

VIRAL ANTIBODIES IN BLOOD IN OBSESSIVE COMPULSIVE DISORDER

SUMANT KHANNA, V. RAVI, POORNIMA K. SHENOY,
A. CHANDRAMUKHI & S.M. CHANNABASAVANNA

ABSTRACT

IgG viral antibodies for herpes simplex virus -1, varicella zoster virus, cytomegalovirus, measles and mumps were studied in 76 subjects with obsessive compulsive disorder and compared with a control population. There was a significantly higher titre for some of the antibodies, most specifically for herpes simplex virus type 1 and mumps. This suggests a possible role for these viral infections in the pathogenesis of obsessive compulsive disorder.

Key words : viral antibodies , OCD, herpes simplex, measles, varicella, CMV, mumps

Obsessive Compulsive Disorder (OCD) is a relatively chronic disorder characterised by repeated thoughts, actions, impulses, ideas, images or actions, which are recognised as being irrational and are resisted. Although most of the earlier theorists regarded OCD to have a psychodynamic basis (Freud, 1909), recent work has focussed on its biological correlates (Jenike, 1984). Neurochemically the most robust observation has been a serotonergic dysfunction (Yarvura-Tobias et al., 1976), probably involving specific 5HT receptors (Zohar et al., 1987). Neuroanatomically there has been evidence to suggest frontal (Khanna, 1988) and basal ganglia (Rapoport and Wise, 1988) dysfunction. However the reasons for such a dysfunction has yet to be elucidated.

There are reports in the literature suggesting that obsessions and compulsions were frequently encountered in subjects with von Economo's encephalitis (von Economo, 1920; Claude et al., 1927; Jelliffe, 1932; Lewis, 1935). Oculogyric crisis were observed to be provoked by obsessional thoughts or rituals (Claude et al., 1927). Noting the association of OCD with encephalitis, Schilder (1938) speculated on an organic etiology in the majority of OCD cases. Grimshaw (1964) found significant histories of

CNS infections in 6 cases.

An encephalitic syndrome developing after a wasp sting, with OCD, associated with pallido-striatal necrosis has been described (Laplane et al., 1989). Post-encephalitic parkinsonism, diabetes insipidus and OCD was reported by Courtney (1928). Another case of post-encephalitic coexisting diabetes insipidus and OCD has also been described (Barton, 1965). There is a recent report of two cases of catatonic stupor, obsessional symptoms and depression thought to be due to encephalitis lethargica (Johnson and Lucey, 1987). Severe OCD was observed in a subject with MRI evidence of progressive caudate and frontal atrophy (Tonkonogy and Barreira, 1989). Although the temporal lobes were spared the compulsive eating was similar to that observed in Kluver Bucy syndrome. The onset was related to a viral infection. Thus, although there is no consistent series, other than that of von Economo's encephalitis, there are many case reports linking encephalitis with OCD.

A higher rate of obsessive compulsive phenomena were observed in patients with rheumatic chorea (Swedo et al., 1989). More subjects reported illness as a significant life event, specifically, illness or bereavement in the

VIRAL ANTIBODIES IN BLOOD IN OCD

year prior to onset of OCD (Khanna et al., 1988). These observations also suggest a link with an infectious etiology.

In an earlier investigation we had documented higher levels of immunoglobulins, specially IgG levels (Khanna and Gokul, 1989 unpublished data); this change was not a function of the clinical state and persisted after recovery. One of the possible explanations for this was our hypothesis that there might be a viral infection in OCD.

Torrey (1986) has consistently proposed a theory suggesting a viral etiology for psychosis, specially schizophrenia. The absence of significant viral antibodies in the CSF of schizophrenia subjects has limited the generalisability of this hypothesis (Morozov, 1983). However many patients with viral encephalitis can present in their 'pre-encephalitic' or encephalitic phase with predominant psychiatric manifestation. More recently there has been major interest in Chronic Fatigue Syndrome as a post-viral behavioural disorder (Abbey and Garfunkel, 1990).

