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Disproportionate Elevation of the Immunoglobulin G1 Concentration in Cerebrospinal Fluids of Patients with Multiple Sclerosis

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We determined immunoglobulin G (IgG) subclass concentrations and studied their distributions in the cerebrospinal fluids of patients suffering from multiple sclerosis, other inflammatory neurological diseases, and non-inflammatory diseases of the nervous system in comparison with a control group. In addition, the four subclass concentrations were measured in serum specimens of the multiple sclerosis and control groups. These data were correlated with the extent of local IgG synthesis in the subarachnoid spaces of the patients belonging to the different groups. We found a selective elevation of the IgG1 subclass in the cerebrospinal fluids of multiple sclerosis patients, and there was only a very small overlap of the IgG1 ranges of the multiple sclerosis and control groups. No major differences were detected between the IgG subclass distributions in different courses of multiple sclerosis nor between multiple sclerosis and control sera. The group with non-inflammatory diseases showed a uniform elevation of all four subclasses and a greater overlap with the normal range. This latter feature was combined with an elevated IgG1 concentration in the group with other inflammatory diseases. It is concluded that locally synthesized IgG in the cerebrospinal fluids of multiple sclerosis patients consists mainly of IgG1.

Local immunoglobulin G (IgG) production in the subarachnoid space is a hardly understood phenomenon which occurs in patients with chronic inflammatory diseases of the central nervous system (7, 12, 22, 25). To reveal the underlying mechanisms and the significance of this phenomenon, a detailed characterization of the cerebrospinal fluid (CSF) IgG fraction is in progress with regard to different molecular properties, such as antibody specificity (21, 27, 28), light-chain ratios (1, 2, 16, 21), electrophoretic mobility, isoelectric point (5, 13, 28, 29), and IgG subclass membership (29). Tourtellotte (25) proposed a formula which can calculate the amount of IgG synthesized per day in the subarachnoid space. IgG subclasses in the CSF have, as of yet, attracted very little attention, and merely qualitative and incomplete data are available in this field (29; D. L. Palmer, B. J. Minard, and N. J. Witt, Am. J. Clin. Pathol. **59**:140, 1973). It is still an unanswered question whether infectious diseases bring about characteristic patterns of the IgG subclass distribution in CSF or serum which could be helpful in identifying individual diseases or groups of such and determining those patterns.

In this communication we present the distribution of the four IgG subclasses in the CSF and sera of patients with neurological diseases and control persons and correlate these data with the extent of local IgG production in the subarachnoid space. Special interest has been dedicated to multiple sclerosis (MS), one of the most frequent neurological diseases in Europe and North America.

MATERIALS AND METHODS

Patients. The study included 25 control persons, 26 cases of MS, 8 cases of other inflammatory neurological diseases (OID), and 28 cases of non-inflammatory diseases of the nervous system (NID). The control persons were selected out of a number of psychiatric patients and patients with lumbar disk protrusions, guided by the criteria of normal cell contents, total protein, albumin, IgG, and IgG/albumin as well as IgG/total protein ratios in the CSF (21, 25). The diagnosis of MS was made on the basis of the Schumacher criteria (23) in a modification additionally

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taking CSF alterations into consideration (20). The OID and NID groups were constituted randomly according to the sequence of admissions to the hospital during the period of examination. CSF specimens were obtained by lumbar puncture (Table 1).

Cell counts and protein determinations. The cell contents of all CSF specimens were determined in a Fuchs-Rosenthal counting chamber.

For measurement of total protein we used a modified Biuret reaction after denaturation with trichloroacetic acid. Albumin and IgG were quantitated by the technique of Mancini et al. (17) on low concentration Partigen dishes using standard human serum and IgG standard solution (all from Behringwerke, Marburg, W. Germany) for calibration. Regular quality controls with Hyland control CSF (Travenol Gesellschaft mit beschräukter Haftung, Munich, W. Germany) for total protein and diluted Fluinorm N (Behringwerke, Marburg, W. Germany) for albumin and IgG resulted in the following coefficients of variation for the whole period of examination: total protein, 5.6%; albumin, 4.3%; IgG, 5.8%.

