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HEPATITIS B AND HERPES VIRAL COMPONENTS IN THE CEREBROSPINAL FLUID OF CHRONIC SCHIZOPHRENIC AND SENILE DEMENTED PATIENTS

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Summary. — Cerebrospinal fluids (CSF) or sera or both from 57 chronic schizophrenics and 18 senile demented patients were examined by various tests for HB_sAg. Both CSF and serum were positive in 2 schizophrenics while in six HB_sAg was detected in the CSF only. Elevated values of circulating immune complexes were found in positive patients. Most CSF positive for HB_sAg also contained neutralizing antibodies to Herpesvirus hominis type 1. Ultramicroscopic structures similar to hepatitis B virus (HBV) components and herpesviral particles were visualized in the CSF of one patient on electron microscope (EM) grids coated with anti-human IgG serum. Most HB_sAg positive patients appeared to be liver-symptoms-free carriers. In the CSF of a 79 years old senile demented man HB_sAg was proved serologically. Several herpesviral particles complexed with globular material and spherical structures from 15 to 25 nm in diameter were visualized in the same CSF on EM grids coated with anti-human IgG serum. The findings support the importance of herpesviruses in mental illness. Penetration of HB_sAg through the blood-brain barrier might be involved as an iatrogenic factor in the course of late psychoses.

Key words: schizophrenia; senile dementia; HB_sAg; herpesvirus; cerebrospinal fluid

Introduction

This work was stimulated by some phenomena which have been observed in the course of a long-term study on viruses, viral components, antibodies and interferon in chronic psychiatric patients (Libíková *et al.*, 1979*a*, *b*, 1980*a*). Increased amounts of circulating immune complexes were found in senile demented (Pogády *et al.*, 1979) and chronic schizophrenic patients (Libíková *et al.*, 1980*b*). Patients with both clinical forms need repeated hospitalizations and various medical procedures. Iatrogenic HBV infection — mainly in the past when disposable syringes and needles were not available —

has to be presumed. Persistent HBV infection may occur even after a mild liver infection, has mostly no clinical symptoms and usually is associated with histologically normal liver and normal liver functions (Robinson, 1979); HB_sAg circulates partly free, partly in complexes with anti-HB_s antibody. Such immune complexes (IC) may be deposited in vessel walls and cause arteritis (Nowoslawski *et al.*, 1972; Gocke, 1975; Michalak, 1978). The localization of experimental IC in vessels of plexus chorioideus which is an organ of the blood-brain barrier was proved experimentally in rabbits (Harbeck *et al.*, 1979). Formation of HB_sAg-anti HB_s complexes in the circulation and their deposition in or penetration through the damaged blood-brain barrier into the CSF is predictable mainly in long-term psychiatric patients. The aim of our study was to search for HB_sAg in the blood and CSF of such patients.

Materials and Methods

Sera were separated from clotted blood samples obtained by ve in puncture and stored at 4 and −20 °C for IC detection and serological assays, respectively.

CSF were obtained by lumbar puncture, and examined immediately or after storage at −20 °C.

Electron microscopy (*EM*). Carbon-coated formvar grids were coated for 30 min with swine anti-human-IgG serum (Institute of Sera and Vaccines, Prague) diluted 1 : 50. The serum was then sucked off and the grid surface was washed with distilled water 3 times to remove non-adsorbed material. A drop of native CSF was placed for 10 min on the sensitized grid, and then sucked off. It was presumed that antigenic structures connected with IgG would selectively bind to the antibody molecules coating the grid. The material adsorbed on the grid was finally negatively stained with 2 % phosphotungstic acid at pH 7.0. Some CSFs were also examined on non-sensitized grids. The preparations were examined in a Philips EM 300 electron microscope at 80 kV.

Circulating IC were estimated spectrophotometrically after selective precipitation with polyethylene glycol (Hašková *et al.*, 1978; Kočišová and Libíková, 1980). Mean values (± standard deviations) in healthy adults (19-59 years) and in healthy geronts (60-90 years) were 33 ± 16 and 60 ± 37, respectively.