Due to the relatively chronic nature of the psychiatric disorders studied, and the absence of recent clinical infection data, the major focus of work has been on the latent viruses. As Torrey (1986) observed, the viruses most likely to cause behavioural disturbances belong to the herpes family. In addition to herpes simplex virus (HSV) and cytomegalovirus, there has been recent evidence to suggest that varicella zoster can also be isolated from trigeminal nuclei, while it is latent (Mahalingam et al., 1990). Measles and mumps also can cause cerebral dysfunction after a long incubation period (Swoveland and Johnson, 1989). In the current investigation we studied these viruses in OCD and normal controls, based on our earlier speculations regarding a viral etiology for OCD.

MATERIAL & METHOD

Subjects who met DSM-III criteria for OCD (American Psychiatric Association, 1980) formed the patient population for this study.

Subjects with coexistent depression were included provided (1) Hamilton Depression Rating Scale (Hamilton, 1960) score were less than 11, (2) the obsession and compulsions preceded onset of depression by at least 2 months, (3) the patient attributed the depression as being secondary to obsessive compulsive phenomena and (4) there were no psychotic or melancholic features. Informed consent was taken from all subjects prior to entry into the study. Sociodemographic and clinical variables were entered on a semistructured proforma. Ratings were done on Hamilton Depression Rating Scale (Hamilton, 1960), Leyton's Obsessional Inventory (Cooper, 1970) and Comprehensive Psychopathological Rating Scale-Obsessive Compulsive Subscale (Insel et al., 1985). Blood samples were collected for baseline analysis. Controls for blood samples were normal healthy volunteers (N=55). Subsequently some of the subjects were allotted double blind to a drug trial comparing nortryptiline and clomipramine for a period of 6 weeks. After 6 weeks repeated measures on the rating scales and blood samples were collected.

IgG antibodies to herpes simplex virus type 1 (HSV1), cytomegalovirus (CMV), varicella zoster virus (VZV), mumps and measles virus, were estimated in an indirect ELISA using reagents obtained from Flow Laboratories (UK). The procedure adopted was that described by the manufactures. Briefly, 100 microL per well of viral antigen was coated onto NUNC (Denmark) ELISA plates and incubated overnight at a 4 deg C. Following this plates were washed thrice with phosphate buffered saline (pH 7.2) containing 0.05 % Tween 20 (PBST) and quenched with 1% BSA in PBS for 1 hour at room temperature. 100 microL of sample was then added in duplicates and incubated for 2 hours at room temperature and washed thrice with PBST. Subsequently 100 microL of rabbit anti-human IgG peroxidase conjugate (Dakopats, Netherlands) was added (1:1000 dilution) and incubated for 1 hour at room temperature. Subsequently 100 microL of OPD with H₂ O₂ was added as a substrate and

the colour reaction developed for 20 minutes in the dark and the optical densities were measured at 490 nm in a Dynatech Micro ELISA reader MR700 after arresting the reaction with 50 microL of 4N H₂ SO₄. All samples were similarly tested on a control antigen coated plate and the ODs obtained were subtracted from that obtained with virus antigen. Serum samples were tested at dilutions of 1:100. Appropriate positive and negative controls were included in each assay as recommended by the manufacturer.

Optical densities for paired readings were converted into units using the equation $\{(O:N)/(P-N)\} \times 100$ where O=observed value, N=negative control, P=positive control. The units for all viruses were compared with normal for blood using two-tailed Mann Whitney U Test. Subsequently discriminant function analysis was used to determine which blood viral antibodies (units), taken separately were the most discriminating between variables.

For paired samples comparison was done using Wilcoxon signed rank test. Since distributions of most of the variables were not normally distributed, non-parametric tests were used to test for significance.

RESULTS

There were 76 subjects with OCD who underwent baseline viral antibody estimations in blood; of these 33 also underwent repeat

TABLE 2
DISCRIMINANT FUNCTION ANALYSIS FOR VIRAL ANTIBODIES IN SERA

SERA	
Eigen value	.1409397
Canonical correlation	.35147
Wilks lambda	.8764705
Chi square	16.547450
P	.00544
STANDARDISED DISCRIMINANT FUNCTION COEFFICIENTS	
Herpes	.59544
Measles	.12740
Varicella	.34380
CMV	.04932
Mumps	.54952
PREDICTED CLASSIFICATION RESULTS	
OCD	42 (55.26 %)
Normals	40 (74.07 %)

estimations after 6 weeks. The sample has a mean age of 27.88 (SD 5.92) years and comprised 46 males and 30 females. The mean duration of illness was 4.82 years (SD-7.93). The scores on various scales were as follows; CPRS-OC 5, mean-9.44, S.D.-2.18; HDRS-