Determination of local IgG production in the subarachnoid space. It was necessary for the interpretation of IgG subclass concentrations in the various groups of persons to construct a frame of reference which had to provide tools for the detection of disproportionately elevated IgG concentrations in the CSF, thereby giving a measure for local IgG synthesis in the subarachnoid space. This information could be obtained by several methods (4, 9, 12, 21, 25). The procedure described by Delpech and Lichtblau (4) is based on a correlation of the IgG/albumin ratios in CSF and serum, which implies the strict requirement of simultaneous collection of the CSF and corresponding serum specimens. Similar conditions are valid for the method of Ganrot and Laurell (9). We found the IgG/albumin ratio (IgG concentration expressed as percentage of albumin concentration in the CSF) to give satisfying results and to be more sensitive in discriminating cases with local IgG production in the subarachnoid space from those without that condition than the older test of Kabat (12), which is in accordance with the observations of other investigators (21, 25). Using this method, we had to consider its inability to indicate blood-brain barrier dysfunctions occurring alone as well as in combination with other defects.

TABLE 1. *Grouping of the patients according to their clinical diagnoses*

Group	Diagnosis/course of disease	No. of patients
MS	Relapsing	10
$n = 26$	Relapsing and progressive	10
	Chronic progressive	6
OID	Meningitis (viral)	1
$n = 8$	Encephalitis	3
	Polyradiculitis	1
	Radiculomyelitis	2
	Neurosyphilis	1
NID	Epilepsy	1 (3.6%)[a]
$n = 28$	Brain tumor	11 (39.3%)
	Tumor of the spinal cord	1 (3.6%)
	Subarachnoid hemorrhage	1 (3.6%)
	Polyneuropathy	5 (17.9%)
	Hydrocephalus	1 (3.6%)
	Brain infarction	5 (17.9%)
	Neurofibromatosis (von Recklinghausen's disease)	1 (3.6%)
	Palsy of the VIth cranial nerve	1 (3.6%)
	Amyotrophic lateral sclerosis	1 (3.6%)

[a] Numbers in parentheses are the percentages of the total NID group ($n = 28$).

Determination of IgG subclasses. IgG subclasses were measured in a solid phase radioimmunoassay as described previously (18). Myeloma proteins of the respective subclasses were prepared by diethylaminoethyl chromatography or by preparative electrophoresis followed by Sephadex G200 gel filtration. Subclass-specific antisera, anti-IgG1, -IgG2, -IgG3, and -IgG4, were raised in sheep. For calibration of the radioimmunoassay we used serial dilutions of the World Health Organization reference serum pool 67/97 the IgG subclass concentrations of which are known (18).

Statistical calculations. Evaluation of data was performed by the method of Cavalli-Sforza (3), making use of *Documenta Geigy* (10).

RESULTS

A presentation of the basic CSF data of the patient groups included in our study is necessary in order to point out some special features of these groups. The characteristics of the MS group were moderately elevated cell count, total protein, and albumin in connection with markedly elevated IgG and IgG quotients (Table 2). The OID pattern showed a strong elevation of all parameters, including pathological IgG ratios which corresponded to blood-brain barrier dysfunction combined with local IgG synthesis in the subarachnoid space of some of these patients (21). The NID group turned out to be more heterogenous, as far as blood-brain barrier function is concerned (W. P. Kaschka, unpublished data). This heterogeneity was not unexpected because neoplastic and nonneoplastic diseases were included in this group. One common feature should, however, be pointed out—namely, the fact that local IgG production in the central nervous system essentially did not occur in these patients, as judged from the IgG quotients. In a number of cases a correlation of CSF/serum concentration gradients was made for IgG and albumin, according to the method of Ganrot and Laurell (9), with a modification (6) which additionally allowed the diagnosis of blood-brain barrier disturbances. As for local IgG production in the subarachnoid space, the results were in good accordance with those obtained from CSF IgG/albumin ratios (W. P. Kaschka, unpublished data) (Table 2).

