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Diagnostic value of anti-VZV IgG in neurological diseases among varicella unvaccinated individuals

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Abstract

Varicella zoster virus (VZV) is a neurotropic alphaherpesvirus that causes neurological manifestations either as a complication of primary infection or reactivation. VZV induced neurological diseases have a good prognosis when confirmed early and treated with anti-viral therapy. Myelitis, encephalitis, ventriculitis or meningitis can occur without a telltale rash in immunocompetent and immunocompromised individuals making the diagnosis difficult. We analyzed CSF and serum samples from 30 unvaccinated study participants (17 male and 13 female) to determine the presence of VZV DNA by PCR in CSF and to estimate serum and CSF anti-VZV IgG and albumin levels in participants with neurological manifestations with/without rash. Anti-VZV IgG was detected in CSF ($n=22$, [73%]) and serum ($n=29$, [97%]) of pediatric and adult participants. Anti-VZV IgG were detected in CSF of participants with varied clinical presentation altered sensorium ($n=8$, [36%]), meningitis ($n=4$, [18%]), acute febrile illness ($n=3$, [14%], encephalopathy/meningoencephalitis ($n=2$, [9%]), irritability ($n=2$, [9%]) and each patient from cerebrovascular stroke, demyelinating disorder and febrile seizure ($n=1$, [4.5%]). VZV DNA was detected from one participant and CSF serum albumin levels were elevated in 53% of study participants. VZV DNA is present up to 1–2 weeks post onset of disease, after which anti-VZV antibody may be the only indicator of disease and therefore both VZV DNA and anti-VZV IgG need to be tested for in CSF. As VZV DNA and VZV IgG antibody are both good indicators of VZV reactivation, routine testing would result in reduced morbidity and mortality by early detection of disease and antiviral treatment.

Keywords VZV · Neurological manifestations of VZV · anti-VZV IgG · VZV DNA PCR

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Introduction

Varicella is a vaccine preventable and self-limiting disease. Central nervous system (CNS) complications of varicella zoster virus (VZV) following primary infection and reactivation are known to occur especially in unvaccinated individuals. Complications of primary varicella in the CNS include meningitis, encephalitis, cerebellar ataxia, seizure, myelitis and vasculopathies (Lenfant et al. 2022; Science et al. 2014). Reactivation of VZV in adults in the cranial nerve and trigeminal ganglia causes CNS manifestations that are life-threatening if not diagnosed early and treated promptly (Lenfant et al. 2022). Both immunocompetent and immunocompromised individuals are prone to VZV CNS infections, but in immunocompromised hosts it is well described (Science et al. 2014). There is a marked decreased incidence of varicella and associated CNS complications in children in countries which adopted routine universal immunization programs (UIP). Zoster vaccines are also known to reduce zoster and neurological complications in adults (Grahn and Studahl 2015).

The use of high sensitivity PCR in routine clinical practice enabled the rapid diagnosis of the viral infections of the CNS and assists in potential use of antiviral therapy (Ihekwaba et al. 2008). During acute phase of the disease, in the absence of rash, routine diagnosis is done for herpes simplex virus (HSV), but not for VZV. Detection of VZV DNA in CSF during acute phase of the disease strongly points to active infection. Productive virus particles are eliminated by host immune response within one to two weeks. In such instances, anti-VZV antibody in the CSF may be detected, which is not normally found in CSF of healthy individuals (Gilden et al. 1998). Unlike HSV-1 which usually presents as an acute CNS infection, neurological complications due to varicella or zoster may present as acute, subacute, or chronic infection. Thus in protracted VZV diseases like encephalitis or myelitis, diagnosis of VZV DNA in CSF has less utility compared to acute HSV encephalitis. (Gilden et al. 1998).

To detect the neurological diseases caused by VZV, anti-VZV IgG in CSF is a more reliable method (Nagel et al. 2007) and the role of anti-VZV IgG in vasculopathy is well established (Gilden et al. 2009; Nagel et al. 2007). The diagnosis of VZV vasculopathy is missed most of the time, due to the long duration between the appearance of rash and stroke, no rash, or the absence of VZV DNA and pleocytosis in CSF and hence antiviral treatment is not initiated (Nagel et al. 2007). Due to rapid viral clearance in the CNS for most of the viral infections, detection of viral DNA by PCR rarely confirms the diagnosis. Demonstration of intrathecal virus specific antibody confirms the diagnosis of infection, especially in PCR negative case (Shamier et al. 2021).

