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Narrative Review

The role of antibody indexes in clinical virology

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ABSTRACT

Background: Serological techniques are an essential part of the diagnostic tools used in clinical virology. Among these techniques, antibody indexes are not novel, but do require specific expertise. Their niche has expanded substantially in recent years due to increasing evidence of their performance to diagnose viral infections.
Objectives: This narrative review describes the background and clinical applications of antibody indexes. The first objective is to provide an overview of the theoretical background, insights for implementation, limitations and pitfalls. The second objective is to review the available evidence for the diagnostic performance, with a specific focus on viral encephalitis and uveitis.
Sources: A comprehensive literature search was performed in PubMed, including original studies and reviews, with no time limit on the studies included. The following search terms were used: antibody index, Goldmann–Witmer coefficient, Reibergram, viral encephalitis, viral uveitis, herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein–Barr virus, rubella virus, measles virus, enterovirus, influenza virus, flaviviruses.
Content: Antibody indexes can support the diagnosis of a spectrum of viral infections in immune privileged sites such as the central nervous system and the eye, through the demonstration of virus-specific intrathecal or intraocular antibody production. This is especially useful in situations where PCR has a lower positivity rate: infections with rapid viral clearance due to natural immunity or treatment and chronic stages of viral infections.
Implications: Antibody indexes expand the clinical microbiologist's diagnostic toolbox. Careful interpretation of the results of these assays is crucial and further standardization of methods is required to improve interchangeability of results between laboratories. **Marc C. Shamier, Clin Microbiol Infect 2021;27:1207**

Introduction

In clinical virology, serological tools are an indispensable part of the diagnostic toolbox. They can complement molecular techniques to identify the viral cause of infection. The aim of this narrative review is to discuss the background and evidence for the clinical applications of antibody indexes.

Antibody index serology

The calculation of an antibody index (AI) is useful to confirm a suspicion of infection in immune-privileged sites such as the central nervous system (CNS) and the eye. When no pathogen is detected by direct methods, an AI can provide evidence for infection by demonstrating local pathogen-specific antibody synthesis.

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Barriers restrict leakage of systemic antibodies into these compartments, but their function changes in the presence of inflammation. Therefore, to distinguish between locally produced antibodies and systemic antibodies, a correction is needed for the barrier function, which is the basis of AI calculations.

The calculation of an AI starts with quantification of total and pathogen-specific immunoglobulin in serum and cerebrospinal fluid (CSF) or aqueous humour (AH). There are two commonly used calculations: The Goldmann–Witmer coefficient (GWC) [1], used for diagnosing eye infections; and the AI according to Reiber, used for diagnosing CNS infections. The GWC is the simplest version, calculated according to the following formula:

$$\mathrm{GWC} = \frac{\text{specific Ig}_{\mathrm{AH}}/\text{specific Ig}_{\mathrm{serum}}}{\text{total lg}_{\mathrm{AH}}/\text{total lg}_{\mathrm{serum}}}$$

GWC values around 1 indicate equal AH and serum antibody ratios, thus absence of intraocular synthesis of pathogen-specific antibodies. Although there is limited literature on the ideal cut-off, there is a consensus that a cut-off of 3 provides the best trade-off between sensitivity and specificity [2,3]. The GWC is less reliable when there is pronounced dysfunction of the blood-ocular barrier and an alternative calculation including a correction was proposed by Quentin [4].

The groundwork for the study of intrathecal antibodies was laid by Reiber and colleagues [5,6]. Antibodies found in CSF represent two fractions: (a) a brain-derived fraction, produced by perivascular B-cells, and (b) a blood-derived fraction, the result of passive diffusion across the blood–CSF barrier. It is well known that inflammation increases the rate of diffusion. This phenomenon is frequently referred to as leakage, attributed to pathological changes in the capillary wall. However, strong evidence supports that CSF flow rate is the main modulator of protein diffusion into the CNS. A decrease in flow rate has been shown to increase the concentrations of blood-derived proteins in CSF [6]. The finding that molecular size-dependent selectivity is maintained in patients with severe CSF barrier dysfunction, supports this theory [7]. To discriminate between brain-derived and blood-derived protein fractions, it is essential to take the blood–CSF barrier function into account and correct for polyspecific antibody production in the brain. An AI calculation therefore requires measurements of CSF/serum albumin (Q_{Alb}) and immunoglobulin quotients (Q_{Ig}). Q_{Alb} is an important indicator of barrier function, since all CSF albumin is blood derived. Q_{Ig} indicates the amount of total intrathecal antibody production. Based on a study on 4300 subjects, Reiber and Peter defined a hyperbolic function between Q_{Alb} and Q_{Ig}, representing the discrimination between brain- and blood-derived antibody fractions (Reibergram) [6]. An individual patient's Q_{Ig} can be classified according to the Reibergram, to identify an increase in pathogen-specific intrathecal antibody synthesis.

