COMPREHENSIVE ASSESSMENT OF NEUROLOGICAL COMPLICATIONS FOLLOWING COVID-19 VACCINATION

Nilufar S. Rashidova – MD, D.M.Sc., professor
Javlon J. Salimjonov – Ph.D. student
Tashkent state medical university (Tashkent, Uzbekistan)
javlon.doctor@gmail.com

Abstract. *Background: Neurological complications following COVID-19 vaccination have been reported worldwide, yet their frequency and clinical significance remain subjects of active evaluation. Although SARS-CoV-2 infection itself is associated with severe and diverse neurological manifestations, post-vaccination events appear to be substantially rarer. This study provides a comprehensive assessment of neurological outcomes, functional status, autonomic symptoms, psychological well-being and biomarker profiles among individuals who developed neurological complications after COVID-19 vaccination compared with fully vaccinated individuals without complications.*

Methods: *A total of 100 patients were analyzed, including 50 with neurological complications temporally associated with COVID-19 vaccination and 50 fully vaccinated controls without neurological symptoms. All participants underwent structured assessment using WHODAS 2.0 (12-item), HADS-A, HADS-D and COMPASS-31 scales. Serum IL-6 and Syndecan-1 levels were measured using ELISA. Correlation analyses were performed to examine relationships between biomarker levels and clinical indicators.*

Results: *Patients with neurological complications demonstrated significantly higher WHODAS 2.0 (26.9 ± 13), HADS-A (10.3 ± 1.1), HADS-D (8.1 ± 1.3) and COMPASS-31 (28.5 ± 5.5) scores compared with controls ($p < 0.001$ for all). IL-6 and Syndecan-1 levels were elevated in the main group (12.1 ± 4.3 pg/mL and 39.1 ± 4.3 ng/mL, respectively) relative to controls (4.9 ± 0.4 pg/mL and 22.7 ± 5.3 ng/mL; $p < 0.001$). Strong correlations were observed between biomarkers and clinical parameters, including IL-6 with WHODAS ($r = 0.60$), HADS-A ($r = 0.71$), HADS-D ($r = 0.67$) and COMPASS-31 ($r = 0.74$), as well as Syndecan-1 with WHODAS ($r = 0.58$), HADS-A ($r = 0.85$), HADS-D ($r = 0.81$) and COMPASS-31 ($r = 0.82$) (all $p < 0.001$). Despite these findings, neurological complications after vaccination were rare and far less severe than complications associated with SARS-CoV-2 infection.*

Conclusions: *Integrated clinical and biomarker analysis demonstrates that neurological complications following COVID-19 vaccination, although possible, are exceedingly rare and significantly less severe compared with the extensive and often debilitating neurological consequences of COVID-19 itself. Vaccination remains a safe and essential public health measure, with an overwhelmingly favorable benefit–risk profile. The observed associations between IL-6, Syndecan-1 and clinical severity may reflect underlying susceptibility in a small subset of individuals and highlight the value of comprehensive assessment for accurate diagnosis and management.*

Key words: *COVID-19 vaccination; neurological complications; IL-6; Syndecan-1; endothelial dysfunction; neuroinflammation; WHODAS 2.0; HADS; COMPASS-31; autonomic dysfunction; vaccine safety; SARS-CoV-2.*

Introduction. The coronavirus disease 2019 (COVID-19) pandemic has placed an unprecedented burden on global health systems and societies. Mass vaccination against SARS-CoV-2 has been the cornerstone of pandemic control, substantially reducing severe disease, hospitalization and mortality worldwide [1,2]. Multiple vaccine platforms—including

mRNA, adenoviral-vector and inactivated or protein-subunit vaccines—were developed and deployed at record speed, prompting the rapid establishment of enhanced pharmacovigilance frameworks at national and international levels. The World Health Organization (WHO) and its Global Advisory Committee on Vaccine Safety (GACVS) have emphasized the need for robust surveillance of adverse events following immunization (AEFI), including neurological adverse events of special interest (AESI), as a prerequisite for maintaining confidence in COVID-19 vaccination programmes [1,3,4]. Regulatory agencies such as the European Medicines Agency (EMA) have similarly mandated detailed risk-management plans (RMPs) for COVID-19 vaccines to ensure systematic identification, assessment and mitigation of potential risks in real-world use [5,6].