In immune privileged areas like the CNS, calculation of antibody index in CSF is helpful to confirm the clinical suspicion of infection. When no pathogen is detected by direct methods, the antibody index provides the evidence of infection by demonstrating pathogen specific intrathecal antibodies. The blood-brain barrier usually restricts the systemic antibodies to enter the brain. However, the function changes if there is inflammation (Shamier et al. 2021).

The CSF albumin to antibody ratio, also known as the CSF/serum albumin ratio, IgG index used to assess blood-brain barrier integrity elevated ratio indicates increased permeability of blood brain barrier, allowing antibodies to enter CNS thus acting as an indirect measure of blood-brain barrier dysfunction. Since the elevated ratio is associated with various neurological conditions, measuring the ratio aids in diagnosis and differentiation of the conditions in combination with other clinical and laboratory findings (Shamier et al. 2021).

In France, VZV is the commonest herpesvirus to cause human infections and second cause of viral encephalitis. The incidence of HSV and VZV associated encephalitis has increased over the last decade (Mirouse et al. 2022).

In this report we investigated the presence of VZV DNA and anti-VZV IgG in CSF and serum, and albumin levels in CSF and serum of 30 varicella unvaccinated individuals with acute, sub-acute and chronic neurological conditions.

Materials and methods

Study design and ethics approval

The study design was conducted adhering to the declaration of Helsinki, 1964 and was approved by the Institutional Ethics Committee of Sri Ramachandra Institute of Higher Education and Research (IEC-NI/17/JUN/60/64).

Participants and clinical samples

The study participants $n = 30$ was enrolled (0–75 years of age) based on the inclusion and exclusion criteria. Inclusion and exclusion criteria were listed in Table 1. A written informed consent/assent form was collected from all participants/immediate relative before enrolment. Clinical proforma was maintained for all the study participants with all relevant clinical details. The CSF and serum samples ($n = 30$) were processed, aliquoted and stored in -80°C.

Quantitative real time PCR

VZV DNA real-time quantitative PCR was performed using Artus ^{R} VZV RG PCR kit (Qiagen, Hilden, Germany) using

Table 1 Inclusion and exclusion criteria of study participants

Inclusion criteria	Exclusion criteria
Patient with evidence of neurological symptoms (fever/vomiting/headache/altered sensorium/neck stiffness, seizure) with or without rash.	Patients with pyogenic or fungal meningitis Patients on anti-viral therapy Pregnant women

Extraction of DNA: DNA was extracted using QIAmp DNA Blood Mini kit (Qiagen, Hilden, Germany)

Rotor-Gene Q 5 plex platform Real-time PCR. The analytical sensitivity of the assay is 0.136 copies/µl ($p = 0.05$).

>Quantitative anti-VZV IgG ELISA

Anti-VZV IgG antibodies were estimated by quantitative ELISA using a VZV IgG ELISA kit (Abnova, Taiwan). Absorbance was measured at 450 nm with reference reading at 670 nm using microplate reader (ThermoFischer Scientific, India). The concentrations of anti-VZV antibodies (mIU/mL) were calculated by antibody (mIU) in sample from calibration curve with the sample dilution of 101x for serum and 2x for CSF. The lower limit of quantification of the assay was 30 mIU/mL. A total of 30 samples were tested as paired samples with serum and CSF were analyzed along with other CSF samples in the same run with reference to the standard curve.

Albumin levels were estimated in CSF and serum samples. CSF Serum albumin index is the ratio of CSF albumin and serum albumin, that indicates the integrity of blood brain barrier. In clinical practice, the index value greater than 9 is considered abnormal and indicative of blood brain barrier dysfunction.

Statistical analysis: Statistical analysis was done using R software version 4.3.2 to calculate the p value using paired T test for anti-VZV IgG and albumin levels in serum and CSF samples.

Results

Combined clinical and laboratory analyses were completed for 30 patients including pediatric (aged 0–18 years) ($n = 7$) and adults (> 18 years) ($n = 23$). Among the 30 participants 17 (57%) were male and 13 (43%) were female.

