

Intrathecal synthesis of antiviral IgG antibodies in multiple sclerosis

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The Measles-Rubella-Zoster (MRZ) reaction is a test for the intrathecal synthesis of IgG antibodies against measles, rubella and varicella zoster viruses. Since the 1990s, it has been used as an adjunctive test to support the diagnosis of multiple sclerosis (MS), although it has no formal role in current McDonald diagnostic criteria and its clinical relevance remains debated. While early studies considered a single elevated antibody index (M, R or Z) as a positive result, the practice today requires at least two elevated antibody indices (M+R, M+Z, or R+Z), referred to as a polyspecific MRZ reaction (MRZ-2). MRZ-2 is the most specific laboratory marker for MS, with reported specificity exceeding 90%. However, sensitivity varies widely across studies, ranging from approximately 30% to over 70%. In the Czech adult MS population, MRZ-2 sensitivity was recently reported at 32%, markedly lower than the 67% pooled sensitivity reported in a meta-analysis of predominantly German cohorts. Broadening the panel of anti-viral antibodies (MRZ+) has been proposed to improve sensitivity, with parvovirus B19 and mumps virus being the most promising candidates. Further studies are required to determine whether an extended panel can increase sensitivity while maintaining high diagnostic specificity.

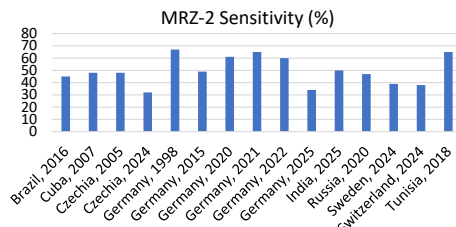
INTRATHECAL SYNTHESIS OF ANTIVIRAL ANTIBODIES IN MULTIPLE SCLEROSIS

MRZ reaction – intrathecal synthesis of IgG antibodies against Measles, Rubella and Zoster viruses determined by Antibody Index (AI) calculation:

$$AI = \frac{Q_{IgG\ spec}}{Q_{IgG\ total}} \text{ if } Q_{IgG\ total} \leq Q_{lim\ IgG}; AI = \frac{Q_{IgG\ spec}}{Q_{lim\ IgG}} \text{ if } Q_{IgG\ total} > Q_{lim\ IgG}$$

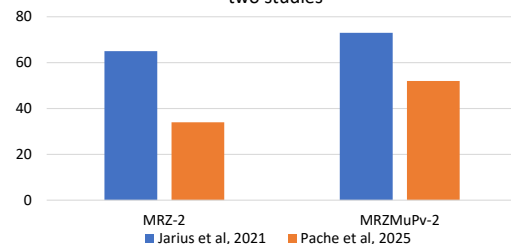
Normally, AI should be close to 1.0 (specific antibodies cross the blood-CSF barrier at the same rate as other antibodies of the same immunoglobulin class)
AI > 1.4 indicates intrathecal synthesis.

Intrathecal IgG synthesis against ≥ 2 of the viruses ("polyspecific", MRZ-2) is highly specific for multiple sclerosis (> 90 %) but sensitivity varies across studies:



MRZ plus concept: IgG antibodies against other antigens tested in addition to M, R, Z: Mumps (Mu) and Parvovirus B19 (Pv) appear as most promising.

MRZ-2 and extended MRZ-2 sensitivity in the first two studies



Specificity of any extended MRZ plus panel should be tested: high specificity for multiple sclerosis is the key feature that makes the test useful in MS diagnosis.

Limited sensitivity drives the need for extended MRZ-2 panels, but specificity of any extended MRZ-2 panel should be carefully tested.

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INTRODUCTION

Measles-Rubella-Zoster (MRZ) reaction is a term used for combined determination of IgG antibodies to the three named viruses in cerebrospinal fluid (CSF) and serum.

The concentrations of these antibodies are expressed in arbitrary units and compared with total IgG concentrations in CSF and serum, enabling to estimate intrathecal synthesis of anti-measles, anti-rubella and anti-varicella zoster virus IgG by calculating antibody index (AI; see be-

low for detailed explanation). The test was first described by Felgenhauer et al.¹ in 1985 and further improved by Reiber and Lange² in 1991. However, the conceptual basis for calculating local production of specific antibodies had been proposed much earlier by Goldmann and Witmer³. These authors described local synthesis of anti-microbial antibodies in the aqueous humour of the eye and, for the first time, used a ratio analogous to that used today in antibody index calculation. The presence of antiviral antibodies in the CSF of patients with multiple sclerosis (MS) was described in the 1960s (ref.⁴), although their intrathecal synthesis was inferred rather than directly determined. Up to now, measurement of specific antibodies in the CSF alone is still occasionally performed, despite its limited diagnostic value, as it does not distinguish between antibodies passively transferred from the blood and those produced intrathecally⁵.

The MRZ reaction was mentioned as an optional test in the first consensus report on cerebrospinal fluid (CSF) analysis in the diagnosis of MS (ref.⁶), but it is not included in more recent reports^{7,8} or in the latest revision of the McDonald diagnostic criteria⁹. MRZ reaction is described in the German guidelines for lumbar puncture and CSF diagnostics¹⁰ and in the Method catalogue of the German Society for CSF Diagnostics and Clinical Neurochemistry¹¹. Outside German speaking countries, the test is rarely performed.

In this narrative review, we summarize the analytical aspects, principles of interpretation and clinical relevance of the detection of microbe-specific IgG intrathecal synthesis in the context of MS diagnosis, with particular emphasis on the MRZ reaction. We also discuss the perspectives of broadening the MRZ antigen panel with the aim of increasing the overall sensitivity of the test for MS.