Serological methods and interferon assay. Neutralizing antibodies to Herpesvirus hominis 1 (HVH 1) were tested in vitro in the presence (C+) or absence (C−) of guinea pig complement with a highly cytopathic HVH 1 variant as antigen. Haemagglutination inhibitiong (HI) antibodies to measles virus were assayed by a micromethod with viral antigen and *Cercopithecus aethiops* erythrocytes supplied by the Institute of Sera and Vaccines, Prague. For technical details including the description of the in vitro neutralization test with tick-borne enecephalitis virus (TEV) and the interferon test in human diploid cells with challenging vesicular stomatitis virus see Libíková *et al.* (1979*b*).

Skin tests made intradermally with solubilized HVH 1 antigens containing predominantly quantitated neutralizing antigen were done as described (Libíková *et al.*, 1980*b*).

HB_sAg detection in patient's sera and CSF. The following two *enzyme-linked immunosorbent assay* (*ELISA*) systems were employed: microELISA Hepanostika (Organon Teknika) and Enzygnost HB_sAg (Behring) kits; the producers' instructions were followed. The results of the tests were read either visually or spectrophotometrically (Vitatron or Elisa-Reader Dynatech). In *radioimmunoassay* (RIA), AusRIA II (Abbot) kits were used throughout according to the recommended procedure. *Passive reverse haemagglutination* (*PRHA*) *systems*: Hepatest (Wellcome) Cellognost HB_sAg (Behring) or Sevatest HB_sAg (Immuna) kits were employed separately or in parallel with either ELISA or RIA tests for HB_sAg. All tests were performed and read as recommended by the producers. HB_sAg specificity in all PRHA and ELISA assays was checked by adequate confirmatory tests.

Biochemical examinations. Direct bilirubinaemia and the activity of serum transaminases were assayed with the Bio-La test Lachema. The physiological value (p.v.) for total bilirubin is 5.1 — 19.0 μmol/l. Values of serum glutamate oxalate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT) are given in units per liter (U/l). P.v. for SGOT and SGPT are 4.2 — 25 U/l (70 — 417 nkat) and 2.5 — 25 U/l (42 — 417 nkat), respectively.

Results

Studies on schizophrenics

First examinations of CSF for HB_sAg were carried out in a group of patients with schizophrenia (SCH) and related clinical forms, hospitalized in the Regional Psychiatric Hospital, Pezinok. Their illness was of various duration and with various syndromes: incipient (9 %) and processual (20 %) SCH; SCH with defects of personality (27 %); SCH paranoides (57 %); SCH catatonica (11 %); and SCH-related clinical forms: paraphrenia (5 %) and schizoaffective psychosis (11 %). CSF of these patients were examined with the Hepanostika microELISA test and all were HB_sAg-negative (Table 1). CSF of some patients had antibodies to HVH 1, TEV and measles virus and contained interferon. The antibody titres were low, from 1 (undiluted CSF) to 4. CSF antibodies to TEV were were found mostly in patients with absent or low serum antibodies while all patients with CSF antibodies to HVH 1 or measles virus had serum antibody titres either elevated or corresponding to the norm (mean geometric titres $\pm$ SD in the norm: 10.3 $\pm$ 1.6 and 5.3 $\pm$ 1.3 bits for C+ HVH 1 and measles antibodies, respecitively.)

Table 1. Findings in CSFs negative for HB_sAg in the microELISA test (Hepanostika)

Test	Schizophrenia		Senile dementia	
	I	II	I	II
HVH 1 neutralizing C+ antibodies	44	13.6	18	33.3
Measles HI antibodies	43	4.6	18	0
TEV neutralizing antibodies	43	20.9	18	11.1
Interferon	29	17.2	18	66.7

I — No. of CSF tested; II — % of CSF positive in the given test.