Neurological manifestations are now well-recognized both in the context of acute SARS-CoV-2 infection and, more rarely, following COVID-19 vaccination. Infection itself has been associated with a broad spectrum of central and peripheral nervous system complications, including encephalopathy, cerebrovascular events, seizures, demyelinating disorders and peripheral neuropathies [7,8]. Against this background, careful differentiation between neurological sequelae of infection and those potentially triggered by vaccination has become a major clinical and epidemiological challenge. Early safety signals from spontaneous reporting systems led to focused investigations of specific post-vaccination neurological entities such as Guillain–Barré syndrome (GBS), Bell's palsy, transverse myelitis, central nervous system (CNS) demyelination and cerebrovascular events, particularly in temporal association with adenoviral-vector vaccines [3,9–12].

Large population-based studies have provided important quantitative estimates of these risks. In a nationwide analysis from the United Kingdom, Patone et al. reported small but statistically significant excess risks of GBS and other selected neurological outcomes within 28 days after the first dose of ChAdOx1 nCoV-19; however, the corresponding risks following SARS-CoV-2 infection were several-fold higher, underscoring the overall favorable benefit–risk profile of vaccination [10]. Walker et al. similarly observed a short-term increase in GBS and Bell's palsy after the first dose of ChAdOx1 in a self-controlled case-series study, again with low absolute risk [11]. By contrast, Li et al. did not detect clear safety signals for immune-mediated neurological events such as Bell's palsy, encephalomyelitis and GBS after mRNA or adenoviral-vector COVID-19 vaccines in a large observational analysis, highlighting heterogeneity across platforms and populations [12].

Complementing these epidemiological data, systematic reviews have synthesized the rapidly expanding body of case reports and small series describing post-vaccination neurological events. Finsterer summarized a wide range of reported neurological adverse reactions—including headache, small-fiber neuropathy, myasthenic syndromes, demyelinating disease, stroke and functional neurological disorders—while emphasizing the rarity of serious events relative to the number of doses administered [13]. A more recent systematic review focusing on cardiac and neurological complications identified myocarditis, GBS, ischemic stroke and exacerbations of multiple sclerosis as the most frequently reported serious outcomes, yet concluded that these events remain uncommon and must be interpreted in the context of background incidence and infection-related risk [14]. Specific attention has also been directed to GBS: narrative reviews of post-SARS-CoV-2 vaccination GBS indicate that, while a temporal association has been described—particularly with adenoviral-vector vaccines—the overall risk appears lower than that associated with several prior vaccines and substantially lower than after COVID-19 itself [9,15].

Global pharmacovigilance networks have played a central role in interpreting these findings. WHO GACVS statements on thrombosis with thrombocytopenia syndrome (TTS) and

GBS following specific viral-vector vaccines have consistently reaffirmed that the benefits of COVID-19 vaccination in preventing severe disease and death outweigh the risks of these rare adverse events, while recommending continued active surveillance and clear risk communication [4,16]. Multi-country analyses from the Global COVID Vaccine Safety (GCoVS) project and regional reports have further confirmed that rates of AESI after COVID-19 vaccination generally remain within expected background ranges or show only modest elevations, depending on the outcome and platform [3,17]. At the same time, specialized national networks in various countries have documented a heterogeneous spectrum of neurological AEFI, with paresthesia, Bell's palsy and other sensory or motor phenomena constituting a large proportion of referrals, and encouraging outcomes after revaccination in most patients [18].

Despite this growing evidence base, several important knowledge gaps remain. First, the majority of available data derive from passive surveillance systems, administrative databases or highly selected case reports, which may be subject to under-reporting, reporting bias and limited clinical detail [3,10,11,14]. Second, many studies focus on single diagnostic entities (e.g. GBS or stroke) rather than providing a comprehensive overview of the full spectrum of nervous system complications temporally associated with vaccination. Third, standardized, in-depth neurological evaluations—integrating detailed clinical phenotyping, temporal patterns, neuroimaging, electrophysiological data and functional outcomes—are seldom reported in consecutive cohorts of patients evaluated in routine clinical practice [13,18]. As a result, the real-world burden, phenotype diversity and medium-term impact on disability and quality of life among individuals with suspected post-vaccination neurological complications remain incompletely characterized.

In this context, there is a clear need for structured, clinic-based studies that apply a uniform, "comprehensive assessment" approach to all patients presenting with neurological symptoms after COVID-19 vaccination. Such an approach should capture not only traditional diagnostic outcomes (e.g. specific syndromic labels), but also the severity of neurological impairment, the degree of functional limitation, and the relationship with prior SARS-CoV-2 infection and comorbidities. By systematically characterizing these patients, it becomes possible to refine clinical case definitions, identify patterns that may suggest plausible causal links, and distinguish them from coincidental events occurring against a background of high vaccination coverage.