ANTIBODY INDEX CALCULATIONS

In the absence of proven intrathecal synthesis of total IgG, the antibody index (AI) is calculated as follows:

$$AI = \frac{Q_{IgG\ spec}}{Q_{IgG\ total}} = \frac{IgG\ spec_{CSF}/IgG\ spec_{serum}}{IgG\ total_{CSF}/IgG\ total_{serum}}$$

If the total IgG quotient exceeds Q_{lim} , i.e. intrathecal IgG synthesis, the Q_{lim} value should replace $Q_{IgG\ total}$ in the denominator:

$$AI = \frac{Q_{IgG\ spec}}{Q_{lim\ IgG}} = \frac{Q_{IgG\ spec}}{0.93 \cdot \sqrt{(Q_{Alb}^2 + 0.000006)} - 0.0017}$$

This equation uses Reiber formula¹² for $Q_{lim\ IgG}$ calculation. CSF and serum concentrations should be expressed in identical units (i.e., arbitrary units for IgG_{spec} and mg/L for IgG_{total} and albumin, respectively).

Alternative approaches to estimating Q_{lim} include the Auer and Hegen formula¹³ or $0.7 \cdot Q_{Alb}$ which corresponds to the Q_{lim} derived from the cut-off value of 0.7 for IgG

index. Opinions differ in the scientific community about the best way to calculate $Q_{lim\ IgG}$ (ref.¹⁴). Most laboratories, including ours, prefer the Reiber formula since it is both empirically and biophysically derived, whereas all other formulas are purely empirical. In addition, the mean Q_{IgG} and the lowest plausible Q_{IgG} dependent on Q_{Alb} can be calculated using different parameters, whereas other formulas describe only the Q_{IgG} upper reference limit. Substitution of Q_{IgG} or $Q_{lim\ IgG}$ by Q_{Alb} in the denominator, as proposed by several authors¹⁵⁻¹⁷, is based on a similar assumption as the total IgG index (values above a cut-off, usually 0.7, are considered to represent intrathecal synthesis) but has a principal disadvantage that one does not compare like with like any more, i.e. the theoretically expected value in the absence of intrathecal synthesis of the respective antibodies differs from 1.0.

In patients with $Q_{IgG} \leq Q_{lim\ IgG}$, conventionally defined AI represents the relation between the ratios of particular specific IgG to total IgG in CSF (R_{CSF}) and serum (R_S) (ref.^{5,18}):

$$AI = \frac{R_{CSF}}{R_S} = \frac{IgG_{spec\ CSF}/IgG_{total\ CSF}}{IgG_{spec\ S}/IgG_{total\ S}}$$

A procedure for the determination of specific IgG concentrations in mg/L has been proposed by Conrad et al.¹⁹ and Jacobi et al.²⁰. Conversion factors are determined by measuring total IgG in IgG standards (using wells coated with an anti-IgG antibody, preferably $F(ab')_2$ specific) and specific IgG standards in the same type of wells coated with the respective antigen under the same conditions. An IgG calibration curve is then used for the conversion of arbitrary units in specific IgG standards to μg , under the definition that 1 mg specific antibodies has the same optical density as 1 mg total IgG.

In practice, this method may be difficult to implement unless the antiviral antibodies are measured using an in-house method, since the type of ELISA plate and details of the coating procedure (which should be similar for both IgG standard and specific IgG measurement) are usually not provided by ELISA kit manufacturers. Even if all these preconditions are fulfilled, the definition above may be susceptible to some criticism because of possible differences in antibody avidity, competition of other antibody classes for the antigen, and the exact molecular mode of binding. Nevertheless, at least three independent research groups¹⁹⁻²¹ have reported consistent and clinically meaningful results with this method with respect to the differentiation between antigen-driven response in infectious CNS diseases and polyspecific antibody response in MS.

In cases of a positive AI and $Q_{IgG} \geq Q_{mean\ IgG}$, the proportion of intrathecally synthesised specific antibodies out of intrathecally synthesised total IgG, F_S (in %) can be calculated as:

$$F_S = \frac{IgG_{spec\ Loc\ (mean)}}{IgG_{total\ Loc\ (mean)}} \cdot 100$$

where locally synthesised fractions are calculated with reference to $Q_{mean\ IgG}$ instead of $Q_{lim\ IgG}$.

$Q_{mean} IgG$ is calculated as:

$$Q_{mean} IgG = 0.65 \cdot \sqrt{Q_{Alb}^2 + 0.000008} - 0.0014$$

and $IgG_{Loc (mean)}$ as:

$$IgG_{Loc (mean)} = (Q_{IgG} - Q_{mean} IgG) \cdot IgG_S$$

The measurement of specific antibody concentrations in mg/L has not yet been implemented in routine diagnostic laboratories. However, it may be valuable for both theoretical considerations regarding the origin of the intrathecal immune response and for clinical differentiation between antibody response directed to a causative agent in CNS infection and the polyspecific antibody response typical for MS (ref.¹⁸⁻²⁰). This distinction may be particularly relevant for VZV. In one study²¹, F_s values were markedly higher in 7 patients with CNS infections caused by VZV (range, 13.5–73%) than in 20 patients with MS (range, 0.3–5.3%) with no overlap between groups, whereas there was a significant overlap of AI values (range, 2.1–8.1 in VZV CNS infections and 1.6–14.8 in MS). In general, F_s for any particular specificity usually remains below 5% in MS. In CNS infections, F_s is significantly higher, although it rarely exceeds 50% (ref.¹⁸⁻²⁰).