In the patient groups and controls thus characterized, the four IgG subclasses were measured

TABLE 2. *Comparison of patient groups and controls with regard to age, CSF cell contents, total protein, and IgG concentrations, as well as CSF IgG quotients*[a]

Group	Age (years)	Cells/μl	Total protein (mg/100 ml)	Albumin (mg/100 ml)	Total IgG (mg/100 ml)	IgG × 100/albumin = Q_G	IgG × 10/total protein
Normal Controls $n = 25$	46.8±15.0	1.40±1.21	36.40±13.41	17.60±7.42	2.13±1.15	12.24±5.45	0.59±0.22
MS $n = 26$	33.9±9.5	14.55±20.27 Control[b] OID[b]	56.51±18.60 Control[b] OID[b] NID[b]	30.77±13.66 Control[b] OID[b] NID[b]	10.62±5.24 Control[b] OID[b] NID[b]	35.37±12.50 Control[b] NID[b]	1.85±0.66 Control[b] NID[b]
OID $n = 8$	45.6±13.7	106.42±217.60 Control[b] MS[b] NID[b]	196.63±292.87 Control[b] MS[b]	69.78±55.28 Control[b] MS[b]	37.35±63.29 Control[b] MS[b]	35.86±28.0 Control[b] NID[b]	1.55±0.55 Control[b] NID[b]
NID $n = 28$	50.9±16.5	14.33±32.43 Control[b] OID[b]	183.46±212.02 Control[b] MS[b]	117.73±110.16 Control[b] MS[b]	20.08±19.8 Control[b] MS[b]	19.54±12.0 Control[b] MS[b] OID[b]	1.14±0.59 Control[b] MS[b] OID[b]

[a] Normal values (W. P. Kaschka and H. Bauer, unpublished data): cells ≤4/μl; total protein, ≤60 mg/100 ml; albumin, ≤34 mg/100 ml; IgG, ≤4 mg/100 ml; IgG × 100/albumin, ≤22%; IgG × 10/total protein, ≤1.3.
[b] Significantly different from the groups indicated at $P < 0.05$.

TABLE 3. *IgG subclass concentrations in the CSF of three groups of neurological patients as compared with control persons: median values and ranges*

Group	IgG1 (μg/ml)	IgG2 (μg/ml)	IgG3 (μg/ml)	IgG4 (μg/ml)
Normal controls, $n = 25$	7.3 4.6–18.2	5.2 2.5–15.6	1.0 0.2–3.4	0.6 0.1–1.4
MS (all subgroups), $n = 26$	60.5 15.0–128.0	10.4 5.8–41.0	2.225 0.95–7.15	1.0 0.5–5.0
MS relapsing, $n = 10$	53.5 15.0–88.0	8.7 5.8–25.0	1.9 0.95–4.5	1.1 0.5–3.65
MS relapsing and progressive, $n = 10$	60.5 32.0–128.0	10.9 6.7–19.7	2.475 1.2–7.15	0.825 0.65–1.20
MS chronic progressive, $n = 6$	65.0 34.0–104.0	10.5 5.8–41.0	2.075 1.0–5.55	1.425 0.90–5.00
OID, $n = 8$	66.6 5.2–1530.0	36.75 9.1–1520.0	7.3 0.7–73.0	1.3 0.7–319.0
NID, $n = 28$	34.0 4.3–345.0	36.8 3.9–320.0	6.1 0.2–25.0	1.7 0.5–25.7

in all CSF specimens and in a number of serum specimens (Table 3).

We observed a selective elevation of the IgG1 subclass in the CSF of MS patients, and there was only a very small overlap of the IgG1 ranges of the MS and control groups. No major differences were to be seen between the IgG subclass distributions in different courses of MS (relapsing course: IgG1, 77.1%; relapsing and progressive course: IgG1, 80.3%; chronic progressive course: IgG1, 76.2% of total CSF IgG; Table 3).

The OID and NID groups had two features in common: first, a wide overlap of their IgG1 ranges with that of the control group, and second, an elevation of all four IgG subclass concentrations, as compared with the controls. This latter observation might be astonishing with respect to the NID group, but it is explained by the fact that some patients of this group suffered from neoplastic CNS diseases which can, of course, be accompanied by blood-brain barrier dysfunction. As demonstrated earlier, local IgG

synthesis took place in the subarachnoid spaces of some patients of the OID group. This suggested that the remarkably high IgG1 concentrations in the CSF specimens of this group could be due to local production (Table 4).