Clinical features, CSF analysis and virological studies

Clinical diagnosis, CSF analysis and virological studies of all 30 patients are shown in Table 2. Of the 30 patients, CSF pleocytosis was seen in 15 (50%) and CSF protein level was elevated in 22 (73%). All the adult participants had a history of varicella infection in childhood and none of the pediatric participants had a history of chickenpox. None of our study participants were vaccinated for varicella.

Virological study

VZV DNA was detected in CSF from one patient (3%) (#VZVCS17) admitted with altered sensorium with viral load of 30,564 copies/mL, all others tested negative for VZV DNA. Anti-VZV IgG was detected in CSF from ($n = 22$) 73% and in serum from ($n = 29$) 97% from pediatric and adult patients.

CSF Versus serum antibody

Of the 30 CSF samples tested for anti-VZV IgG antibodies, 22 (73%) had > 150mIU/mL of anti-VZV antibodies with the median of 603.18 mIU/mL. The anti-VZV IgG antibodies were detected in 29 (97%) participants from serum samples with the median of 122607.4 mIU/mL. Anti-VZV IgG were detected in CSF of participants with varied clinical presentation altered sensorium ($n = 8$, [36%]), meningitis ($n = 4$, [18%]), acute febrile illness ($n = 3$, [14%], encephalopathy/meningoencephalitis ($n = 2$, [9%]), irritability ($n = 2$, [9%]) and each patient from cerebrovascular stroke, demyelinating disorder and febrile seizure ($n = 1$, [4.5%]). Anti-VZV IgG was detected in serum samples from all the patients except one (#VZVCS6).

CSF versus serum albumin

CSF and serum albumin levels were tested for all 30 patients. The mean value of CSF albumin was 407.89 mg/dL which is nearly nine times the normal upper range of healthy individuals (normal value of CSF albumin- 11-48 mg/dL) and serum albumin level was 3.363 g/dL, which is normal range (normal value of serum albumin– 3.5–5.2 g/dL). About $n = 16$ (53%) patients of the 30 study participants had blood brain barrier dysfunction.

Statistical analyses were conducted using R software using paired t test for anti-VZV IgG between serum and CSF samples, and it was found to be statistically significant ($p < 0.001$) (Fig. 1). Albumin ratio between CSF and serum samples were analyzed using R software and it was found to be statistically significant ($p < 0.001$) (Fig. 2A).

Table 2 Correlation of demographic, clinical, CSF analysis, serum and CSF albumin analysis and virological studies of paired CSF and serum samples