Mass vaccination in Uzbekistan began on 1 April 2021. By mid-2023, the country had approved and used several COVID-19 vaccines — including ZF-UZ-VAC2001 (produced domestically), AstraZeneca, Sputnik V (and its single-dose variant Sputnik Light), Moderna, Pfizer/BioNTech, and Sinovac. According to official statistics, by 24 September 2023 about 22.09 million people (≈ 64.2 % of population) received at least one vaccine dose; 18.45 million (≈ 53.7 %) were fully vaccinated; and about 16.25 million (≈ 47.3 %) had received a booster dose — total number of administered doses reached ~82.2 million. Earlier, by late 2021, Uzbekistan had imported more than 42.8 million doses of various vaccines, and by early 2022 mass vaccination had already used tens of millions of doses.

The present study draws on this context to provide an integrated evaluation of nervous-system complications observed after COVID-19 vaccination in a defined clinical population, with the aim of contributing nuanced, local data to the global discourse on neurological safety and optimization of post-vaccination monitoring strategies [9].

Materials and methods. This observational, comparative, cross-sectional study included a total of 100 adult patients evaluated in the emergency neurology departments of major clinics in Tashkent, Uzbekistan, during the period 2021–2023, corresponding to the peak of

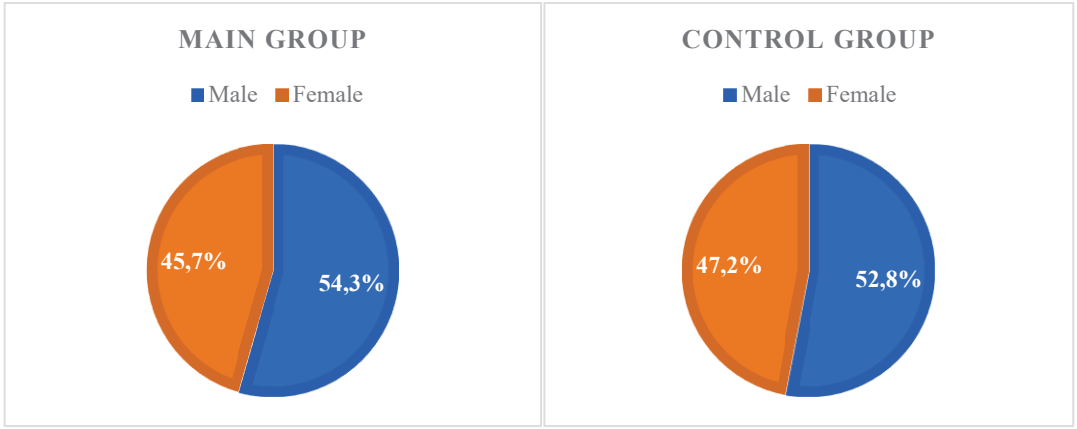
nationwide COVID-19 vaccination. All participants had completed at least one dose of an approved SARS-CoV-2 vaccine, while the control group consisted of fully vaccinated individuals. Patients were consecutively enrolled following neurological consultation or hospital admission. The study population was divided into two major groups: main group (n = 50) — patients who developed neurological complications temporally associated with COVID-19 vaccination. Documented neurological diagnoses included ischemic stroke, Guillain–Barré syndrome (GBS), transverse myelitis, meningoencephalitis, sensorineural hearing loss, transient ischemic attack (TIA), Bell's palsy. Control group (n = 50) — individuals who completed a full COVID-19 vaccination course without neurological complications and who underwent routine clinical follow-up.

To provide a comprehensive evaluation of the physical, neurological and psychosocial status of the participants, the following standardized clinical scales were utilized: Hospital Anxiety and Depression Scale (HADS) — to assess emotional and psychological stress indicators; COMPASS-31 (Composite Autonomic Symptom Score) — to quantify autonomic dysfunction; WHODAS 2.0 (12-item) — to evaluate disability and functional limitations across multiple domains. All patients underwent venous blood sampling within 72 hours of admission or evaluation. Laboratory biomarkers included: Interleukin-6 (IL-6) and Syndecan-1 (SDC-1). Both biomarkers were quantified using standardized enzyme-linked immunosorbent assay (ELISA) kits according to manufacturer protocols. These parameters were selected due to their established relevance in systemic inflammation, endothelial dysfunction and neuroimmune activation.

Ethical Considerations. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All participants provided informed consent prior to enrollment. The study protocol was approved by the institutional ethics committees of the participating Tashkent medical centers.

