# Four formulas for calculating cerebrospinal fluid immunoglobulin G abnormalities in multiple sclerosis

## A comparison

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■ The authors used laser immunonephelometry to measure cerebrospinal fluid and serum immunoglobulin G and albumin in patients with multiple sclerosis and other neurological diseases known to cause increased cerebrospinal fluid immunoglobulin G. The Wilcoxon rank-sum test showed that for four commonly used formulas (Tourtellotte's, Schuller's, the immunoglobulin G index, and immunoglobulin G/albumin) the definite multiple sclerosis group had significantly higher values of these variables than did the normal group or the groups with possible multiple sclerosis, other neurological diseases, or nonimmunological other neurological diseases. McNemar's test of symmetry showed that Tourtellotte's formula was more sensitive than other formulas and that Schuller's formula was slightly more specific than other formulas. Receiver operating characteristic curves showed that there was little difference among the formulas.

□ INDEX TERM: MULTIPLE SCLEROSIS, DIAGNOSIS □ CLEVE CLIN J MED 1988; 55:433–438

VARIOUS procedures, including measurement of cerebrospinal fluid (CSF) parameters, have increased the clinician's ability to diagnose multiple sclerosis (MS).[1] We have compared different formulas that have been developed to increase the sensitivity of CSF evaluation in MS.

## MATERIALS AND METHODS

### Patient selection

Without knowledge of CSF results, we reviewed clinical records of patients who had undergone CSF evaluation at the Cleveland Clinic, and if we thought that MS was a diagnostic possibility, we classified the degree of certainty of diagnosis using the Rose criteria,[2] but we considered abnormal visual evoked responses to be equivalent to clinical evidence of optic atrophy.[3] We used the older Rose criteria rather than the newer Poser criteria,[1] which include consideration of CSF abnormalities, in order to avoid doing a study of CSF abnormalities after we had made a diagnosis with these same CSF abnormalities. Thus we identified 93 patients with definite MS (DMS), 38 patients with probable MS, 175

■ *See also the editorial by Rudick (pp 408–409)*

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**TABLE 1**
OTHER NEUROLOGICAL DISEASES

| Diagnosis | Number of Patients |
|---|---|
| Amyotrophic lateral sclerosis, idiopathic peripheral neuropathy* | 12 (6 each) |
| Parkinson's disease,* idiopathic meningoencephalitis,* pediatric idiopathic degenerative disorder,* spinocerebellar degeneration, radiculopathy, Guillain-Barré syndrome* | 24 (4 each) |
| Seizure disorder | 3 |
| Astrocytoma, central nervous system lymphoma,* cerebral infarct, subacute sclerosing panencephalitis,* acute disseminated encephalomyelitis,* idiopathic brachial plexopathy* | 12 (2 each) |
| Acquired chronic hepatocerebral degeneration, Huntington's disease, Jakob-Creutzfeldt disease, systemic lupus erythematosus,* Meniere's disease, syringomyelia, Arnold-Chiari malformation, post-traumatic brachial plexopathy, diabetic peripheral neuropathy | 9 (1 each) |
| TOTAL | 60 |

*Diagnoses with presumed immunological basis (27 patients).

**TABLE 2**
MEAN AND STANDARD DEVIATION FOR EACH GROUP BY EACH FORMULA*

| Group | No. of Patients | Tourtellotte | Schuller | IgG index | IgG/Albumin |
|---|---|---|---|---|---|
| Normal | 30 | 0.14± 1.79 | 0.72± 8.08 | 0.50±0.08 | 0.11±0.03 |
| DMS | 93 | 15.80±19.47 | 25.53±41.21 | 1.25±1.24 | 0.26±0.22 |
| Probable MS | 38 | 12.12±16.43 | 18.41±26.00 | 0.98±0.63 | 0.22±0.17 |
| Possible MS | 175 | 5.11±10.28 | 7.59±21.52 | 0.69±0.40 | 0.15±0.10 |
| OND | 60 | 4.67±10.87 | 8.78±23.95 | 0.62±0.30 | 0.16±0.10 |
| NOND | 33 | 0.34± 4.08 | 1.05±16.52 | 0.50±0.11 | 0.13±0.06 |