Lab ID #VZVCS	Age/ Sex	Clinical Diagnosis	CSF ANALYSIS				Albumin				VIROLOGICAL STUDIES		
			WBC cells/ cumm	RBC cells/ cumm	Sugar mg/dL	Protein mg/dL	CSF mg/L	Serum g/dL	Serum g/L	CSF Serum Albumin index	CSF antibody (mIU/ml)	Serum antibody (mIU/ml)	VZV DNA (copies/ mL)
							NEONATES (<28 DAYS)						
#VZVCS1	1D/F	Encephalopathy	3	Nil	72	68.6	486	3	30	16.2	646.18	138407.37	BDL
#VZVCS2	1D/F	Altered sensorium	377	13,400	44	141	662	3.6	36	18.3	711.54	63539.1	BDL
#VZVCS3	1D/M	Irritability	Nil	Nil	43	124.8	786	4.3	43	18.2	455.26	34696.53	BDL
#VZVCS4	1D/M	Irritability	10	1	51	93.6	606	4.2	42	14.4	491.36	565,600	BDL
#VZVCS5	9D/M	Acute febrile illness	5	Nil	76	104.3	40	3.2	32	1.3	146.74	9504.10	BDL
							PEDIATRIC (1 MONTH- 18 YEARS)						
#VZVCS6	6/M	Meningitis	5	Nil	62	26	130	4	40	3.3	<30	<30	BDL
#VZVCS7	7/M	Acute febrile illness	3	1100	52	41.6	84	3.6	36	2.3	<30	6170.09	BDL
#VZVCS8	16/M	Encephalitis	Nil	Nil	53	62.7	309	4.1	41	7.5	142.76	13806.7	BDL
							ADULT (> 18 YEARS)						
#VZVCS9	21/M	Acute febrile illness	30	Nil	68	468	2195	3.4	34	64.5	1915.78	47791.18	BDL
#VZVCS10	31/F	Intracranial hypertension	10	Nil	84	18.3	61	3.0	30	2	74.36	59196.1	BDL
#VZVCS11	33/F	Encephalitis	1	Nil	44	17.4	54	2.8	28	1.9	217.42	65015.72	BDL
#VZVCS12	34/M	Meningitis	350	Nil	175	54	335	4.2	42	7.9	272.8	204606.81	BDL
#VZVCS13	34/M	Altered sensorium	28	1000	96	48.1	209	2.9	29	7.2	241.26	52192.76	BDL
#VZVCS14	36/F	Febrile seizure	Nil	Nil	90	19	49	3.1	31	1.5	82.06	42593.72	BDL
#VZVCS15	41/F	Meningitis	121	Nil	69	117.6	581	2.6	26	22.3	1297.14	141688.86	BDL
#VZVCS16	43/M	Meningoencephalitis	202	100	81	66.6	371	3.5	35	10.6	<30	15232.82	BDL
#VZVCS17	47/F	Altered sensorium	9	Nil	61	54.2	271	3.7	37	7.3	198.84	46972.07	BDL
#VZVCS18	52/M	Meningitis	5	Nil	68	146.5	409	3.8	38	10.8	2379	49781.89	BDL
#VZVCS19	54/F	Altered sensorium	30	Nil	84	20.1	76	3.6	36	2.1	178.24	93675.48	BDL
#VZVCS20	56/M	Headache	184	Nil	63	26.9	124	2.7	27	4.6	112.14	254586.66	BDL
#VZVCS21	59/M	Meningitis	4	Nil	64	84	763	3.6	36	21.2	4051.62	400340.77	BDL
#VZVCS22	62/F	Demyelinating disorder	Nil	Nil	50	35.4	119	3.9	39	3	237.46	130205.16	BDL
#VZVCS23	63/F	Altered sensorium	3	Nil	108	46	319	3.2	32	10	369.6	36009.53	BDL
#VZVCS24	69/F	Altered sensorium	10	60	90	61.4	212	2.4	24	8.8	338.56	62475.57	BDL
#VZVCS25	70/M	Febrile Seizure	6	Nil	163	141	924	3.3	33	28	2107.48	471095.3	BDL
#VZVCS26	70/M	Acute febrile illness	10	Nil	109	47.7	272	2.8	28	9.7	2926.46	146101.55	BDL
#VZVCS27	70/M	Cerebrovascular stroke	50	6000	104	3935	373	2.8	28	13.3	482.4	8098.18	BDL
#VZVCS28	71/F	Altered sensorium	3	Nil	56	77.4	414	2.9	29	14.2	446.22	100624.28	BDL
#VZVCS29	72/M	Altered sensorium	3	Nil	145	97.5	539	3.8	38	14.2	951.68	607,010	30,564
#VZVCS30	75/F	Acute febrile illness	5	1000	117	90.6	463	2.9	29	15.9	498.28	72814.94	BDL

BDL- below detectable level, BDL for ELISA < 30mIU/mL, Negative- <120mIU/mL, Indeterminate 120-150mIU/mL, Positive - >150mIU/mL, BDL for PCR (< 50 copies/mL). Normal range– CSF cell count WBC- 0–5 cells/cumm, RBC– 0 cells/cumm, Sugar- 40-80 mg/dL, Protein– 15–45 mg/dL, CSF albumin- 11-48 mg/dL, serum albumin– 3.5–5.2 g/dL. CSF Serum albumin index is the ratio of CSF albumin and serum albumin, that indicates the integrity of blood brain barrier. In clinical practice, the index value greater than 9 is considered abnormal and indicative of blood brain barrier dysfunction (Abdalla 2003)