ANALYTICAL ASPECTS OF CSF AND SERUM SPECIFIC ANTIBODY QUANTIFICATION AND ANTIBODY INDEX DETERMINATION

Conventionally, specific antibodies are quantified in appropriately diluted CSF (e.g. 1/2) and serum (e.g. 1/400) within the same run. Values are expressed in arbitrary units (AU) multiplied by the dilution factor (e.g. 2 for CSF and 400 for serum). Concentrations are usually calculated using a 4-point to 6-point calibration curve. Samples with results outside the measurement range should be re-analysed at an appropriate dilution (for a sample with optical density above that of the highest standard, a five- or ten-fold higher dilution may be more appropriate than doubling dilutions recommended by some manufacturers).

An alternative procedure has been proposed using dilution of CSF and serum to exactly the same total IgG concentration (e.g. CSF 1/2 and serum corresponding to the IgG concentration of 1/2 diluted CSF). The ratio of CSF and serum values in AU then directly corresponds to the AI; dilutions are not taken into account for this calculation. Some authors²² have even suggested comparing optical densities (OD) directly (obviating the need for calibration curve construction) using the equation:

$$AI = \frac{OD_{CSF}}{OD_{Serum}}$$

This is, however, unsuitable since the calibration curve is typically non-linear (a 4-parameter function is

the most frequently used, although some manufacturers recommend simple point-to-point function) and the ratio of OD in CSF and serum is not equal to the corresponding ratio of AU calculated from the calibration curve²⁰. Another drawback of dilution to exactly the same IgG concentration lies in the fact that either the AI should be corrected using multiplication by $Q_{IgG}/Q_{lim} IgG$, or a virtual CSF or serum concentration corresponding to Q_{lim} should be calculated in cases where $Q_{IgG} > Q_{lim} IgG$. For all these reasons, and also because different dilutions for each serum sample are more time-consuming, the conventional procedure is preferred in routine practice.

Using two different dilutions (e.g. 1/2 and 1/10 for CSF and 1/400 and 1/2000 for serum) has been recommended to obtain more precise results (using closer optical densities for CSF/serum quotient calculation) but is not always performed for economic reasons.

In the absence of intrathecal immunoglobulin synthesis, AI should have a value of 1.0 since specific antibodies diffuse from blood to the CSF similarly to other antibodies of the same class (minor changes in amino acid composition in complementarity determining regions are not expected to change the diffusion coefficient significantly). In a seminal paper by Reiber and Lange², coefficients of variation (CV %) were 11% for M and R, 9% for Z, and 16% for herpes simplex virus (H) AI. The reference range of AI calculated in this study from 150 control samples was 0.7–1.3; only 1% of results in this group were 1.4. Hence, reference ranges for AI used today in most laboratories (0.7–1.3; 0.6–1.4; 0.5–1.5) cover (at least) the interval mean ± 2 SD, mean ± 2.5 SD, or mean ± 3 SD. In cases without intrathecal IgG synthesis ($Q_{IgG} < Q_{lim} IgG$ and negative oligoclonal IgG bands), AI values < 0.5 are suspicious for an analytical error or mismatched CSF and serum samples. On the contrary, if intrathecal IgG synthesis is demonstrated, AI values lower than 0.5 may occasionally be encountered because of intrathecal synthesis of IgG bearing antigen specificities other than those tested. In the “grey zone” AI range (1.3–1.5), a disproportionate increase in one AI compared with another AI ($> 50\%$) supports intrathecal synthesis of the respective antibody²³.

If CSF IgG_{spec} is not measurable (i.e., below the measuring range of the assay), the test result is considered negative and AI should not be calculated. Only for the purpose of statistical analysis of research data, a theoretical value of 1.0 is sometimes retrospectively imputed in such cases. In the exceptional situation of CSF IgG_{spec} being measurable and serum IgG_{spec} being below the measuring range, re-analysis of the paired CSF and serum samples should be considered, using a lower serum dilution.

Analytical factors may contribute significantly to different study results, as exemplified by recently published, carefully conducted studies^{17,24,25} in which, at variance with most others published so far, elevated antiviral AI in a substantial proportion of controls was found, which poses a substantial limit to the clinical usefulness of such a test. Apart from a slightly different ELISA procedure,

Table 1. Proportion of elevated AI in patients with multiple sclerosis.

Study	Ref.	n	M	R	Z	MRZ-1	MRZ-2
Felgenhauer and Reiber 1992 (Germany)	5	100	79%	70%	62%	94%	72%
Reiber et al. 1998 (Germany)	18	177	78%	60%	55%	89%	67%
Bednarova et al. 2005 (Czechia)	41	42	74%	41%	36%	88%	48%
Robinson-Agramonte et al. 2007 (Cuba)	42	23	78%	30%	59%	100%	48%
Brettschneider et al. 2009 (Germany)	43	49*	59%	49%	42%	n.r.	47%
		40**	33%	24%	32%	n.r.	25%
Jarius et al. 2009 (Germany)	44	42	74%	76%	76%	90%	88%
Pohl et al. 2010 (Germany)	45	43 (pMS)	35%	30%	49%	n.r.	n.r.
		50 (aMS)	60%	42%	32%		
Kulakowska et al. 2012 (Poland)	26	27	55%	63%	50%	81%	n.r.
Hottenrott et al. 2015 (Germany)	46	100 (RR)	48%	43%	39%	68%	43%
		103 (PP)	62%	57%	49%	84%	54%
Stich et al. 2015 (Germany)	31	18 (OCB+)	50%	39%	50%	67%	44%
		17 (OCB-)	29%	24%	24%	41%	24%
Dias-Carneiro et al. 2016 (Brazil)	47	33	52%	46%	33%	67%	45%
Huss et al. 2016 (Germany)	27	8 (CIS)	50%	38%	13%	n.r.	25%
		49 (MS)	33%	37%	35%		33%
Jarius et al. 2017 (Germany)	43	9	78%	67%	67%	89%	78%
Feki 2018 (Tunisia)	48	60	58%	65%	63%	n.r.	65%
Venhoff et al. 2019 (Germany)	49	68 (ANA+)	59%	49%	44%	81%	54%
Largey et al. 2019 (Germany)	50	15	73%	60%	53%	87%	73%
Robinson et al. 2020 (Germany)	51	81 (PP)	47%	42%	47%	78%	46%
Jarius et al. 2021 (Germany)	52	26	77%	62%	58%	81%	65%
Schwenkenbecher et al. 2021 (Germany)	53	30	27%	30%	33%	n.r.	23%
Kyllesbech et al. 2022 (Denmark)	24	26	42%	31%	n.d.	n.d.	n.d.
Gåsland et al. 2023 (Denmark)	25	64 (MS)	66%	50%	67%	88%	61%
		34 (ON)	68%	71%	38%	85%	59%
Zondra Revendova et al. 2024 (Czechia)	54	379 (MS)	27%	42%	39%	64%	32%
		60 (CIS/RIS)	22%	25%	33%	43%	28%
Neidhart et al. 2024	55	184 (Swi)	35%	46%	44%	n.r.	38%
(Switzerland, Sweden) ***		89 (Swe)	39%	35%	34%		39%
Vlad et al. 2024 (Switzerland, Sweden) ***	56	513	38%	40%	41%	n.r.	39%
D'Cunha et al. 2025 (India)	57	96	34%	42%	48%	63%	50%
Pache et al. 2025 (Germany)	58	50	34%	36%	38%	44%	34%
Rodomonti et al. 2025 (Germany)	59	672 (M),	49%	47%	52%	n.d.	n.d.
		608 (R),					
		970 (Z)					