The second group of patients examined consisted of 17 schizophrenics, most of them with deep defects of personality, under long-term hospitalization (mostly 10 years and more) in district psychiatric hospitals Hody and Veľké Zálužie. The mean age was 54.2 years (Table 2). In this group we used three different test systems (PRHA, ELISA and RIA) for HB_sAg detection, but for technical and economical reasons it was impossible to employ all tests in all patients. We also examined the patients sera, including the estimation of circulating IC, total bilirubin and serum transminases. HB_sAg was detected by one or several of the tests used in CSF of 8 patients (47 %). PRHA was used in all CSF examinations and it never failed to detect HB_sAg in a CSF which was found positive by another test. PRHA indicated presence of HB_sAg even in six CSF which in RIA or ELISA or both were negative,

Table 2. Examinations of sera and CSF of chronic schizophrenic patients

Patient No.	Sex, age in years	Circulating IC[1])	Serum			HB_sAg[3])				CSF antibodies[4])	
			Total bilirubin µmol/l	SGOT U/l[2])	SGPT U/l[2])	Serum positive by	Serum negative by	CSF positive by	CSF negative by	C+ to HVH 1	HI to measles virus
1	M 52	51	11.1	5.84	10.0	RIA, PRHA		(PRHA)	RIA	1	0
2	M 69	120	8.55	2.5	15.0		PRHA		RIA, PRHA	0	–
3	M 51	80	5.13	5.84	18.3		PRHA	PRHA 2	RIA, ELISA	1	2
4	M 39	45	12.8	2.5	6.68		PRHA		RIA, PRHA	1	0
5	M 41	45	8.55	2.5	3.34		PRHA	PRHA 4	RIA, ELISA	2	0
6	M 60	60	5.13	8.35	11.65		PRHA		RIA, PRHA	0	0
7	M 42	90	6.84	5.84	11.65		PRHA	(PRHA 2)		2	1
8	M 45	103	11.1	8.35	29.2	RIA, PRHA		RIA, ELISA (PRHA 8)		1	0
9	M 55	73	5.13	16.6	61.8		PRHA		RIA, PRHA	1	0
10	M 70	77	12.8	2.5	3.34		PRHA		PRHA,	1	0
11	M 58	54	6.84	14.2	23.4		PRHA	(PRHA 4)	RIA, ELISA	0	0
12	M 56	25	6.84	20.0	41.7		PRHA		PRHA	2	0
13	M 56	30	5.13	11.0	10.0		PRHA	RIA, (PRHA)	ELISA	2	0
14	F 56	65	6.84	40.0	56.0		PRHA		ELISA, PRHA	2	0
15	M 58	40	5.13	14.2	18.3		PRHA	(PRHA 2)	RIA	1	0
16	M 44	34	8.55	16.6	23.4		PRHA		RIA, PRHA	1	0
17	M 70	77	6.84	16.6	20.8		PRHA		RIA, PRHA	2	0

1) IC values $\geqq 70$ are considered to be significantly elevated in patients of this age group.
2) To obtain values in nkat, the U/l values should be multiplied by 16.7.
3) With PRHA, parentheses indicate a slighly positive reaction (±); figures (2, 4, 8) behind PRHA indicate reciprocals of the highest dilution of CSF positive in a titration test.
4) Reciprocals of highest positive dilution (1 = undiluted; 0 = no antibody detected; – = not tested).

but in which the HB_sAg specificity was confirmed. HB_s-antigenaemia was proved only in 2 of 8 CSF-positive patients; one of them (No. 8) had a high value of circulating IC. Two patients with HB_sAg positive CSF and negative serum (Nos 3 and 7) had also high IC values. Nevertheless, a similar finding was observed in 4 patients completely negative for HB_sAg (Nos 2, 9, 10, 17). Total serum bilirubin and SGOT values were in limits of the norm in all but one patient (No. 14). SGPT exceeded the normal value in 3 patients, 1 positive (No. 8) and 2 negative for HB_sAg (Nos 9, 14). All patients with HB_sAg in CSF — except one (No. 11) — had HVH 1 C+ antibodies in CSF in low titres; the serum/CSF titre ratio was from 512—8192. One patient (No. 3) had measles antibodies and 2 (Nos 4 and 7) antibodies to TEV in their CSF.