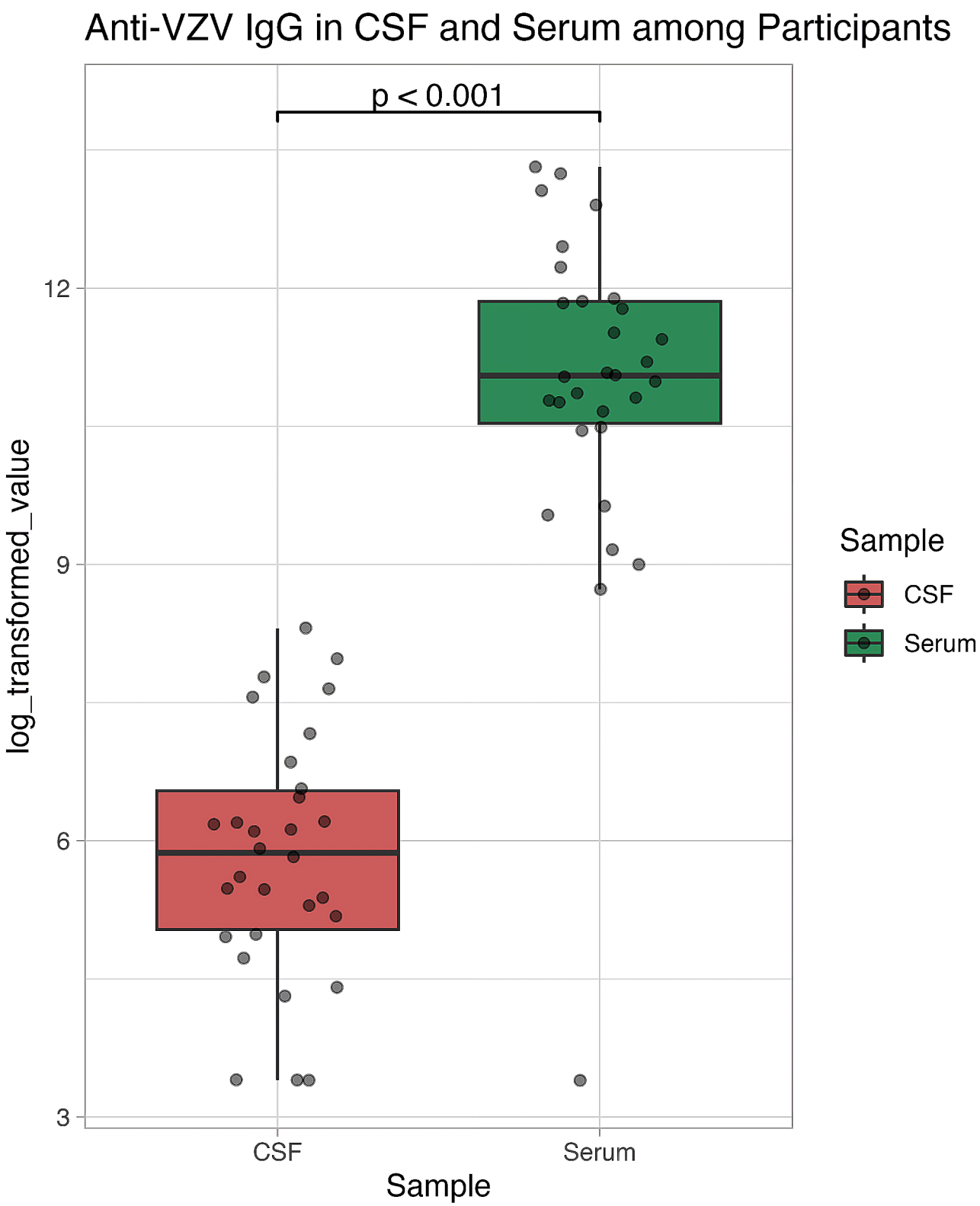

Fig. 1 Box and whisker plot shows anti-VZV IgG titer of serum and CSF from study participants with CNS manifestations. Box represents the interquartile range with median, Whisker extended to minimum and maximum values. Paired t test ($p < 0.001$) was done and found to be statistically significant. The study participants included are unvaccinated for varicella from pediatric ($n = 8$) and adult ($n = 22$) participants