*Values are stated as mean ± 1 standard deviation.
*DMS* = definite multiple sclerosis; *OND* = other neurological diseases; and *NOND* = nonimmunological other neurological diseases.

patients with possible MS, and 60 patients who had diagnoses (*Table 1*) of other neurological diseases (OND). We evaluated data from patients with OND in two ways: using data from all patients with OND (60 patients) and using data from patients in whom immunological factors were unlikely (33 patients). For normal specimens, we used CSF from 30 patients with normal neurological examination who had undergone myelography for spine pain; the myelogram, CSF cell count, and protein determination were normal.

**TABLE 3**
DEFINITIONS

| | |
|---|---|
| True positive (TP) | Number of sick subjects correctly classified by the test. |
| False positive (FP) | Number of healthy subjects misclassified by the test. |
| True negative (TN) | Number of healthy subjects correctly classified by the test. |
| False negative (FN) | Number of sick subjects misclassified by the test. |
| Sensitivity | TP/(TP + FN) |
| Specificity | TN/(TN + FP) |

**TABLE 4**
PERCENTAGE OF PATIENTS ASSOCIATED WITH VALUES AT LEAST 2 STANDARD DEVIATIONS ABOVE MEAN

| Group | No. of Patients | Formula (%) | | | |
|---|---|---|---|---|---|
| | | Tourtellotte | Schuller | IgG index | IgG/Albumin |
| DMS | 93 | 77 | 52 | 57 | 63 |
| Probable MS | 38 | 58 | 29 | 63 | 40 |
| Possible MS | 175 | 34 | 22 | 31 | 25 |
| OND | 60 | 35 | 23 | 28 | 32 |
| NOND | 33 | 15 | 6 | 9 | 15 |

*DMS* = definite multiple sclerosis; *OND* = other neurological diseases; and *NOND* = nonimmunological other neurological diseases.

## Assay procedure

We measured CSF and serum parameters with a PDQ laser nephelometer along with a calculator. CSF and serum immunoglobulin G (IgG) and albumin were measured with anti-IgG and anti-albumin sera, polymeric buffer (pH 7.4), and IgG and albumin standards. CSF was assayed undiluted, and serum was assayed at a dilution of 1:100. Twenty-five microliters of patient or standard sample was mixed with 0.5 mL of anti-IgG serum and 0.5 mL of polymeric buffer, while 3.0 µL of patient or standard sample was mixed with 0.5 mL of anti-albumin serum and 0.5 mL of polymeric buffer.

**TABLE 5**
WILCOXON RANK-SUM TEST

| Formula | Comparison | *P* = |
|---|---|---|
| Tourtellotte | Normal *v* DMS, probable MS | 0.0001 |
| | DMS *v* possible MS, OND, NOND | 0.0001 |
| | NOND *v* probable MS | 0.0001 |
| | Probable MS *v* possible MS | 0.0003 |
| | OND *v* probable MS | 0.001 |
| | Normal, NOND *v* possible MS | 0.02 |
| Schuller | Normal *v* DMS, probable MS | 0.0001 |
| | DMS *v* possible MS, NOND | 0.0001 |
| | DMS *v* OND | 0.0002 |
| | NOND *v* probable MS | 0.0002 |
| | Probable MS *v* possible MS | 0.0003 |
| | OND *v* probable MS | 0.01 |
| IgG Index | Normal *v* DMS, probable MS | 0.0001 |
| | DMS *v* possible MS, OND, NOND | 0.0001 |
| | Probable MS *v* possible MS | 0.0001 |
| | OND, NOND *v* probable MS | 0.0001 |
| | NOND *v* possible MS | 0.009 |
| | Normal *v* possible MS | 0.02 |
| IgG/albumin | Normal *v* DMS, probable MS | 0.0001 |
| | DMS *v* possible MS, OND, NOND | 0.0001 |
| | Probable MS *v* possible MS | 0.0001 |
| | NOND *v* probable MS | 0.0006 |
| | OND *v* probable MS | 0.01 |
| | Normal *v* OND | 0.02 |

*DMS* = definite multiple sclerosis; *OND* = other neurological diseases; *NOND* = nonimmunological other neurological diseases.

