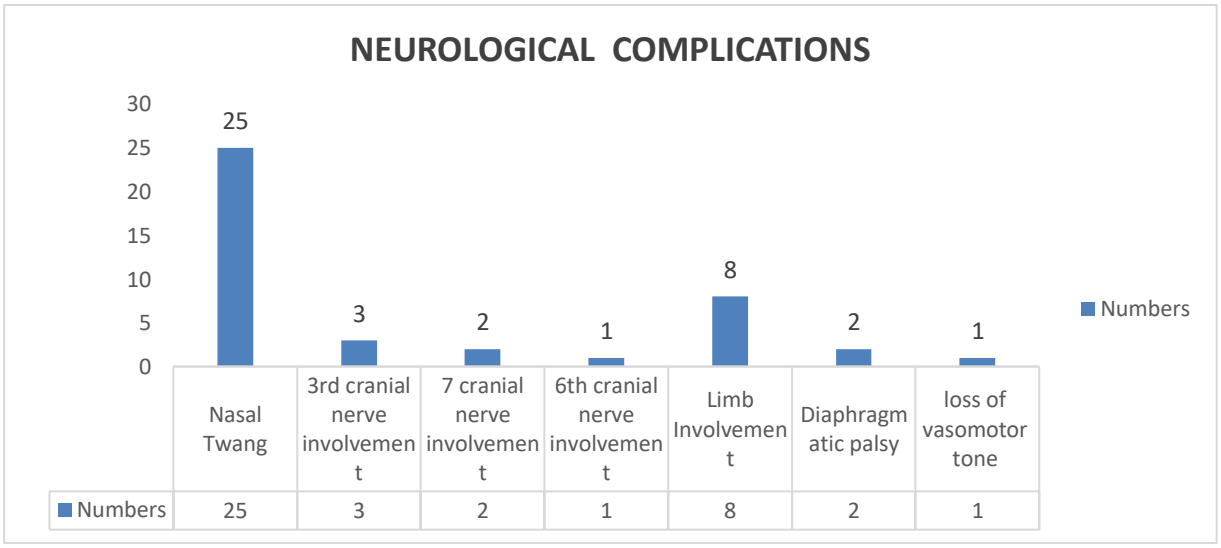

Table 2:Neurological complications of diphtheria in study population

Neurological complication	Number N=25	Percentage %	Onset week*	Recovery week*
Nasal tone of voice	25	100	1-5	4-10
3rd cranial nerve involvement	3	12	2-6	5-10
7th cranial nerve involvement	2	8	2-6	5-10
Limb involvement	8	32	4-10	13-23
Diaphragmatic paralysis	2	8	2-6	7-11
Vasomoter tone loss	1	4	4-5	4-6
*from the onset of respiratory symptoms				

Eight patients underwent the NCV test. Five patients had axonal degeneration due to demyelination, and two cases exhibited acute demyelination. All 25 patients recovered completely. Recovery time they were ranged from 1-6 weeks for isolated bulbar palsy to 10-16 weeks for quadriparesis and 6 weeks for DP (Table 2).

Discussion

Toxic strains of C. diphtheriae produce a toxin that causes pseudomembrane development in the pharynx, larynx, and nasal cavity. (4). The toxin causes widespread toxicity, myocarditis, and neurological implications. (9). Early disease symptoms include paralysis of the pharynx, larynx, and diaphragm muscles, which occur within a few days. (10).

Diphtheria is no longer limited to children under five years old. However, unimmunised and partly immunised youngsters are at higher risk due to diminishing protection from primary immunisation (11) . A serological investigation in the US revealed that 20%-50% of adults and adolescents were losing immunity to diphtheria. (12).During outbreaks, more teens and adults were diagnosed with diphtheria.

Diphtheria infections are on the rise in Pakistan and other nations due to weakened immunity. Most patients in our research were within the average age of 7 years (3-18 years), with around 20% being partly immunised. Jain et al. identified diphtheria in 54% of unimmunised children, which is way more than the results of our study. (13).

The severity of symptoms, membrane size, and toxin absorption by Schwann cells determine Diphtheria's course of illness (8). It impairs myelin production, resulting in neurological symptoms. (8). One study reported Neurological implications in 15%-27% of diphtheria patients. (7). Research by Barla et al. found that neurological problems occurred in 20% of individuals with moderate respiratory diphtheria and 75% of people with severe respiratory illness. (14).Our study indicated that 25 patients out of 28 with respiratory illness (89%) experienced neurological problems. This might be because our hospital is a tertiary care hospital; therefore, many cases have reached us relatively late, even without antitoxin.