No major differences were detectable between the IgG subclass distributions in the sera of MS patients and controls (Table 4). The disproportionate elevation of IgG1 in the multiple sclerosis group was restricted to the CSF. As there is no evidence supporting the notion that a selective transport of IgG1 molecules might occur from the serum across the blood-brain barrier into the CSF, most of this IgG1 has to be synthesized in the subarachnoid space (Fig. 1).

It is hard to draw any conclusions with regard to the type of distribution of the four IgG subclasses in the groups analyzed by us (Fig. 1 to 4); but probably it is not a distribution of Gaussian type, and this is the reason why median values and ranges are presented in Tables 3 and 4 instead of means and standard deviations (3). Larger numbers of patients will be required to come to conclusive statements with regard to this question. It is remarkable, yet, that in the control group all four subclasses were distributed in a very sharp and narrow range (Fig. 1 to 4).

DISCUSSION

After the qualitative observation of Vandvik and co-workers (29) that oligoclonal IgG in the CSF of MS patients belongs mainly to the IgG1 subclass, it appeared desirable to obtain more information on the exact concentrations and distribution of the four IgG subclasses in CSF and sera of neurological patients as compared with control persons. Our study demonstrates that the concentration of the IgG1 subclass is selectively elevated in the CSF of MS patients, which is not the case in the serum. As local IgG production in the subarachnoid space is known to occur in this group of patients, we conclude that the locally synthesized immunoglobulin fraction consists mainly of IgG1. Comparison of different courses of MS shows that the preponderance of IgG1 does not vary to a large extent.

The question of whether a disproportionate elevation of the IgG1 concentration in the CSF of MS patients is a specific criterion for this disease cannot be answered conclusively before extensive studies on neurosyphilis and different groups of encephalitides have been carried out. If we consider that local IgG production in the subarachnoid space takes place at least in some patients of our OID group (Table 2) and that the CSF specimens of this group contain a remarkably high amount of IgG1 (Table 3), we tend to assume that the elevation of IgG1 is not absolutely specific for MS, but might occur in a variety of subacute and chronic encephalitides.

As of yet, nothing is known about a possible functional significance or antibody specificity of the CSF IgG1 fraction, but, as far as MS is concerned, one can draw an indirect conclusion: Vandvik et al. (28) were able to demonstrate measles antibody specificity in oligoclonal IgG bands from CSF of patients with multiple sclerosis and subacute sclerosing panencephalitis. As these oligoclonal bands were shown to consist mainly of IgG1 (29), it is probable that part of the CSF IgG1 fraction has measles antibody specificity. This conclusion does not, however, imply a statement concerning the etiological agent or mechanism of MS.

Compiling the four radioimmunologically determined IgG subclasses in each group (Table 3), a sum should be expected equal to the total IgG (Table 2) that has been measured by a modified technique of Mancini et al. (17). In fact this is not the case. Radial immunodiffusion always gives higher values than the sum of the radioimmunologically determined subclasses, which is consistent with data reported in the literature (18, 24, 26). These differences are probably caused by the higher specificity of the subclass antisera used in the radioimmunoassay

TABLE 4. *IgG subclass concentrations in the CSF and sera of patients with MS and control persons and in reference serum 67/97 (World Health Organization, WHO): median values and ranges*

Group	IgG1		IgG2		IgG3		IgG4	
	CSF (μg/ml)	Serum (mg/ml)	CSF (μg/ml)	Serum (mg/ml)	CSF (μg/ml)	Serum (mg/ml)	CSF (μg/ml)	Serum (mg/ml)
Normal controls, $n = 7$	5.7 4.3–9.6	5.75 3.7–8.6	6.2 3.6–15.6	4.8 1.98–5.25	0.5 0.2–3.4	0.69 0.19–1.18	0.9 0.5–1.2	0.32 0.23–0.67
MS, $n = 10$	63.5 34.0–128.0	6.25 4.3–7.5	7.8 5.8–19.7	2.835 1.86–4.28	2.3 1.45–2.75	0.405 0.18–1.13	0.975 0.65–1.55	0.10 0.03–0.86
WHO serum 67/97 (standard)		5.1		2.5		0.55		0.35