**TABLE 6**
MCNEMAR'S TEST OF SYMMETRY

| Patient Group | Formula | Reference Compared to | *P* = |
|---|---|---|---|
| | | *Sensitivity* | |
| DMS | Tourtellotte | Schuller | 0.0001 |
| | Tourtellotte | IgG index | 0.0001 |
| | Tourtellotte | IgG/albumin | 0.01 |
| | IgG index | Schuller | 0.17 |
| | IgG/albumin | Schuller | 0.0009 |
| | IgG/albumin | IgG index | 0.08 |
| Probable MS | Tourtellotte | Schuller | 0.002 |
| | Tourtellotte | IgG/albumin | 0.04 |
| | IgG index | Tourtellotte | 0.32 |
| | IgG index | Schuller | 0.0008 |
| | IgG index | IgG/albumin | 0.01 |
| | IgG/albumin | Schuller | 0.10 |
| Possible MS | Tourtellotte | Schuller | 0.0001 |
| | Tourtellotte | IgG index | 0.16 |
| | Tourtellotte | IgG/albumin | 0.002 |
| | IgG index | Schuller | 0.0006 |
| | IgG index | IgG/albumin | 0.04 |
| | IgG/albumin | Schuller | 0.06 |
| | | *Specificity* | |
| OND plus normal | Schuller | Tourtellotte | 0.02 |
| | Schuller | IgG index | 0.53 |
| | Schuller | IgG/albumin | 0.03 |
| | IgG index | Tourtellotte | 0.06 |
| | IgG index | IgG/albumin | 0.37 |
| | IgG/albumin | Tourtellotte | 0.01 |

*DMS* = definite multiple sclerosis; and *OND* = other neurological diseases.

Samples were incubated at room temperature for 60 minutes. The blanks consisted of patient or standard samples diluted in 1.0 mL of buffer. The forward light scattered by the IgG and albumin immune complexes was measured within the range of the standard sera with the nephelometer using relative light scatter units. The appropriately programmed calculator transformed relative light scatter units into milligrams of protein per deciliter,[4] but we revised the constants used in our previous papers to reflect newer normative data. We have monitored our results (now approximately 600 CSF specimens) in a number of ways, including calculating sensitivities and specificities.[5]

The formula described by Tourtellotte[6] was modified to conform to our normative data generated for this study:

$$\text{CNS IgG synthesis (mg/day)} = \left\{\left[IgG_{CSF} - \frac{IgG_{serum}}{421}\right] - \left[\left(Alb_{CSF} - \frac{Alb_{serum}}{206}\right)\left(\frac{IgG_{serum}}{Alb_{serum}}\right)0.43\right]\right\}X5, \quad (1)$$

where *Alb* is albumin and all parameters are measured in

**TABLE 7**
RECEIVER OPERATING CHARACTERISTIC CURVES: DIFFERENCES IN AREAS

| Comparison | *P* = |
|---|---|
| *Part A* | |
| Tourtellotte *v* Schuller | 0.009 |
| IgG index *v* Schuller | 0.04 |
| Tourtellotte *v* IgG index | 0.05 |
| Tourtellotte *v* IgG/albumin | 0.07 |
| IgG/albumin *v* Schuller | 0.11 |
| IgG index *v* IgG/albumin | 0.18 |
| *Part B* | |
| Tourtellotte *v* Schuller | 0.04 |
| IgG index *v* Schuller | 0.05 |
| Tourtellotte *v* IgG/albumin | 0.07 |
| IgG index *v* IgG/albumin | 0.12 |
| Tourtellotte *v* IgG index | 0.48 |
| IgG/albumin *v* Schuller | 0.56 |

Sensitivity was calculated from the definite MS group.
In Part A, specificity was calculated from the normal and OND groups combined; in Part B, specificity was calculated from the non-immunological OND group.