* patients with CIS who converted to RRMS within 2 years of follow-up; ** patients with CIS who did not convert to RRMS within 2 years of follow-up; *** partly identical patient population; aMS, adult multiple sclerosis; ANA, antinuclear antibodies; CIS, clinically isolated syndrome; n.d., not determined; n.r., not reported; MS, multiple sclerosis; ON, optic neuritis; pMS, pediatric multiple sclerosis; PP, primary progressive; RR, relapsing-remitting; Swe, Sweden; Swi, Switzerland.

the source of antigen might contribute to this difference and raises the interesting question of whether the use of recombinant antigens brings additional, as yet undiscovered, analytical challenges.

OTHER METHODS FOR DEMONSTRATING THE INTRATHECAL ORIGIN OF SPECIFIC ANTIBODIES

ELISA remains the gold standard method for AI determination, although multiplex assays based on antigen-coated beads and fluorescent detection have been described^{26,27}. Broad antibody profiling of the entire known

human virome, based on phage immunoprecipitation sequencing technology²⁸, has become an interesting research tool, but has no role in clinical routine because intrathecal synthesis cannot be appropriately assessed by this kind of assay, in addition to its complexity and high costs. However, a feasible and attractive alternative to AI determination remains, namely the detection of antigen-specific oligoclonal IgG. Similarly to total IgG, specific IgG can be compared in CSF and serum by isoelectric focusing followed by affinity-mediated immunoblotting. This method was published in 1984 by two independent research groups^{29,30} and has a much wider application for detailed studies of various proteins, in particular immunoglobulins and free light chains³¹. The blotting membrane is

coated with the respective antigen, and the remaining protein binding sites are blocked before protein transfer from the gel after separation. In principle, the method is quite similar to an ELISA test described above. Either chromogenic^{32,33} or more sensitive luminescent detection^{34,35} can be used. Concordance between AI and antigen-specific oligoclonal IgG was fair, but far from perfect in several studies performed up to now^{34,36-38}. The inclusion of a positive control (if available), and especially a negative control with CSF-restricted oligoclonal IgG bands of unrelated specificity, is important to ensure valid results. In general, CSF and sera should be diluted to the same IgG concentration. However, in case of pronounced intrathecal IgG synthesis, dilution of either serum or CSF to an IgG concentration corresponding to $Q_{lim\ IgG}$ (i.e., higher dilution of serum or lower dilution of CSF) can be considered to obtain more precise results. This consideration is usually neglected when analyzing total IgG, but is relevant for specific antibodies (as well as for free light chains) with an intrathecal fraction exceeding 90%. (In an extreme case, when the specific antibody or free light chain concentration in the CSF is higher than in serum, dilution of both fluids to the same analyte concentration would result in higher dilution of CSF than of serum; this is obviously nonsensical and may even lead to a false impression of a mirror pattern). In general, the method requires significantly less material (typically less than 10 μ L versus about 100 μ L for an ELISA test) but is not standardized, requires significantly more manual labour and time compared to ELISA, and is not used in routine diagnostic laboratories.

FREQUENCY OF POSITIVE ANTIBODY INDICES AND COMPOSITE MRZ REACTION IN MS AND OTHER DISEASES

Two comprehensive reviews^{39,40} have provided meta-analyses of earlier MRZ studies. To highlight discrepancies across cohorts, Table 1 summarizes the frequency of positive AI reported in both older and recent MRZ studies^{5,18,24-27,39,41-59}.