TABLE 1
VIRAL ANTIBODY UNITS IN SERA OF PATIENTS WITH OCD AND NORMALS

	OCD		Normals		Mann Whitney U Test Z
	Mean	SD	Mean	SD	
CMV	64.81	97.70	50.53	62.19	.18
Varicella	100.70	114.00	63.75	58.36	1.61
Mumps	83.81	69.42	52.60	30.73	2.35*
Measles	89.48	69.34	78.77	51.46	.46
Herpes	94.48	75.14	62.32	40.10	2.10*

*-p<.05

VIRAL ANTIBODIES IN BLOOD IN OCD

TABLE 3
PAIRED SERA SAMPLE VIRAL ANTI-BODY UNITS IN OBSESSIVE COMPULSIVE DISORDER

	PRE		POST		Wilcoxon Signed Rank Test Z
	Mean	SD	Mean	SD	
CMV	48.52	43.86	70.36	65.14	2.50*
Varicella	101.96	146.34	133.23	113.86	1.65
Mumps	82.58	81.53	60.90	46.44	1.38
Measles	102.55	81.94	69.29	54.15	2.66
Herpes	99.73	81.88	72.73	77.32	1.93

*-p<0.05, ** -p < 0.01

mean-7.32, S.D.-3.45; LOI symptom score-mean-25.66, S.D.-14.36; LOI interference score-mean-54.32, S.D.-13.88; LOI resistance score-mean- 57.91, S.D.-18.64.

Significantly higher units were observed for serum mumps and HSVI IgG (table 1). On discriminant function analysis the discriminant function were significant with HSVI, IgG differentiating best between OCD and normals (table 2).

When samples collected after 6 weeks were compared with the original samples, there was a significant increase in serum cytomegalovirus igG and decrease in measles and herpes (approaching significance, but not significant at .05 levels (table 3).

DISCUSSION

The current investigation has attempted to look at selected viral infections in subjects with OCD. The most striking finding has been with regards to IgG antibodies to HSVI.

However there are various confounding observations which need to be addressed. There seems to be a trend for greater IgG levels for the various viruses studied in OCD subjects as compared to controls. This could be a function of (i) an increased exposure to these viruses, (ii) a nonspecific increase due to polyclonal activation of B cells or (iii) due to inadequate or nonrepresentative control group.

With paired samples while changes are

observed for three viruses it can be seen that the variations are within the normal range i.e. mean \pm 2 SDs. Thus, although there were significant changes observed, these were largely within the normal range of the virus, did not indicate a 4 fold increase or changes significant increases to values $>$ Mean + 2 or 3 SDs.

There is no epidemiological evidence regarding exposure to HSVI in the Indian setting. One report from Saudi Arabia (Hossain, 1989) suggests that 60% of children and 90% of adults show presence of antibodies to this virus in the blood. As our sample is small it is difficult to generalise, but there are some normal subjects who have antibodies in their CSF.

It is perhaps not surprising that we found an excess of antibodies to HSVI in subjects with OCD. HSVI has a selective predisposition for temporal and frontal structures. There are two major reasons proposed for this. The earlier school of thought was that this was due to the proximity of these olfactory pathways after nasal inoculation (Johnson and Mims, 1968) or from the trigeminal ganglion along the tentorial branches of the trigeminal nerve (Davis and Johnson, 1979). Damasio & van Hoesen (1985) suggest that it may be due to a special affinity of the HSV for the limbic cortices, where due to their distinctive neurochemical, neuroanatomical and neuroimmunological properties, the virus is able to manifest its destructive properties.