A, B

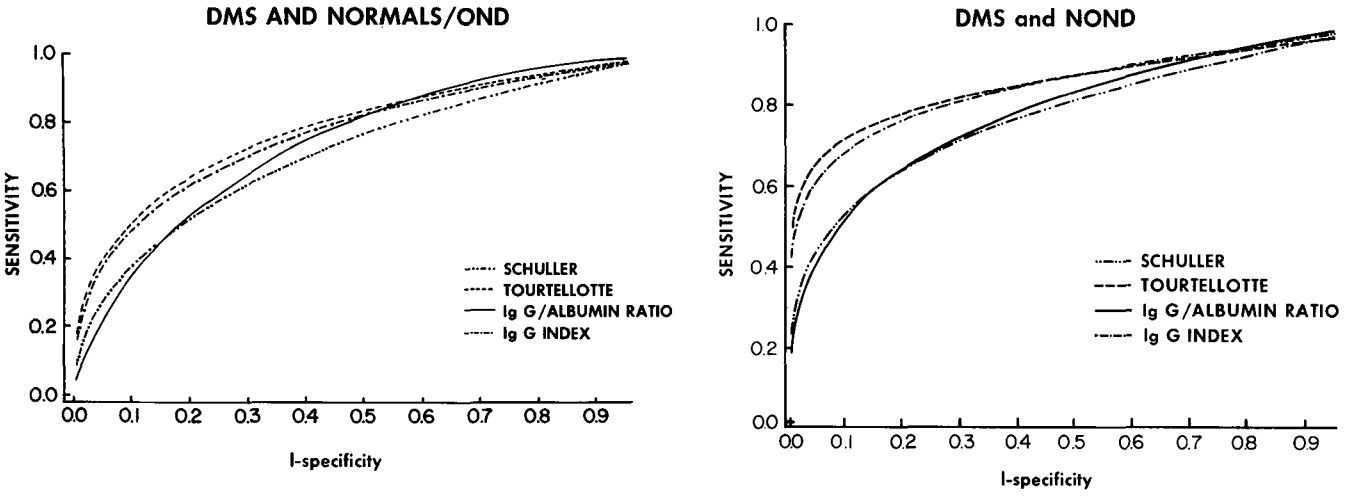


**FIGURE 1A. Receiver operating characteristic curves comparing definite multiple sclerosis (DMS) patients *v* normals plus other neurological disease (OND) patients. The closer a curve is to the upper left corner of the graph, the better the clinical performance of the test. FIGURE 1B. Receiver operating characteristic curves comparing definite multiple sclerosis (DMS) patients *v* nonimmunological other neurological disease (NOND) patients. The closer a curve is to the upper left corner of the graph, the better the clinical performance of the test.**

TABLE 8
MULTIPLE SCLEROSIS CASES (% POSITIVE)

| Previous study | Tourtellotte | Schuller | IgG index | IgG/ albumin |
|---|---|---|---|---|
| Bloomer and Bray[15] | 75 | | | 67 |
| Bynke et al[16] | | | 50 | |
| Caroscio et al[17] | 30–88 | | 56–94 | 11–59 |
| Hershey and Trotter[18] | 78 | | 64–91 | 23–59 |
| Hutchinson et al[19] | | | | 90 |
| Lefvert and Link,[20] Laurenzi et al,[21] Link and Kostulas,[22] Link and Laurenzi,[23] and Link and Tibbling[24] | 91 | | 72–92 | 80 |
| Livrea et al[25] | 70 | | 63 | |
| Mattson et al[26] | 82 | | | |
| Pearl et al[27] | | | 88 | |
| Perkin et al[28] | | | 78 | 63 |
| Poloni et al[29] | | | 60 | |
| Schuller and Sagar[30] and Schuller et al[31] | | 74–79 | | |
| Sun et al[32] | | | 60 | 69 |
| Tourtellotte,[6] Tourtellotte and Ma,[33] and Maurice et al[34] | 76–92 | | 92 | |
| Trojaborg et al[35] | | | 90 | |

milligrams per deciliter. We considered the formula described by Reiber[7] to be essentially similar. Similarly we modified the formula derived by Schuller[8] to conform to our own normative data:

Local IgG synthesis (mg/L)=

$$IgG_{CSF} - \left[ 23.8 + \left( \frac{Alb_{CSF} - 266}{60} \right) \left( \frac{IgG_{serum}}{1{,}000} \right) \right], \quad (2)$$

where all parameters are measured in milligrams per liter. The IgG index[9,10] is defined by the formula:

$$IgG\ index = \frac{IgG_{CSF}/IgG_{serum}}{Alb_{CSF}/Alb_{serum}} . \quad (3)$$

We also evaluated IgG/albumin.

*Table 2* shows the mean and standard deviation for each of our patient groups as determined by each formula.

## RESULTS

The definitions we used to analyze our results are shown in *Table 3*.[11]

We considered two standard deviations above the mean as being the upper limit of normal: 3.7 mg/day for Tourtellotte's formula, 17 mg/L for Schuller's formula, 0.66 for the IgG index, and 0.17 for IgG/albumin. Thus we found abnormal values for each patient group by each

formula as shown in *Table 4*. The Wilcoxon rank-sum test showed significant differences between pairs of groups for all four formulas (*Table 5*).

We used McNemar's test of symmetry to evaluate the hypothesis that there is no difference between sensitivities or specificities for any pair of formulas calculated on the same patients. *Table 6* indicates, for example, that when we used the DMS group to calculate sensitivities, we found that Tourtellotte's formula was more sensitive than Schuller's formula ($P = 0.0001$). As a measure of specificity, we looked at the ability of each of the formulas to classify correctly the OND and normal groups combined, and we found, for example, that Schuller's formula was more specific than Tourtellotte's formula ($P = 0.02$).

Using arbitrary cutpoints, we calculated sensitivity and specificity for each of the four formulas. We then used these arbitrary cutpoints to construct receiver operating characteristic curves[12] (*Figures 1* and *2*), calculate the area under each curve, and determine the likelihood that these areas were different,[13] as shown in *Table 7*. For example, when we calculated sensitivities from the DMS group and specificities from the normal and OND groups combined, we found that the difference in areas between Tourtellotte's formula and Schuller's formula were statistically significant ($P = 0.009$).

## DISCUSSION

Measurement of CSF IgG, reported in different ways, is useful for the diagnosis of MS.[1] In our previous studies,[4,5,14] we tried to determine the predictive value of CNS IgG synthesis in MS. We were careful about selecting patients with clearcut diagnoses so that expressions like "true positive" and "false positive" were as accurate as possible. Such patient selection was not attempted in this study. Therefore, the results of this study reflect more closely what would be seen in clinical practice. The data shown in *Table 8* indicate that most patients with MS have quantitative abnormalities of CSF IgG. However, the various studies are not quite comparable because different laboratory techniques and different definitions of MS were used for different populations.

Evaluations of CSF in MS patients have been studies of patients identified by clinical criteria without autopsy confirmation. One could suggest that variable changes in the blood-brain barrier render accurate calculation impossible and that the IgG index is the quantitative test least subject to error while the qualitative detection of oligoclonal IgG bands is the most appropriate CSF test.[20] Alternatively, one could argue that Tourtellotte's formula is better than others because only this formula has been validated with an isotopic tracer technique.[33] Determining which arguments are more valid may be impossible at this time.[36] Our analysis of our own data indicates that Tourtellotte's formula is more sensitive than Schuller's, the IgG index, and IgG/albumin. However, the formulas are not strikingly different in terms of specificity.

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