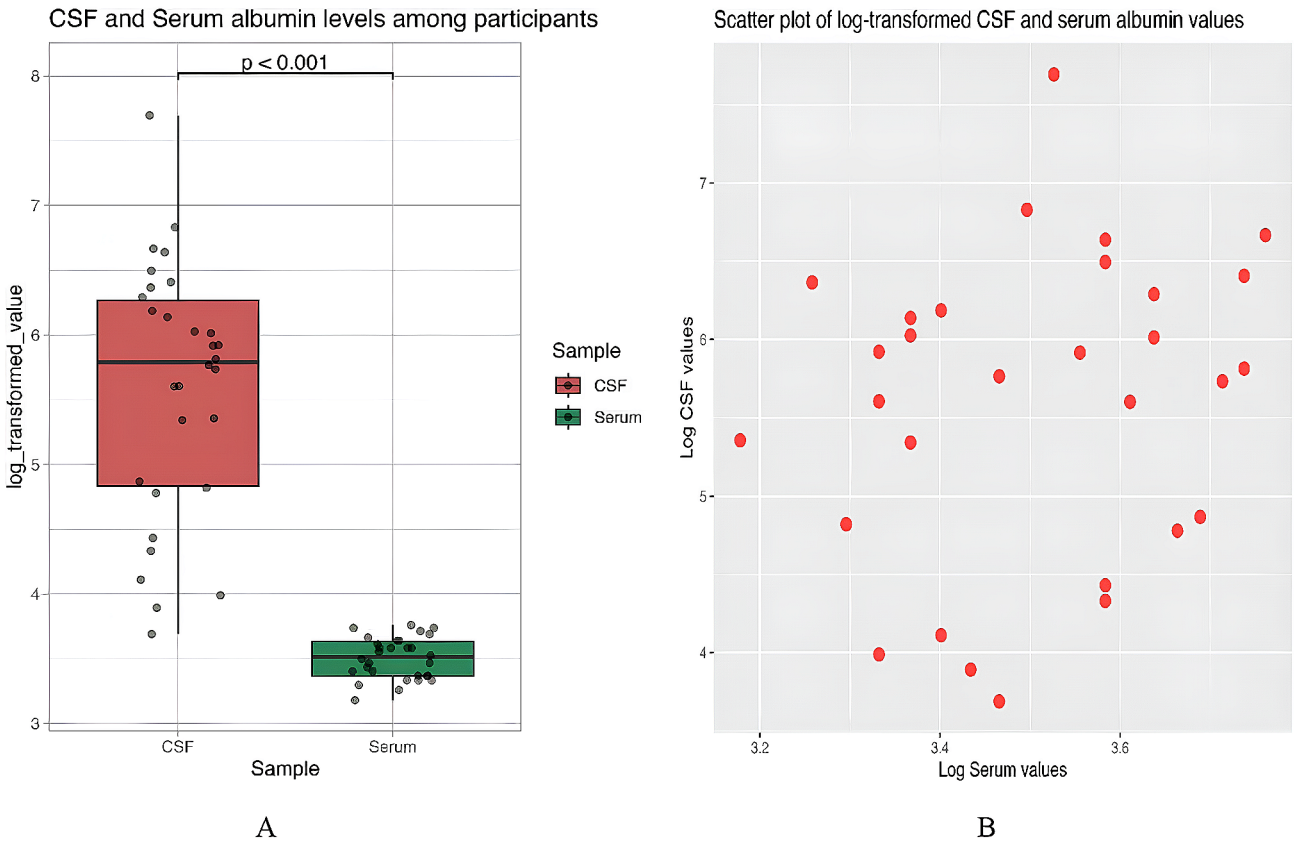

Fig. 2 **A**. Box and Whisker plot shows serum and CSF albumin levels from study participants with CNS manifestations. Box represents the interquartile range with median, Whisker extended to minimum and maximum values. Paired t test ($p < 0.0001$) was done and found to be statistically significant. **B**. Scatter plot shows the differences in the albumin levels against CSF and serum samples

Treatment and outcome All the patients that tested positive for VZV DNA or anti-VZV IgG antibodies were treated with intravenous acyclovir for 14 days duration and all of them showed clinical improvement.

Discussion

Globally, stroke is one of the common causes of high mortality and morbidity. The known risk factors for stroke include hypertension, obesity, and diabetes. Recently, viral etiology was also found to be associated as risks factor for stroke, which includes VZV, human immunodeficiency virus (HIV) and cytomegalovirus. VZV is the only virus that can directly invade the cerebral arteries and cause vasculopathy (Nagel et al. 2010).