Psychiatric disturbances with HSV have been described in the literature, predominantly

presenting with a schizophrenic profile (Drachman and Adams, 1962; Wilson, 1976). Current understanding of brain dysfunction in schizophrenia suggests a major role for the hippocampus (Altschuler *et al.*, 1990), which is selectively affected in herpes simplex encephalitis has not been difficult, and there has been little evidence to suggest that the encephalitis masqueraded as a psychosis alone (Torrey, 1986). Although these reports suggest that a schizophreniform picture with viral encephalitis should be kept in mind, a primary aetiological role for HSV has never been proved. However what is interesting is that it is the hippocampus and related structures which are currently thought to be dysfunctional in OCD (Insel, 1988), which correlates with the site specificity of the HSV1.

Three other viruses have also been implicated in this study. The titres for Mumps antibodies have also been high, while there have been changes in the titres for CMV and measles. The latter may reflect fluctuations in antibody production during the course of the study, specifically in the form of reactivation or subsidence of chronic infections.

The current study is the first to explore the relevance of viral antibodies in the etio-pathogenesis of OCD. However the results have been mixed and a wide spectrum of viruses have been implicated. The most important have been HSV1 and mumps which have shown raised antibody titres. The importance of these observations has to be reviewed with CSF studies and in a longitudinal course with an attempt to correlate with disease profile and severity.

REFERENCES

- Abbey, S.E. & Garfunkel, P.E. (1990) Chronic fatigue syndrome and the psychiatrist. *Canadian Journal of Psychiatry*, 35, 625-633.
- Altschuler, L.L., Casanova, M.F., Goldberg, C.E. & Kleinman, J.E. (1990) The hippocampus and parahippocampus in schizophrenia, suicide and controls. *Archives of General Psychiatry*, 47, 1029-1034.
- American Psychiatric Association (1980) DSM III : Diagnostic and Statistical Manual for mental disorders. Washington : American Psychiatric Press Inc.
- Barton, R. (1965) Diabetes insipidus and obsessional neurosis. *Lancet*, i, 133-135.
- Claude, H., Bourk, H. & Lamache, A. (1927) Obsessions-impulsions consecutives a l'encephalite epidemique. *Encephale*, 22, 716-722.
- Cooper, J. (1970) Leyton's Obsessional Inventory. *Psychological Medicine*, 1, 47-64.
- Courtney, J.W. (1928) A case of post-encephalitic Parkinsonian diseases with polydipsia. *Archives of Neurology and Psychiatry*, 19, 188-190.
- Damasio, A.R. & Van Hoesen, G.Y. (1985) The limbic system and localisation of herpes simplex encephalitis. *Journal of Neurology, Neurosurgery and Psychiatry*, 48, 297-301.
- Davis, L.E. & Johnson, R.T. (1979) An explanation for the localisation of herpes simplex encephalitis. *Annals of Neurology*, 5, 2-5.
- Drachman, D.A. & Adams, R.D. (1962) Herpes simplex and acute inclusion body encephalitis. *Archives of Neurology*, 7, 45-63.
- Freud, S. (1909) Notes upon a case of obsessional neurosis. In : *Collected Papers (1925) vol. 3*, pp 293-303 London : Hoggarth Press.
- Grimshaw, L. (1964) Obsessional disorder and neurological illness. *Journal of Neurology, Neurosurgery and Psychiatry*, 27, 229-254.
- Hamilton, M. (1960) A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, 23, 56-62.
- Hossain, A. (1989) Herpes simplex virus Type 1 and Vancella zoster virus infection in Saudi Arabia. *Journal of Tropical Pediatrics*, 35, 171-174.
- Insel, T.R. (1988) Obsessive compulsive disorder : A neuroethological perspective. *Psychopharmacology Bulletin*, 24, 365-369.
- Insel, T.R., Mueller, E.A., Alterman, I., Linnoila, M. & Murphy, D.L. (1985) Obsessive Compulsive Disorder and serotonin: Is there a connection. *Biological Psychiatry*, 20, 1174-1188.
- Jelliffe, S.E. (1932) Psychopathology of forced movements in oculo-gyric crisis of lethargic encephalitis. *Nervous and Mental Disease Mono-*

VIRAL ANTIBODIES IN BLOOD IN OCD

graph Series, 1, 1-200.

Jenike, M.A. (1984) Obsessive compulsive disorder : A question of neurological lesion. *Comprehensive Psychiatry*, 25, 298-304.