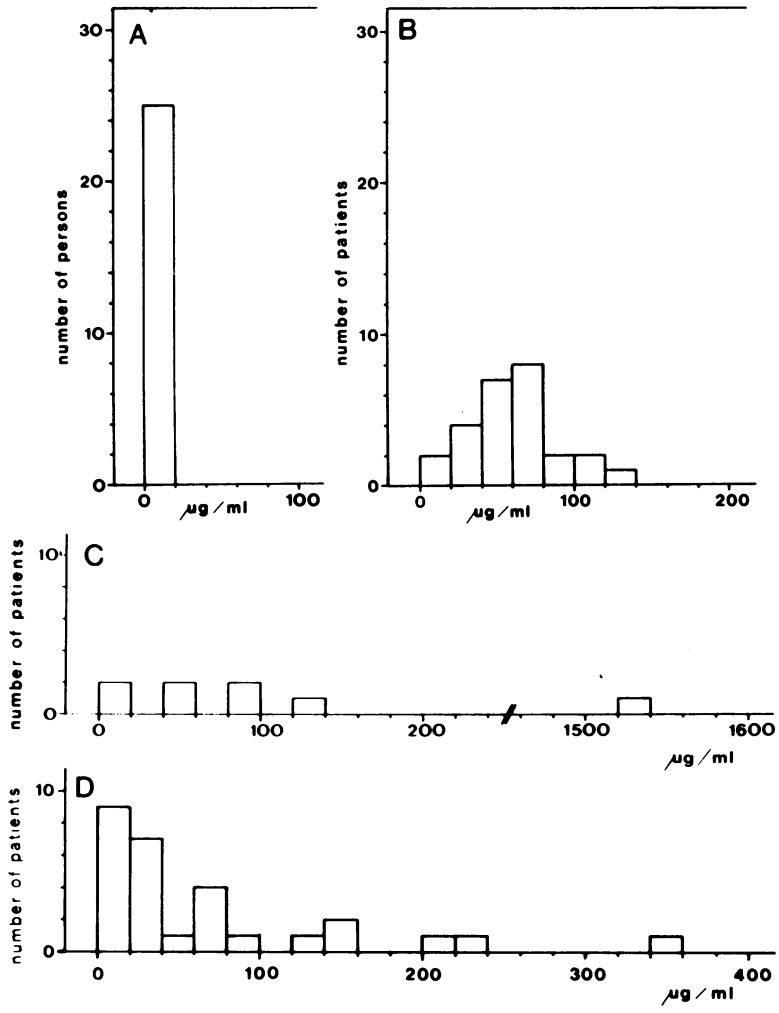

FIG. 1. *Distribution of IgG1 in the CSF of three groups of neurological patients as compared with healthy control persons. (A) Controls (n = 25); (B) MS (n = 26); (C) OID (n = 8); (D) NID (n = 28).*