The MRZ pattern is usually constant in an individual MS patient⁶⁰, although an expansion of antibody reactivity in the CSF can occasionally be seen in follow-up lumbar punctures^{60,61}. Pohl et al.⁴⁵ found somewhat higher frequencies of anti-measles and anti-rubella (but somewhat lower frequencies of anti-VZV, anti-HSV, anti-EBNA-1 and anti-EBV-VCA) IgG intrathecal synthesis in adult-onset MS compared to pediatric-onset MS patients. A lower frequency of the polyspecific MRZ reaction has been observed in pediatric (40%) compared to adult (67%) MS (ref.⁶⁰). On the contrary, Süße et al. (ref.⁶²) reported a somewhat higher MRZ positivity rate in clinically isolated syndrome (72%) than in MS (61%), and Kauth et al.⁶³ reported an even higher positivity rate of 79% among children with optic neuritis who subsequently developed MS (73/92, versus 8/136, i.e. 6% children with optic neuritis who did not develop MS). The last result, however, should be interpreted with some caution, given

that Chen et al.⁶⁴ from the same research group reported only a 24% positivity rate among 68 children with MS. This obvious discrepancy is not discussed in either paper. No significant differences in MRZ positivity have been found between early- and late-onset MS or between relapsing-remitting and progressive MS (ref.^{54,65-68}). One study reported a higher MRZ positivity rate in female than male MS patients⁶⁸.

Substantial variability in MRZ positivity rates has been observed across studies, even among cohorts from similar time periods and geographic regions. Several factors may contribute to this heterogeneity. Analytical aspects include differences in various antigen sources (virus-infected cell line lysates versus purified or recombinant viral proteins) and assay methodologies (various commercially available ELISA assays predominantly used in clinical routine versus in-house assays or substantially modified commercially available ELISAs frequently applied in research settings). Additional factors may be even influential: evolving MS diagnostic criteria, recognition of novel disease entities such as neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) which may have been classified as MS in older studies, and variations in seroprevalence of specific IgG antibodies across populations and time periods. The latter reason has been discussed most extensively, since either natural infection or vaccination are necessary preconditions for an intrathecal synthesis of any specific antibody¹⁸. This has been indirectly demonstrated by a comparative study in German and Cuban MS patients, which demonstrated a twofold lower frequency of elevated anti-R AI in Cuban patients (30% vs. 60%). The sex distribution among Cuban patients with an elevated anti-R AI was markedly skewed (m:f 1:6). This has been explained by the low incidence of rubella infections in Cuba in the relevant time period and the fact that male population was not offered vaccination in Cuba before 1986 (ref.⁴²). Pache et al.⁵⁸ demonstrated that intrathecal synthesis was almost absent in MS patients seronegative for the respective virus, with the only exception being 2 out of 50 MS patients where anti-measles AI was elevated despite seronegativity. Ruprecht et al.⁴⁰ proposed providing seroprevalence-corrected frequencies of elevated AIs; however, waning antibody response after infection or immunization⁶⁹ should be taken into account when deciding whether to test only seropositive patients. In addition, individual serostatus is usually not known before AI determination.

In Germany, seropositivity among MS patients is high for all viruses included in the MRZ reaction. A recent large study⁵⁹ reported seropositivity rates 98% for M, 95% for R, and 98% for Z. For additional viruses tested in that cohort, seropositivity was 100% for EBV, 93% for mumps virus, 75% for HSV and 54% for CMV. A smaller study of 50 MS patients originating from the same population⁵⁸ found somewhat lower seropositivity rates of 82% for M, 88% for R, 94% for Z, 66% for HSV-1/2 and 42% for CMV. Seropositivity for other antigens was tested in this study and found to be 100% for both EBNA-1 and VCA EBV antigens, 70% for mumps virus, 52% for parvovirus B19,

16% for tick-borne encephalitis virus, 24% for *Toxoplasma gondii* and 6% for *Borrelia burgdorferi*. However, seropositivity rates may be different in different populations.

A change in the interpretation of the MRZ reaction was promoted by the study of Brettschneider et al.⁴³, which introduced a score of 9 points for M, 8 points for R, and 1 point for Z, and a score of >10 for the MRZ reaction to be considered positive. Although this scoring system is no longer in use, this study demonstrated that the relative importance of individual AI values differs, M and R being more important than Z. Apart from common CNS infections caused by VZV, VZV reactivation has been described e.g. in patients with ischemic stroke or transient ischemic attack⁷⁰, probably contributing to the relatively lower specificity of an increased VZV AI for MS.

In almost all subsequent studies, at least two positive AI have been required for the MRZ reaction to be considered positive. Some clinicians consider isolated M or R (but not Z) AI positivity supportive of MS; however, CNS infections by these viruses, although rare in developed countries, remain possible. In cases of isolated positivity of the M AI, rare possibility of SSPE should be considered in differential diagnosis, including atypical adult-onset cases⁷¹. Besides infection-related AI elevation, an isolated case of astrocytoma with positive M AI has been reported that dropped to negative values after appropriate tumor treatment⁷².

Although MRZ reaction was initially proposed as a marker of chronic autoimmune CNS inflammation in general^{18,73}, subsequent studies and meta-analyses^{39,44,48,57,61,74-78} have demonstrated low or absent MRZ positivity in most

Table 2. Proportion of elevated AI in patients with other diagnoses.