Diphtheritic polyneuropathy is a severe consequence of diphtheria produced by C. diphtheria e's exotoxin (15). The phrase "diphtheritic polyneuropathy" refers to a range of neurological manifestations, beginning with palatal paralysis. Palatal paralysis is a frequent neurological problem that can develop alone or in combination with bulbar palsy. In our investigation, isolated palatal palsy was seen in 15 patients (60%).Manikyamba et al. identified isolated palatal palsy in 56% of patients. (16). This result is in line with the findings of our study; however, in contrast to our results, Mateen et al. identified palatal palsy in just 13% of patients. (17).

In our series, neurological problems appeared between 4 and 48 days (mean, 18 days) following respiratory symptoms. In a Latvian investigation involving 50 adults with diphtheritic paralysis, neurological problems emerged 2-50 days (mean, ten days) after the beginning of respiratory diphtheria. (18). It was a bit early in our series as compared to other studies. This might be due to severe diphtheria at the time of presentation.

Our study found 28 cases of bulbar palsy, with onset ranging from 2 to 6 weeks. Symptoms of diphtheritic polyneuropathy range from moderate to severe and usually appear within the first two weeks. These results are in line with the findings of previous research (10, 19).

Diphtheria can also affect cranial nerves. In our investigation, oculomotor nerve involvement was seen in four patients (12%).In addition to the third cranial nerve, facial paralysis was seen in just three patients (8%). Manikyamba et al. identified oculomotor nerve involvement in 15% of cases. (16) .These findings are the results of previous research, as mentioned before.Gampa et al. discovered it in 84% of patients (20), while Tejan noted it in 30% (8), contradicting our findings.

Eight children (32%) experienced symmetrical limb weakness. Six patients (75%) had ascending paralysis, and two (25%) had descending paralysis. Barla et al. found that paralysis was ascending in 33%, descending in 27%, and unclear in 40% of patients, but primarily symmetric (14) .In contrast to our study, descending quadriparesis was reported in 60%-90% of patients in one study (21).

Diphtheritic polyneuropathy is typically thought to be a demyelinating illness without axonal damage.In our study, Eight patients underwent the NCV test. It showed that five patients had axonal degeneration due to demyelination, and two cases exhibited acute demyelination. There is limited literature on axonal neuropathy in diphtheria. Swollen neurones apply external pressure, causing axonal injury. (7).

All 25 patients recovered completely. Recovery time ranged from 1-6 weeks for isolated bulbar palsy to 10-16 weeks for quadriparesis and six weeks for DP. Other studies also had similar results.(8, 19).

Diphtheria can result in autonomic dysfunction, including loss of vasomotor tone (8). In our investigation, just one case reported a loss of vasomotor tone; in contrast to the findings of our study, Jaya discovered that diphtheria is frequently associated with autonomic dysfunction (15). The results of CSF testing may indicate normal or increased protein levels. In this study, eight individuals underwent CSF examination. Four had normal CSF, whereas four had increased protein levels. Mateen found that all patients' results were expected (17). contrary to this, Manikyamba

found increased protein content in most cases (16). Mortality from diphtheria varies from 8% to 46% in various studies (1, 2).In this research, just nine (25%) patients died. Our study had many limitations that should be considered while interpreting these results. First, the small sample size limits the generalisation of the findings. Second, the limited sample size reduces the research's statistical significance. The research also has other limitations, including a lack of consideration for different complications in the study population.

Conclusion

Paediatricians should be concerned about diphtheritic polyneuropathy due to the recent recurrence in Pakistan. If a child is diagnosed with diphtheria, they should be provided with ADS immediately and monitored for neurological sequelae for 3-6 months. Diphtheritic polyneuropathy has a fair prognosis, but rapid identification and distinction from other neuropathies is crucial for effective therapy and contact tracing.

Declarations

Data Availability statement
All data generated or analysed during the study are included in the manuscript.
Ethics approval and consent to participate
Approved by the department concerned.
Consent for publication
Approved
Funding
Not applicable

Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

SALMAN ALI (Assistant Professor)
Conception of Study, Development of Research Methodology Design, Study Design, manuscript Review, and final approval of manuscript.
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Coordination of collaborative efforts.
AYESHA SADDIQUE (Assistant Professor)
Study Design, Review of Literature.
NOOR ZAHRA (Demonstrator)
Conception of Study, Final approval of manuscript.
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Manuscript revisions, critical input.
SYED ZEESHAN HAIDER NAQVI (Director IMBB, UOL)
Data entry and data analysis, as well as drafting the article.

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