Johnson, J. & Lucey, P.A. (1987) Encephalitis lethargica, a contemporary cause of catatonic stupor. A report of two cases. *British Journal of Psychiatry*, 151, 550-552.

Johnson, R.T. & Mims, C.A. (1968) Pathogenesis of viral infection of the nervous system. *New England Journal of Medicine*, 278, 23-38, 84-92.

Khanna, S. (1988) Obsessive compulsive disorder: Is there a frontal lobe dysfunction? *Biological Psychiatry*, 24, 602-613.

Khanna, S., Gokul, B.N., Reddy, P.L., Khanna, N. & Channabasavanna, S.M. (1990) Humoral immune function in Obsessive Compulsive Disorder. *Indian Journal of Psychological Medicine*, 13, 31-37.

Khanna, S., Rajendra, P. & Channabasavanna, S.M. (1988) Life events: at onset of obsessive compulsive disorder. *International Journal of Social Psychiatry*, 34, 305-309.

Laplane, D., Levasseur, M., Pillon, B., Dubois, B., Baulac, M., Mazoyer, B., Dinh, S.T., Sette, G., Denze, F. & Baron, J.C. (1989) Obsessive compulsive and other behavioural changes with bilateral basal ganglia lesions. *Brain*, 112, 699-725.

Lewis, A.J. (1935) Problems of obsessional illness. *Proceedings of Royal Society of Medicine*, 29, 325-336.

Mahalingam, R., Wellish, M., Wolf, W., Dueland, A.N., Cohrs, R., Vafal, A. & Gilden, D. (1990) Latent varicella zoster DNA in human trigeminal and thoracic ganglia. *New England Journal of Medicine*, 323, 627-631.

Morozov, P.V. (1983) Research on the viral hypothesis of mental disorders. Basel : Karger.

Rapoport, J.L. & Wise, S.P. (1988) Obsessive compulsive disorder: evidence for basal ganglia dysfunction. *Psychopharmacology Bulletin*, 24, 380-384.

Schilder, P. (1938) The organic background of obsessions and compulsions. *American Journal of Psychiatry*, 94, 1397-1432.

Swedo, S.E., Rapoport, J.L., Cheslow, D., Leonard, H., Ayoub, E., Hosier, D. & Wald, E. (1989) Increased incidence of obsessive compulsive features in patients with Sydenham's chorea. *American Journal of Psychiatry*, 146, 246-249.

Swoveland, P.T. & Johnson, K.P. (1989) Subacute sclerosing panencephalitis and other paramyxovirus infection. In : *Handbook of clinical Neurology*, Vol. 12 (56) (Ed.) R.R. McEndall, Viral diseases, Amsterdam : Elsevier Science Publishers.

Tonkonogy, J. & Barreira, P. (1989) Obsessive Compulsive Disorder and caudate-frontal lesion. *Neuropsychiatry, Neuropsychology and Behavioural Neurology*, 2, 203-209.

Torrey, E.F. (1986) Functional psychosis and viral encephalitis. *Integrative Psychiatry*, 4, 224-236.

Von Economo, C. (1920) Die encephalitis lethargica deuticks, Vienna 1917-1918. Rome : L. Encephalik Lethargica Polyclinica.

Wilson, L.G. (1976) Viral encephalopathy mimicking functional psychosis. *American Journal of Psychiatry*, 133, 165-170.

Varvura-Tobias, J.A., Neziroglu, F. & Bergman, L. (1976) Chlorimipramine for Obsessive Compulsive neurosis. *Current Therapy and Research*, 20, 541-547.

Zohar, J., Mueller, E.A., Insel, T.R., Zohar-Kadouch, R.C. & Murphy, D.L. (1987) Serotonergic responsivity in obsessive compulsive disorder. *Archives of General Psychiatry*, 44, 946-951

SUMANT KHANNA¹, V. RAVI², POORNIMA K. SHENOY², A CHADRAMUKHI³, S.M. CHANNABASAVANNA¹,
Departments of ¹Psychiatry, ²Virology and ³Microbiology, National Institute of Mental Health and Neurosciences,
Bangalore.

*correspondence