Study	Ref.	disease	N	M	R	Z	MRZ-1	MRZ-2
Graef et al. 1994	73	Neuro-lupus	9	3	3	4	44%	33%
		GPA*	3	1	0	1	33%	33%
		Sarcoidosis*	4	0	0	0	0%	0%
Bednarova et al. 2005	41	NB	27	4%	4%	0%	7%	0%
		OND	15	0%	0%	0%	0%	0%
Jarius et al. 2009	44	PNS	34	3%	6%	12%	21%	0%
Huss et al. 2016	27	OND	39	0%	0%	8%	8%	0%
Jarius et al. 2017	39	Neuro-Behçet	5	0%	0%	20%	20%	0%
		Neuro-lupus	6	17%	0%	0%	17%	0%
		Vasculitis	2	0%	50%	0%	50%	0%
		AQP+NMOSD	2	0%	0%	0%	0%	0%
		NB	9	0%	11%	22%	22%	11%
		NIND	10	20%	10%	0%	30%	0%
Hottenrott et al. 2018	79	Primary CNS lymphoma	37	14%	5%	19%	32%	8%
		Psychiatric disorders	78	3%	0%	10%	10%	3%
Hottenrott et al. 2018	75	RDwCNS	23	9%	4%	9%	13%	9%
		OIND	48	6%	13%	15%	23%	8%
Venhoff et al. 2019	49	RDwCNS	40	10%	10%	13%	20%	13%
Jarius et al. 2021	52	OND	26	0%	0%	0%	0%	0%
Schwenkenbecher et al. 2021	53	AE	27	15%	15%	26%	n.r.	19%
		aNMDAR	21	14%	19%	33%		24%
		aLGI1	6	17%	17%	0%		0%
		NIND	22	0%	0%	0%	0%	0%
Kyllesbech et al. 2022	24	HC	15	20%	7%	n.d.	n.d.	n.d.
Gäslund et al. 2023	25	OND	11	9%	18%	n.d.	n.d.	n.d.
Vlad et al. 2023a	77	Neuro-sarcoidosis	27	4%	7%	4%	n.r.	4%
Vlad et al. 2023b	78	MOGAD	30	13%	13%	7%	33%	0%
Zondra Revendova et al. 2024	54	IND-C	168	7%	8%	7%	14%	6%
		IND-P	52	6%	4%	6%	14%	2%
		NIND	464	4%	1%	3%	7%	1%
		SC	628	2%	1%	4%	6%	1%
D'Cunha et al. 2025	57	AQP4+ NMOSD	12	33%	17%	25%	58%	8%
		MOGAD	33	18%	33%	24%	45%	21%
Pache et al. 2025	58	NIND	20	0%	0%	5%	5%	0%

*the only patient with CNS involvement in the GPA group was MRZ positive; the only patient with CNS involvement in the sarcoidosis group was MRZ-negative.

n.d., not determined; n.r., not reported. ADEM, acute demyelinating encephalomyelitis; AE, autoimmune encephalitis; GPA, granulomatosis with polyangiitis; HC, healthy controls; IND-C, inflammatory CNS diseases; IND-P, inflammatory peripheral nervous system diseases; NMOSD, neuromyelitis optica spectrum diseases; NIND, non-inflammatory neurological diseases; OND, other (than MS) neurological diseases; PNS, paraneoplastic neurological syndrome; SC, symptomatic controls.

other inflammatory neurological diseases, including Neuro-Behçet disease, neuro-lupus, vasculitis, NMOSD, MOGAD, acute demyelinating encephalomyelitis (ADEM) and paraneoplastic neurological syndromes, although a relatively high proportion of MRZ-positive MOGAD patients (21%) has been recently found in a study by D'Cunha et al. from India⁵⁷. Studies with published proportions of patients with positive M, R and Z AI in non-MS diseases and healthy controls are summarized in Table 2 (ref.^{24,25,27,39,41,44,49,52-54,57,58,73,75,77-79}).

In 2021, a surprisingly high frequency of positive MRZ was reported in anti-NMDAR encephalitis (5/19 patients, i.e. 21%) (ref.⁵³). An interesting study performed by Brauchle et al.⁸⁰ describes 25 cases of patients without a definitive diagnosis with positive MRZ reaction, formally not fulfilling MS diagnostic criteria. Diagnoses were assigned by voting of four neuroimmunology experts: 3 patients were considered to have MS, 16 to have other autoimmune neuroinflammatory disease, and 6 to have non-autoimmune neurological disease. It should be noted that the study was performed on patients with positive CSF oligoclonal bands older than 50 years; hence, no calculations of sensitivity and specificity are meaningful. Nevertheless, the study provides a warning that positive MRZ reaction might not be as specific for MS as is generally assumed.

In conclusion, however, the specificity of the MRZ reaction remains high across various studies, anti-NMDAR encephalitis probably being the only condition in which MRZ reaction positivity can significantly exceed 10%. On the other hand, very different sensitivities of the MRZ reaction for MS have been reported, with a tendency to lower sensitivities in newer studies.

PROGNOSTIC VALUE OF THE MRZ REACTION IN MULTIPLE SCLEROSIS

Positive MRZ reaction increases the risk for the development of definitive MS in patients with a first demyelinating episode^{43,63}. In one study, measles AI correlated weakly but significantly with cerebral MRI T2 lesion load⁸¹. In pediatric MS, MRZ reaction was not significantly associated with relapse rate in the first two years, time to the second attack, or MRI measures⁶⁴. In primary progressive MS patients, MRZ-positive patients had significantly higher CSF (but not serum) neurofilament light chain concentrations compared to MRZ-negative patients, but no difference was noted in the Expanded disability status scale (EDSS) at diagnosis or follow-up⁵¹.

CORRELATION WITH OTHER CSF AND IMMUNOLOGICAL PARAMETERS

The MRZ reaction is generally associated with inflammatory CSF changes – leukocyte count^{56,68}, total IgG intrathecal synthesis^{18,23,56,68}, oligoclonal bands^{18,27}, and kappa free light chain intrathecal synthesis^{62,82,83}. Although it

was initially recommended to perform MRZ testing only in patients with positive IgG oligoclonal bands (OCB) (ref.¹⁸), several studies have demonstrated MRZ positivity in a small but significant proportion of OCB negative MS patients^{27,34,38,45,47,48,84}. Notably, intrathecal synthesis of specific antibodies in IgG OCB negative patients can be even more frequently observed in patients with CNS infections, such as VZV ganglionitis^{5,85}.

MRZ reaction has also been associated with the HLA-DRB1*15:01 genotype⁵⁵.

BROADENING THE MRZ PANEL

Antibodies to several other viruses as well as other microbial antigens have been tested in MS, either in search of an infectious cause of MS, in an attempt to increase combined test diagnostic sensitivity, or to resolve more fundamental scientific questions.