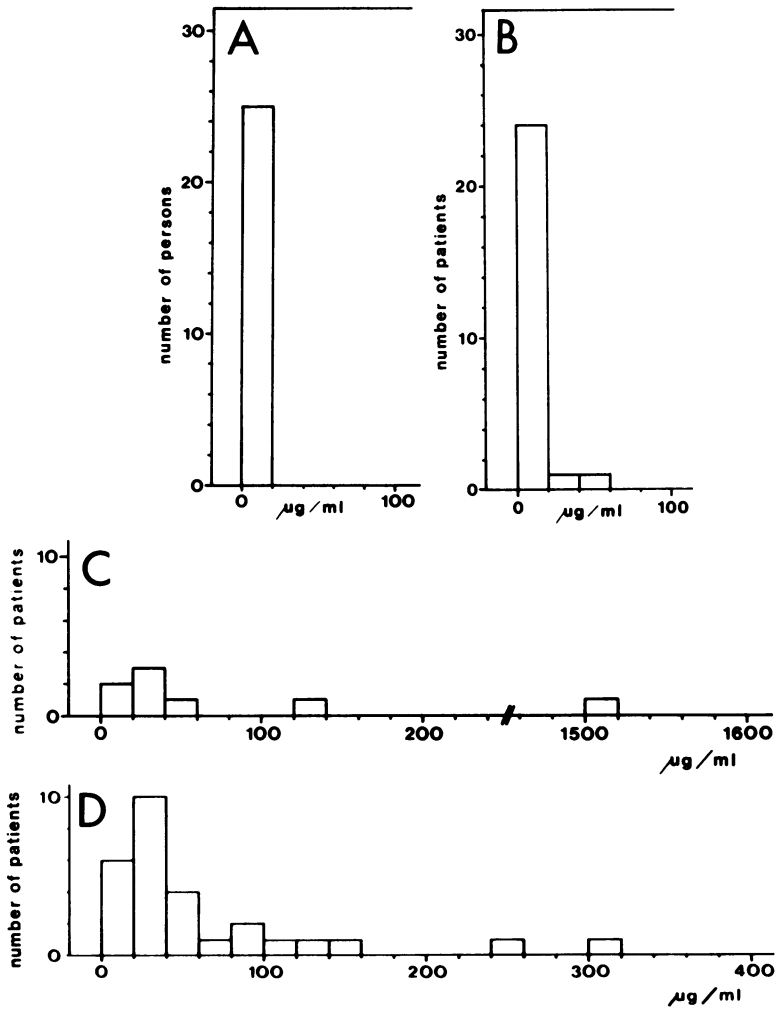

FIG. 2. *Distribution of IgG2 in the CSF of three groups of neurological patients as compared with healthy control persons. (A) Controls (n = 25); (B) MS (n = 26); (C) OID (n = 8); (D) NID (n = 28).*

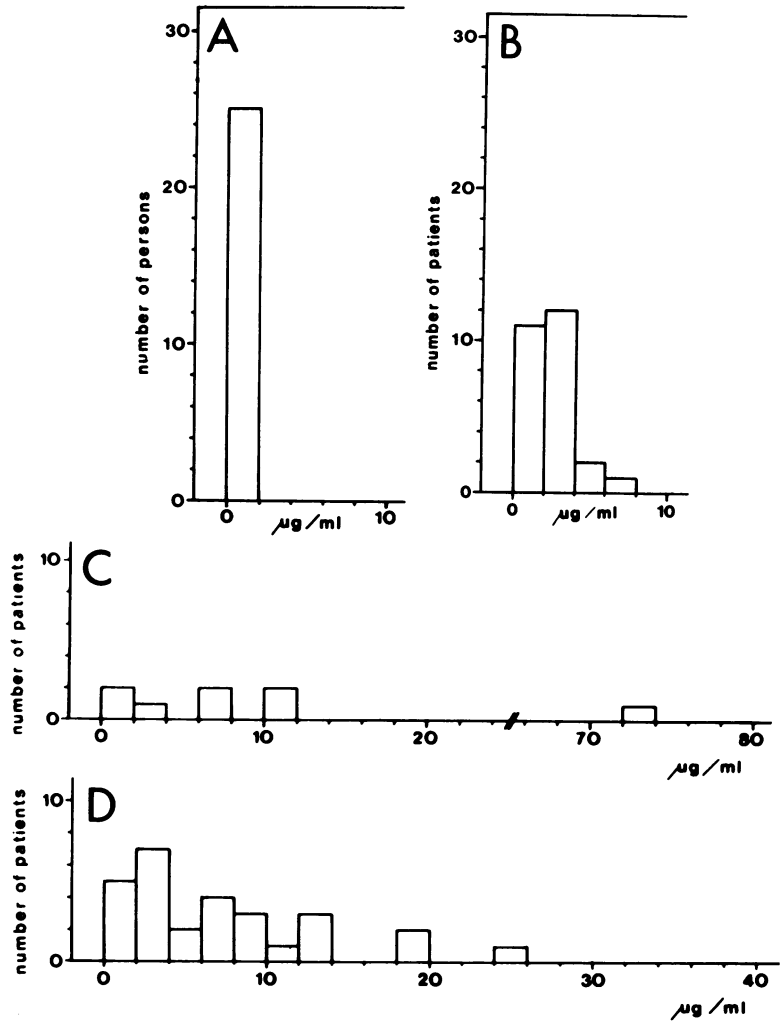

FIG. 3. *Distribution of IgG3 in the CSF of three groups of neurological patients as compared with healthy control persons. (A) Controls (n = 25); (B) MS (n = 26); (C) OID (n = 8); (D) NID (n = 28).*