The incidence and prevalence of VZV associated stroke is unknown, while in children it is estimated to cause 7 to 31% of arterial ischemic stroke and 44% of cases of transient cerebral ischemia (Nagel et al. 2010). In adults, VZV associated vasculopathy is was detected in 1.5 to 4.4% of immunocompromised adults (Nagel et al. 2010). In a review from China VZV associated ischemic stroke (74%) has been reported to be more common than other strokes in adults (Wu et al. 2022). The increased risk of stroke after zoster was reported to be 30% in Taiwan (Gershon et al. 2015; Kang et al. 2009), 17% in Denmark (Sreenivasan et al. 2013) and a 1.74-2.24-fold increase in the UK (Breuer et al. 2014). There is a reduced risk of stroke in about 55% of patients who received antiviral therapy compared with untreated zoster patients, proving the importance of antiviral treatment in zoster patients (Amlie-Lefond and Gilden 2016).

Diagnostic value of detection of anti-VZV IgG in vasculopathy and hemorrhagic stroke is well established (Gilden et al. 2009; Nagel and Bubak 2018; Wu et al. 2022) though well-established CSF antibody are not routinely determined. Previously we have documented the importance of detection of anti-VZV IgG from CSF samples of unvaccinated pediatric and adults' participants with diverse neurological manifestations (Srikanth et al. 2024).

In our study, the anti-VZV IgG was detected in 73% of study participants with different neurological manifestations. The antibody titer was high in CSF samples among adults, which is statistically significant ($p = 0.03$).

The antibody titer between serum and CSF samples is ($p < 0.001$). The anti-VZV IgG antibody was detected from those with altered sensorium ($n = 8/8$), irritability ($n = 2/2$), cerebrovascular stroke ($n = 1/1$), and demyelinating disorder ($n = 1/1$), 80% of meningitis ($n = 4/5$), 67% of encephalitis ($n = 2/3$) and 60% with acute febrile illness ($n = 3/5$) of study participants. A proportion 53% of the study participants were observed to have increased CSF serum albumin levels, which is indicative of blood brain dysfunction.

Normally, presence of IgG antibody in serum maybe due to current infection or vaccination. Since none of our study participant were vaccinated for VZV, the presence of anti-VZV IgG in CSF and serum indicates recent infection. The possibility of the anti-VZV IgG leaking into the CNS is to be understood in the context of lack of varicella vaccination. Most of varicella vaccinated individuals will have IgG antibodies in serum. In varicella unvaccinated individuals anti-VZV IgG will represent past or recent infection and its presence in the CNS is indicative of disease especially among those with CNS manifestations.

VZV vasculopathy can be acute or chronic manifestation due to VZV reactivation (Bubak et al. 2023); detection of VZV DNA in CSF using PCR in particular poses diagnostic challenge. The detection rate of VZV DNA in CSF in vasculopathies was 30%, whereas anti-VZV antibody were present in 93% (Gilden et al. 2009).

Neurological disease produced by VZV has a good prognosis when detected early and treated with anti-viral therapy. However, the challenge is in identifying the cases with VZV involvement. Atypical manifestations make clinical diagnosis and identification difficult. CNS diseases like myelitis, granulomatous arteritis (large vessel encephalitis), small vessel encephalitis, ventriculitis and meningitis can occur without a telltale rash in both immunocompetent and immunocompromised individuals. (Gilden et al. 2000) Thus, the methods of diagnosis need to be updated. PCR detection of VZV DNA and antibodies to VZV are strong indicators of disease. (Grahn and Studahl 2015). In VZV induced myelitis, evidence of VZV infection can be demonstrated by detection of VZV DNA and VZV antibody in the CSF (Gilden et al. 1994; Hung et al. 2012). The detection of VZV DNA in CSF sample from patient with large vessel encephalitis proves the direct invasion of VZV in cerebral arteries (Melanson et al. 1996). Detection of anti-VZV IgG and VZV DNA from four patients with encephalitis was proved the diagnosis of encephalitis in CNS manifestations of VZV disease (Gilden et al. 1998). Detection of antibodies to VZV in the sera is not a good indicator of ongoing infection, since most adults will have serological IgG antibodies that persisted from childhood infection, subclinical infection or following vaccination (Vafai et al. 1988; Zerboni et al. 1998). Therefore, there is a need for routine CSF analysis for VZV DNA and antiviral antibodies in CNS disease. (Grahn and Studahl 2015).