Statistical Analysis included descriptive analysis, comparison of means, correlation analysis and evaluation of the association between biomarkers and clinical scale scores. Quantitative variables were expressed as mean ± standard deviation, and categorical variables as percentages.

Results and discussion. In the main group, the mean age was 42.7 ± 9.7 years (range: 22–61 years) (Table 2.1). Among these patients, 38 (54.3%) were male and 32 (45.7%) females. In the control group, the mean age was 41.7 ± 9.9 years (range: 21–60 years). The sex distribution was identical: 38 males (54.3%) and 32 females (45.7%). There were no statistically significant baseline differences in age or sex between the two groups (pic.1.).



Pic. 1. **Distribution of patients by sex**

A total of 100 patients were analyzed, divided into a main group with neurological complications after COVID-19 vaccination and a control group without neurological complications. The comparison between the groups demonstrated pronounced differences in clinical status, functional capacity, psychological well-being, autonomic function and biomarker levels. Patients in the main group exhibited substantially higher functional impairment, as reflected by a mean WHODAS 2.0 score of 26.9 ± 13, compared with 9.4 ± 0.5 in the control group ($p < 0.001$), indicating a significant reduction in daily activity performance and a moderate degree of disability. Psychological assessment also revealed notable differences: anxiety levels measured by HADS-A were 10.3 ± 1.1 in the main group versus 6.1 ± 0.3 in controls ($p < 0.001$), while depressive symptoms measured by HADS-D reached 8.1 ± 1.3 versus 4.8 ± 0.2 ($p < 0.001$), demonstrating elevated emotional distress and psychological burden among patients with neurological complications. Similarly, autonomic dysfunction was markedly more severe in the main group, where the average COMPASS-31 score reached 28.5 ± 5.5 compared with 14.6 ± 0.7 in controls ($p < 0.001$), reflecting significant impairment of autonomic regulatory mechanisms across cardiovascular, gastrointestinal, sudomotor and vasomotor domains.

Table 1.

Results of evaluation scales

Scales	Main group (n=50)	Control group (n=50)	P
WHODAS 2.0	26.9 ± 13	9.4 ± 0.5	p < 0.001
HADS A	10.3 ± 1.1	6.1 ± 0.3	p < 0.001
HADS D	8.1 ± 1.3	4.8 ± 0.2	p < 0.001
COMPASS-31	28.5 ± 5.5	14.6 ± 0.7	p < 0.001

Biomarker profiling further supported these findings. IL-6 levels were significantly elevated in the main group, measuring 12.1 ± 4.3 pg/mL compared with 4.9 ± 0.4 pg/mL in the control group ($p < 0.001$), indicating heightened systemic inflammation. Syndecan-1 levels were likewise substantially higher among patients with neurological complications (39.1 ± 4.3 ng/mL) compared with controls (22.7 ± 5.3 ng/mL; $p < 0.001$), suggesting marked endothelial glycocalyx degradation and microvascular instability.

Table 2.

Results of biomarker indicators

Biomarkers	Main group (n=50)	Control group (n=50)	P
IL-6	12,1 ± 4,3	4,9 ± 0,4	p < 0,001
SDC1	39,1 ± 4,3	22,7 ± 5,3	p < 0,001

Correlation analyses demonstrated strong and statistically significant associations between biomarker levels and clinical measures. IL-6 showed a positive correlation with WHODAS 2.0 scores ($r = 0.60$; $p < 0.001$), indicating that higher inflammation was associated with greater functional disability. IL-6 also correlated strongly with anxiety (HADS-A; $r = 0.71$; $p < 0.001$) and moderately with depressive symptoms (HADS-D; $r = 0.67$; $p < 0.001$), suggesting that inflammatory activation contributes to both emotional distress and mood dysregulation. The association between IL-6 and autonomic dysfunction was even more pronounced, as

reflected by a strong correlation with COMPASS-31 scores ($r = 0.74$; $p < 0.001$), highlighting the role of systemic inflammation in destabilizing autonomic regulatory pathways.