Several earlier reports found intrathecal anti-mumps IgG synthesis in MS using either AI assessment^{1,16} or antigen-specific oligoclonal IgG analysis^{32,33,86}. Jarius et al.⁵² suggested broadening the MRZ panel by including mumps virus and parvovirus B19 antigens, which increased sensitivity from 65% to 73%. This observation was confirmed by Pache et al.⁵⁸, who reported an increase from 34% to 52%. In these two studies, parvovirus B19 showed slightly higher frequencies of elevated AI (42% and 38%, or 73% among seropositive patients) compared with mumps virus (28% and 26%, or 37% among seropositive patients). In one cohort, the median parvovirus B19 AI in MS was the highest among all AI tested specificities (3.97). However, unlike anti-mumps IgG assays, no commercially certified ELISA test for anti-parvovirus B19 IgG is currently available for CSF analysis and AI calculations. An in-house assay or in-house modification of a commercially available anti-parvovirus B19 IgG ELISA test is necessary, which may pose substantial problems for introducing the test into routine use in the increasingly regulated clinical laboratory environment.

Among other viruses, EBV has been most extensively studied due to its nearly 100% seroprevalence in MS and supposed implications in MS pathogenesis⁴⁰. Nevertheless, frequencies of elevated anti-EBV IgG AI in MS are almost uniformly reported as very low (2–8%) (ref.⁴⁰), except for two studies^{24,25} that, however, reported positive results in significant proportion of controls (48% and 96% MS versus 11% and 73% controls). A hypothesis has been proposed by Ruprecht⁴⁰ that antibody producing B cells invade the CNS predominantly at the time of acute primary EBV infection, when EBV IgG producing B cells have not yet matured. This can partly explain an apparent “EBV paradox” (near-universal seropositivity but rare intrathecal anti-EBV AI elevation in MS).

Historically, HSV was frequently included in extended panels (termed MRZH reaction). However, intrathecal anti-HSV IgG synthesis is substantially less frequent than that directed against measles, rubella, or VZV. Addition of HSV does not significantly improve sensitivity^{18,39} and

in the study of Jarius et al.⁵² HSV AI positivity was even more common in controls than in MS patients. Moreover, HSV-specific intrathecal synthesis was characteristic for non-MS inflammatory diseases rather than MS in another study⁸⁰. Elevated HSV AI has been described in about 30% of patients with chronic HIV encephalitis^{1,18}. Importantly, the combination H+Z cannot be considered truly polyspecific due to documented cross-reactivity between these viruses in CNS infections^{5,22}. Therefore, although anti-HSV IgG AI remains clinically useful when HSV encephalitis is suspected and PCR reaction is negative¹⁰, it does not seem reasonable to include HSV in the MRZ panel for MS diagnostic purposes.

Intrathecal IgG synthesis directed against numerous additional viral and non-viral microbes has been studied in MS with partly divergent results. HHV-6 (ref.⁸⁷), influenza A and B viruses^{50,52,58}, JC virus^{25,50}, parainfluenza type 2 virus¹⁶, respiratory syncytial virus¹⁶, *Chlamydia pneumoniae*^{37,50,88} and *Clostridium tetani* toxin^{50,52} have consistently shown intrathecal IgG response in a substantial proportion (>15%) of MS patients, whereas it seems to be rare for other antigens – cytomegalovirus^{50,52,53,59}, enterovirus⁵⁰, tick-borne encephalitis⁵⁸, *Bordetella pertussis* toxin⁵², *Corynebacterium diphtheriae* toxoid^{50,52}, or *Toxoplasma gondii*⁵⁸. More microbial species have been hypothesized to be implicated in MS pathogenesis on the sole basis of elevated specific IgG levels in MS patients' sera, without the respective intrathecal IgG specificity being appropriately tested, but detailed discussion of these hypotheses is beyond the scope of this review.

EFFECT OF IMMUNOMODULATORY TREATMENT TO INTRATHECAL ANTIVIRAL ANTIBODY SYNTHESIS IN MS

Neidhart et al. did not find a significant difference in proportions of patients positive for M, R, Z, or MRZ-2 between therapy-naïve patients and patients receiving various disease-modifying therapies⁵⁵. More specifically, Largey et al. investigated the effect of natalizumab on intrathecal antiviral antibody synthesis in 15 MS patients⁵⁰. Only intrathecal synthesis of anti-JCV and BKT polyoma viruses antibodies present in 3 patients was lost after 12 months of natalizumab treatment, whereas intrathecal synthesis of other antibodies present before treatment mostly persisted. Further studies evaluating the impact of other high-efficacy therapies on intrathecal antiviral response are warranted.

PATHOPHYSIOLOGICAL SIGNIFICANCE OF INTRATHECAL ANTIVIRAL ANTIBODY SYNTHESIS IN MS

In CNS infections, protective role of intrathecal synthesis of antibodies to the causative agents is assumed. In MS, however, the respective viral nucleic acids mostly cannot be demonstrated in the CSF or brain^{89,90}, and MRZ

antibodies are regarded as part of a polyspecific intrathecal immune response with unknown pathophysiological relevance. Importantly, polyspecific antibody concentration is 20–60-fold lower compared to the concentration of antibodies of the same specificity produced in an antigen-driven reaction^{20,23}.