Patient No. 8 had HB_sAg in CSF and serum as demonstrated by all tests used — PRHA, ELISA and RIA. His CSF was examined by EM but characteristic HB_sAg structures were not found. On anti-human IgG serum coated grids we observed large filaments formed by fine globular and filamentous material. The CSF from patient No. 13 (positive for HB_sAg in RIA) contained structures corresponding to HB_sAg in size and shape (Figs 1 and 2), and also some cored forms with the size of Dane particles (Fig. 3). Moreover, five herpesvirus-like partially disintegrated virions were seen in the same CSF on two grids (Figs 4 and 5). This finding corresponds with that of HVH 1 antibodies in the CSF of patient No. 13.

Studies on senile dementia

Hepanostika microELISA test used for the examination of HB_sAg in CSF from 18 senile demented patients gave negative results. The patients revealed signs of cerebral atherosclerosis (50 %), confused dementia (28 %) and sometimes depressive or paranoid syndromes. A part of them had CSF antibodies to HVH 1 and TEV and in most CSF interferon was found (Table 1).

Another 25 senile demented patients were examined for HB_sAg in serum by PRHA (Hepatest) and 2 (8 %) were clearly positive. One positive patient was kept under observation for nearly two years (Table 3).

The patient, a 79 years old man, was physically apparently healthy. His social behaviour and especially attitude were formally enough preserved and he looked much younger. His dementia has been developing progressively for one year until the beginning of our observations. Very high values of circulating IC stimulated us to assay the serum and CSF for HB_sAg and the results were positive. The ratio of C+ to C— HVH 1 antibodies indicated HVH 1 activation within the period of observation. The skin tests, mainly the Arthus reaction in July, indicated possible involvement of HVH 1 Ag-antibody complexes — besides complexed HB_sAg — in the high IC values. HVH 1 C+ antibodies in the CSF were low and their serum/CSF ratio was high.

On EM grids coated with anti-human IgG serum the CSF was found to contain herpesviral nucleocapsids, non-enveloped (Fig. 6) or with damaged

Table 3. Findings in a senile demented patient

Examinations	Samples taken on Feb. 6, 1979	July 10, 1979	Oct. 11, 1979	Oct. 31, 1980
Serum				
Circulating IC	206	145	119	77
Positive test for HB_sAg	NT	PRHA	PRHA	RIA
HVH 1 antibodies				
C+	512	256	4096	4096
C−	256	64	512	256
ratio C+/C−	2	4	8	16
measles HI antibodies	32(64)	32	64	64
CSF				
HB_sAg	NT	NT	NT	PRHA ±
HVH 1 C+ antibodies	NT	NT	NT	undil.*
Ratio serum/CSF HVH 1 antibodies				4096
Skin tests with solubilized HVH 1 antigens				
Anaphylactic reaction (I)	Medium	Strong	NT	NT
Arthus reaction (III)	Negative	Strong	NT	NT
Delayed type hypersensitivity (IV)	Slight	Slight	NT	NT

NT — not tested.
*Detectable only in undiluted CSF.

envelope (Fig. 7). Globules of various sizes situated in the vicinity were agglomerated to complexes coherent with the particles. Similar complexed globules were also found in fields of view with absent particles. The same CSF was slightly positive for HB_sAg in PRHA. On sensitized grids we found large groups of spherical particles corresponding in size (15—25 nm in diameter) with HB_sAg, but no rod-like particles. Complexes of similar globular material were also observed in the patient's serum on non-sensitized grids (Fig. 10).

Discussion

It has been shown in a series of studies that hepatitis B is endemic in sanatoria for mentally handicapped children and adults. The more frequent detection of HB_s antigenaemia is associated with a longer period of hospitalization (for references see Kingham *et al.*, 1978; Pečenková *et al.*, 1979). Our finding of HB_s antigenaemia in 11 % chronic schizophrenics and 8 % senile demented persons who had been living long in social institutions or had been repeatedly hospitalized, is consistent with the observations mentioned.

The assays for HB_sAg in CSF showed a surprisingly high incidence of positivity in schizophrenics with lengthy hospitalizations (47 %), mostly in patients with HB_sAg-negative serum. The presence in CSF of HB_sAg, free or in small clusters originating probably from crumbled larger IC which

had penetrated via the blood-brain barrier, is logically acceptable. We only have to discuss why the CSFs positive in PRHA were not positive — with the exception of one case (No. 8) — in ELISA and RIA. This finding might be connected with the fact that complexes of HB_sAg (Pintera, 1979), which on the antibody-coated surface do not stick physically as well as free HB_sAg, may be easily washed off.