The detection of VZV DNA in stroke cases in other studies were found to be 28% and anti-VZV IgG 100% in USA (Nagel et al. 2007) and 20% PCR positive 60% anti-VZV IgG in South Africa (Marais et al. 2022). The detection of VZV DNA from CNS infection varied between 1.6 and 3.1%. In Finland 1.6% (Koskiniemi et al. 2001), in Switzerland 2.1% (Becerra et al. 2013) and in Sweden 3.1% (Bergström 1996a). Gilden et al. have documented several case reports of VZV reactivation disease in the absence of rash. There are mounting body of literature supports the routine use of VZV DNA and VZV antibody in patients with neurological manifestations of disease (Becerra et al. 2013; Bergström 1996b; Echevarria et al. 1997; Gilden et al. 1994; Koskiniemi et al. 2001) as mortality can be prevented by early detection and treatment with antiviral therapy.

In this present study, we have looked for both VZV DNA and VZV IgG antibodies that were tested in the CSF samples of patients with diverse clinical manifestations affecting the CNS. The focus on IgG antibody was deliberate as VZV IgM antibody, an indication of recent infection, has limited value and is present only up to a maximum of 10 weeks (Min et al. 2016; Nagel and Gilden 2013). VZV IgG antibody that can remain positive in the CSF sample for several years, is a better indicator of VZV CNS disease caused by reactivation and is more specific than VZV DNA (Nagel et al. 2007).

In 44 countries varicella vaccination is adopted in UIP either as partial or complete vaccination schedule. In 29 countries, two doses of a complete vaccination schedule was implemented with first dose administered at the age of 12 months and 4–6 years old for the second dose (Lee et al. 2022). In the context of the unvaccinated older Indian population, susceptibility to severe forms of CNS disease, despite having natural immunity from primary infection, remains high. Moreover, the natural seropositive protection against VZV has a delayed peak at 15–25 years of age in India (Venkitaraman et al. 1986). As VZV DNA and VZV IgG antibody are both good indicators of VZV reactivation, routine testing would result in reduced morbidity and mortality by early detection of disease. In 2006, the Advisory Committee on Immunization Practices (ACIP) of the Indian Academy of Pediatrics recommended a two dose vaccination schedule for children in India (*IAP| ACVIP*, n.d.). This recommendation only targets the younger population however and leaves a larger part of the population vulnerable.

Conclusion

As the increased risk of stroke in zoster patients is well established with certain neurological conditions following reactivation of VZV, early detection of either VZV DNA or anti-VZV IgG in CSF of patients with neurological manifestations is crucial. The respective antiviral treatment with acyclovir will reduce the incidence of VZV associated vasculopathy among zoster patients.

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Author contributions IA-Contributed to the study design, collection of clinical samples, processing, Realtime PCR assay, ELISA, CSF and serum albumin ratio, data interpretation and preparation of the manuscript. SSR data analysis and drafted the manuscript. GK contributed to laboratory work and drafting the manuscript. SG contributed to data analysis and drafted the manuscript. SNJ contributed to data analysis and drafted the manuscript. JA and RS contributed to sample collection, performance of assay. RR, SV, KK, LNR and UB contributed to the collection of clinical samples and clinical details. RM contributed to the conception and design of the study and preparation of the manuscript. JTB contributed to sequence analysis and interpretation of it and preparation of the manuscript. ANB contributed to data analysis and preparation of the manuscript. MAN contributed to the conception and design of the study and preparation of the manuscript. PS contributed to the conception and design of the study, preparation of manuscript and interpretation of data and critical revision of intellectual content and final approval of the version to be published.

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Data availability All data (deidentified) generated data in this study will be made available. The comprehensive data of this study is available with the corresponding author in case of any clarification. Additional related documents including de-identified participants' data as per ICMJE guidelines, study protocol, informed consent will be made available.

Declarations

Institutional review board statement Institutional Ethics Committee approval was obtained prior to start of the study, the IEC number- IEC-NI/17/JUN/60/64.

Informed consent Informed consent/Assent form was obtained from all the participants/guardian.

Conflict of interest The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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