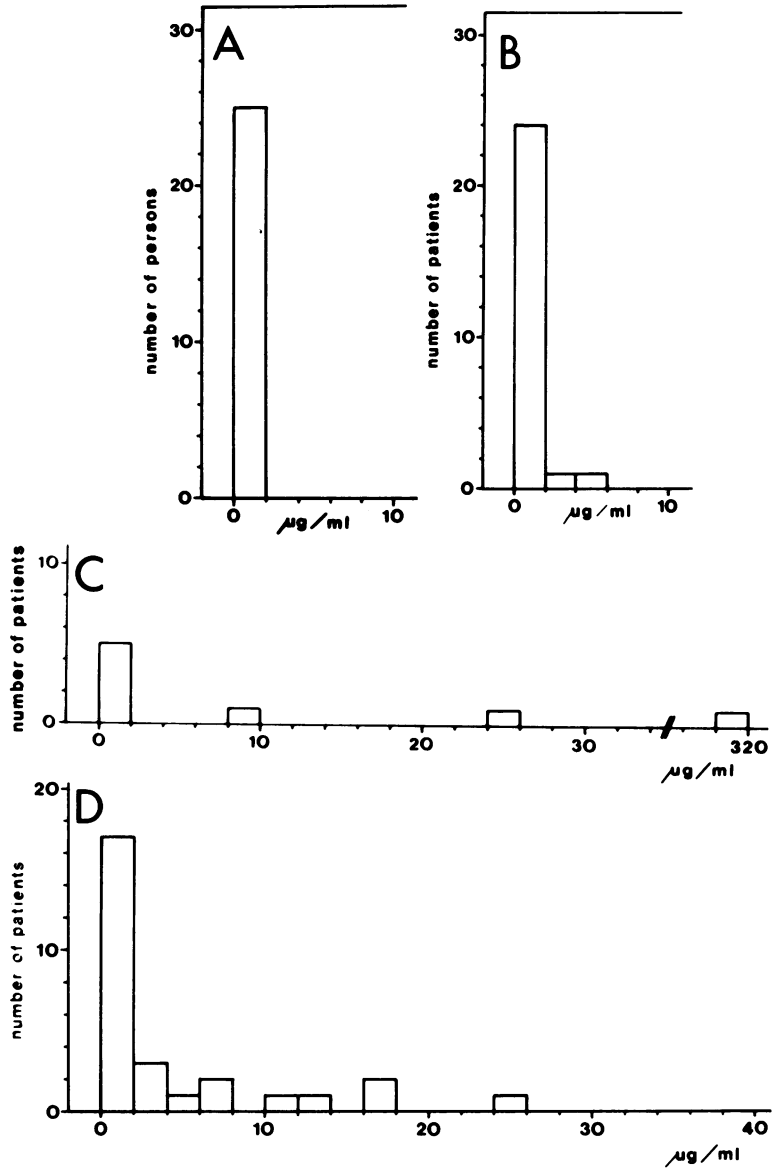

FIG. 4. *Distribution of IgG4 in the CSF of three groups of neurological patients as compared with healthy control persons. (A) Controls (n = 25); (B) MS (n = 26); (C) OID (n = 8); (D) NID (n = 28).*

as compared with the anti-human IgG antiserum used in the technique of Mancini et al. (17). After all, it should be mentioned that our determinations of the IgG subclass concentrations in the sera of healthy control persons (Table 4) are in good accordance with results of other investigators (18, 19).

To understand the IgG subclass distribution pattern in the CSF of MS patients, two independent observations should be considered: incidence of MS and IgG subclass distribution are both, at least in part, determined by inheritable factors (11, 14, 19). It remains to be seen whether there exists an interrelation between these conditions. Recent findings on virus-cell-antibody interactions (8, 15) which, for example, demonstrate the occurrence of molecular association between virus-coded cell surface proteins and transplantation antigens in an adenovirus system and thus the formation of a new antigenic complex might be a hint for the solution of present discrepancies between genetic, viral, and immunological aspects in the etiology and pathogenesis of MS.

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