The absence of HB_sAg in serum of some CSF-positive patients could be speculatively explained by formation in the circulation of complexes of various size which were cleared, phagocytized or deposited in some tissues. This would depend on quantitative relations between the produced amounts of HB_sAg and anti-HB_s (Robinson, 1979).

Assuming that the blood-brain barrier could be damaged by HB_sAg IC deposits, it would appear possible that not only HB_sAg IC but also other high molecular weight substances could pass through this usually invincible barrier. The ratio of serum and CSF titres of HVH 1 neutralizing antibodies was not in favour of this phenomenon in our patients. Nevertheless, HVH 1 C+ antibodies in serum were mostly high (titres of 2048 and more) and persisting HVH 1 had to be considered as actually stimulated (Libíková *et al.*, 1980*a*). Presence of herpesviral particles in the CSF of patient No. 13 suggests local antigenic stimulus and local antibody formation.

In the senile demented patient (Table 3) the following findings were dominant: high level of circulating IC, serum and CSF positivity for HB_sAg and herpesviral structures in CSF at the interval of HVH 1 antibody rise (see also Libíková *et al.*, 1979*a*). Some EM observations in this case suggest that also HVH 1 antigen-antibody complexes (Pogády *et al.*, 1979) could be involved in the pathogenesis of the disease.

The herpesviral particles detected in CSF are most probably incomplete and non-infective or they have been inhibited by specific and nonspecific immune reactions (Malis, 1959).

The eventual role of TEV in psychiatry was analysed elsewhere (Stünzner *et al.*, 1979).

Neuropathological changes were described in the limbic system (Fuller-Torrey and Peterson, 1974) and in the cerebral cortex (Weinberger *et al.*, 1979) in a part of chronic schizophrenic patients. The aetiology and their role in the clinical picture is not known. A syndrome of mental and neuromuscular abnormalities, associated with biochemical alterations resulting from hepatic failure of various severity and called "hepatic encephalopathy" has been reported (Zieve, 1979). However, the values of total bilirubin and serum transaminases were in limits of the physiological norm (Hanták *et al.*, 1980) in most of our patients, who thus appear to be liver symptoms-free HB_sAg-carriers without hepatic failure. On the other hand, HBV infection was confirmed in association with Guillain-Barré syndrome (Martí-Massó *et al.*, 1979 — cit. after Index Medicus *21* (6), 400, 1980; Huet *et al.*, 1980).

The influence of HB_sAg present in serum and CSF could contribute to the development of neuropathological lesions at least in a part of chronic patient with late schizophrenia. It also could play a role in the course of

senile dementia. The detection of HB_sAg in the CSF was possible by serological methods. Its morphological identification (Hoggan and Thomas, 1973) directly in the CSF, even in samples serologically positive, was not easy. We have to presume morphological alterations of HB_sAg which had penetrated from blood plasma to the CSF.

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Explanation of Electron Micrographs (Plates XXVI—XXIX):

Figs 1—5. Viral structures in the AusRIA-positive CSF of patient No. 13 (schizophrenia, 56 years). Spherical structures 20—30 nm in diameter, single or arranged in short chains (*1*, *2*). Cored particle 45 nm in diameter with a 28 nm core consistent with the size of Dane particle (*3*). Herpesviral particles with complete (*4*) or disrupted (*5*) envelope. Figs 1, 4, 5 — ×1400 000; Figs 2, **3** — ×280 000.

Figs 6 and 7. Herpesviral structures in the CSF from a senile demented patient (79 years). EM grid coated with anti-human IgG serum. Non-enveloped capsid particle (*6*), and particle with disrupted envelope (*7*) coherent with complexed globular structures. ×105 000.

Fig. 8. Native serum from a senile demented person (same patient as in Figs 6 and 7). Complexes of spherical structures 15—25 nm on a non-sesitized EM grid. ×72 600.