It is plausible that B cell invasion into the CNS, triggered by primary EBV infection, may be one of the first events in the MS disease process⁴⁰. However, it is unclear which factors select particular B cell clones to enter the CNS, and which factors promote the persistence of intrathecal B cells during the course of MS. Molecular mimicry is perhaps the most discussed mechanism⁹¹, not only for EBV but also e.g. for parvovirus B19 antibodies that can possibly cross-react with myelin basic protein^{91,92}. There is, however, no evidence of a causal relationship between parvovirus B19 and MS, and the intrathecal synthesis may simply reflect the presence of B cells specific for this virus at the time of acute EBV infection, in accordance with Ruprecht hypothesis⁴⁰ that antibody producing B cells invade the CNS predominantly at the time of acute primary EBV infection.

Reiber²³ postulates that the polyspecific antibody response is a general property of the immune system not restricted to the brain, and that the intrathecal polyspecific antibody response in MS is related to immune network connectivity: continuous changes in antibody patterns in blood are not followed by corresponding changes in the CSF since there is no corresponding connectivity of intrathecal B cells. Hence, this hypothesis also assumes that B cell clones within the CNS do not represent B cell clones present in blood at the time of lumbar puncture but rather can represent B cell clones in blood at the time of disease initiation. Still, this hypothesis assumes invasion of B cells responsible for intrathecal antibody production into the CNS as a process occurring only once which appears to be at variance with molecular studies on CSF and the blood B cell repertoire^{93,94}. Hence, the question concerning the EBV paradox remains partly unsolved. The observation of a higher percentage of increased anti-EBV AI in children MS (ref.⁴⁵) is difficult to explain with the Ruprecht hypothesis.

Nevertheless, several lines of evidence exist that antigen specificity of CNS B cells depends primarily on the spectrum of B cell clones at the time of first B cell invasion into the CNS. Factors affecting the selection of B cells for entry into the CNS are unknown; differences between antiviral antibody patterns in CSF and aqueous humor of the eye in the same patients with MS and ocular involvement suggest rather a random selection⁹⁵. In the study of Skorstad et al., in vitro cultured CSF B cells from MS patients synthesized oligoclonal IgG with the same antiviral specificity as that found in patients' CSF; however, the B cell repertoire in CSF was only partially representative of the intrathecal B cell repertoire⁹⁶. The question remains as to how these B cells survive in the CNS and whether they are activated by cross-reactive CNS antigens and/or other mechanisms. Maruyama et al.⁹⁷ showed earlier that the persistence of memory B

cells is not dependent on the persistence of the antigen. Tomescu-Baciu et al. showing preference for the G1m1 allotype in the intrathecal responses against all viruses in the MRZ panel in G1m1/G1m3 heterozygous MS patients supports the notion that the intrathecal humoral immune response could be driven by an antigen-independent mechanism⁹⁸, such as presentation of rare idiotopes of the B cell receptor CDR3 region on HLA-class II molecules to CD4+ T cells⁹⁹.

Future research into additional intrathecal antibody specificities in MS should focus on antigens commonly encountered in adolescence, either as a result of infection (e.g., parvovirus B19, influenza and parainfluenza viruses) or vaccination (e.g., *Clostridium tetani* toxoid). Little is known about differences in antibody response after natural infection (at different ages) and vaccination with various vaccine types, or whether the antibody response could be influenced by simultaneous (polyvalent vaccines) versus sequential (monocomponent vaccines) administration of microbial antigens. Based on lower CSF and serum levels of anti-measles antibodies in patients after measles vaccination compared to patients who had undergone measles infection, it has been speculated that childhood vaccination might decrease the MRZ reaction sensitivity for MS^{56,100}. Integrated studies combining intrathecal antibody synthesis, serostatus, and individual infection or vaccination history evaluation are therefore warranted to clarify both diagnostic implications and broader immunopathophysiological mechanisms.

CONCLUSION

Although MRZ reaction is not included in the most recent revision of the McDonald diagnostic criteria⁹ and does not meet the proposed threshold for a stand-alone diagnostic test (sensitivity + specificity ≥ 1.5) (ref.⁸), it remains one of the most specific CSF-based laboratory findings in MS. Hence, a positive MRZ reaction strongly supports the MS diagnosis, even when other inflammatory CNS diseases are considered (with the possible exception of anti-NMDAR encephalitis, which is typically distinguishable clinically). In contrast, a negative MRZ result has limited diagnostic value, as the majority of MS patients (at least in the Czech population) turn out to have negative MRZ.

Among additional candidates tested to broaden the panel, parvovirus B19 is probably the most promising agent. A substantial disadvantage for routine laboratories lies in the fact that no commercial anti-parvovirus B19 IgG assays are specifically devised for CSF measurements and AI calculation. However, this may change soon if more studies confirm the value of parvovirus B19 AI determination in MS patients. Mumps virus may also increase the sensitivity of the combined test, and commercial assays for CSF anti-mumps IgG are already available. Hence, combined MRZ + parvovirus B19 + mumps may be the most suitable option at present.

Confirming that inclusion of these (or any other) antigens into the “MRZ+” panel will not significantly

decrease specificity is the most important requirement, for any broadened MRZ panel to retain the most valuable diagnostic property of this test, i.e. high specificity for MS. Both oligoclonal IgG and the kappa free light chain index have much higher sensitivity for MS ($\approx 90\%$), and the specificity of both tests approach 90% as well⁸. Hence, a decrease in specificity below 90% would make any extended MRZ panel useless for diagnostic purposes.

Validation of any expanded panel requires sufficiently large control cohorts including other inflammatory neurological diseases. Further research should address analytical standardization, direct comparisons between AI determination and detection of CSF-restricted antiviral oligoclonal IgG bands, and evaluation of the intrathecal fraction (*F_s*) in relation to antigen-specific oligoclonal patterns. Between-method comparisons should answer the question of whether significant differences exist that could partly explain sensitivity differences in various MRZ/MRZ+ studies.

Search strategy and selection criteria

Relevant articles were identified through PubMed searches and by screening reference lists of selected publications.

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