Syndecan-1 demonstrated similar and, in some cases, even stronger associations. A moderate correlation with WHODAS 2.0 ($r = 0.58$; $p < 0.001$) indicated that endothelial injury contributes to functional impairment. The relationship between Syndecan-1 and psychological measures was particularly robust: a very strong correlation with HADS-A ($r = 0.85$; $p < 0.001$) and a strong correlation with HADS-D ($r = 0.81$; $p < 0.001$) suggest that endothelial dysfunction may influence neuropsychological responses and emotional stability. Furthermore, Syndecan-1 correlated strongly with COMPASS-31 scores ($r = 0.82$; $p < 0.001$), illustrating that microvascular and endothelial disturbances are closely linked to autonomic dysregulation. Collectively, these findings demonstrate that elevations in IL-6 and Syndecan-1 are consistently associated with worse functional outcomes, heightened psychological distress and more severe autonomic symptoms, suggesting that combined neuroinflammatory and endothelial mechanisms underlie the clinical manifestations of neurological complications after COVID-19 vaccination.

Conclusions. The results of this study confirm that while neurological complications may occur after COVID-19 vaccination, such events remain extremely rare and are typically far less severe than the well-documented neurological, functional and systemic complications associated with SARS-CoV-2 infection itself. Although patients with post-vaccination neurological manifestations demonstrated higher levels of functional impairment, psychological distress and autonomic dysfunction compared with controls, these cases represent isolated occurrences within the context of millions of vaccine doses administered.

Elevations in IL-6 and Syndecan-1 observed in the affected individuals suggest that inflammatory and endothelial mechanisms may contribute to the development of these rare complications; however, the magnitude of these biomarker changes is substantially lower than what is reported in patients with acute COVID-19 or post-COVID neurological syndromes. Importantly, the strength of the observed correlations reflects pathophysiological processes that can occur in susceptible individuals, but does not indicate a widespread or systemic safety concern.

Overall, the findings reinforce that COVID-19 vaccination remains a safe and essential public health intervention, with a benefit–risk profile overwhelmingly favoring vaccination. The neurological complications associated with vaccination are significantly less frequent, less severe and less clinically burdensome than those resulting from SARS-CoV-2 infection. Vaccination continues to play a critical role in reducing hospitalization, long-term disability and mortality, and the rare neurological reactions identified in this study should be viewed within the broader context of the substantial protective effects of immunization.

REFERENCES

1. Agarwal S., et al. Neurological complications following COVID-19 infection: A systematic review. *Journal of Neurological Sciences.* 2021.

2. Canadian Special Immunization Clinic Network. Report on neurological adverse events following immunization. National Surveillance Summary, 2022.

3. European Medicines Agency (EMA). COVID-19 vaccines: Risk-Management Plans (RMPs). EMA Safety Documents. 2021–2023.

4. Finsterer J. Neurological side effects of SARS-CoV-2 vaccinations. *Acta Neurologica Scandinavica.* 2022;145(1):5–19.

5. Global Advisory Committee on Vaccine Safety (GACVS). COVID-19 vaccine safety updates and statements. World Health Organization, 2021–2023.

6. Li X., et al. Association between COVID-19 vaccination and immune-mediated neurological disorders: Population-based cohort study. *BMJ.* 2022;376:e068373.

7. Patone M., et al. Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection: A population-based analysis. *BMJ.* 2021;374:n1673.

8. Pérez-López S., et al. Neurological manifestations of COVID-19: Updated evidence review. *Neurología.* 2021.

9. Republic of Uzbekistan Ministry of Health. COVID-19 vaccination statistics and national immunization programme reports (2021–2023).

10. Sookaromdee P., Wiwanitkit V. Neurological adverse events following COVID-19 vaccination: Updated clinical review. *Clinical Neurology and Neurosurgery.* 2022.

11. Walker A., et al. Risk of Guillain–Barré syndrome after COVID-19 vaccination: Self-controlled case-series study. *Lancet Neurology.* 2022;21(7):650–660.

12. World Health Organization (WHO). COVID-19 vaccine safety surveillance manual. WHO Press, 2021.

13. WHO. Background rates of adverse events of special interest relevant to COVID-19 vaccines. WHO Technical Document, 2021.

14. WHO Regional Office for the Western Pacific. Regional pharmacovigilance report on COVID-19 vaccine safety. WPRO, 2022.

15. Xu S., et al. Cardiovascular and neurological adverse events following COVID-19 vaccination: A systematic review. *Vaccines.* 2022;10:1320.

16. Yusuf N., et al. Guillain–Barré syndrome following COVID-19 vaccination: Narrative review. *Neurology International.* 2022.

17. Zhang Y., et al. Epidemiology of neurological complications during the COVID-19 pandemic: A global review. *Brain, Behavior, and Immunity.* 2021.

18. Zhang Z., et al. Neurological adverse events following SARS-CoV-2 vaccination: Comprehensive clinical review. *Frontiers in Neurology.* 2022;13:834000.