Accounting for these factors in the AI calculation strongly increases the accuracy and clinical utility. In contrast to the GWC, Reiber and Peter proposed a cut-off of 1.4 [6], depending on the precision of the test used to detect virus-specific antibodies [8].

The Erasmus MC Viroscience laboratory (Netherlands) performs diagnostics for a large tertiary care centre and functions as a national and international reference centre for emerging viral infections, influenza, measles and rubella. Fig. 1 shows the distribution of AIs measured from serum CSF pairs between 2009 and 2019. AIs were most frequently requested for varicella zoster virus (VZV), herpes simplex virus (HSV), measles virus and tick-borne encephalitis virus (TBEV) [9]. Values above 3 provide strong evidence for intrathecal antibody synthesis. We propose careful interpretation of values between 1.5 and 3, combining clinical and laboratory data, considering a high variation coefficient

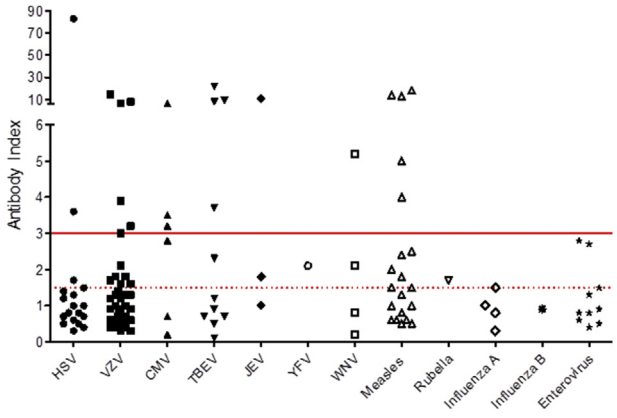

Fig. 1. CSF/Serum Antibody Indexes measured in the ErasmusMC Viroscience Laboratory between 2009 and 2019. The following quantitative assays were used: SERION Enzyme Immunoassay (HSV, VZV, rubella, measles, enterovirus, influenza a, influenza B); Euroimmun Enzyme Immunoassay (TBEV); and Mosaic Laboratories Immunofluorescence Assay (CMV, yellow fever virus, Japanese encephalitis virus, West Nile virus). HSV, herpes simplex virus; VZV, varicella zostervirus; CMV, cytomegalovirus; TBEV, tick-borne encephalitis virus; JEV, Japanese encephalitis virus; WNV, West-Nile virus.

in the commercially available quantitative ELISAs. In addition, the accuracy of immunofluorescence assays depends on the dilution steps chosen. Altogether, the majority of positive AIs ranged in value between 3 and 20.

The reliability of AIs can be hampered by various pitfalls. First, the AI calculations are based on several measurements, all of which are subject to a degree of measurement uncertainty. One important example is the determination antibody concentrations, which requires conversion of immunoassay signal intensity values using a calibration curve. Generally these curves are not completely linear. This emphasizes the need of expertise for validation and interpretation of AI calculations. Next, CNS polyspecific B-cell activation is a well-known phenomenon in multiple sclerosis and other autoimmune diseases; the majority of these patients have positive AIs for measles virus, rubella virus and VZV [10]. Therefore, AI testing should always be done for multiple viruses, and whenever AI positivity is found for several viruses an autoimmune aetiology should be considered. As in all serological tests, cross-reactivity, especially for flaviviruses, should be taken into account, as well as the immune status of a patient. In patients with impaired humoral immunity, an AI has limited value. Finally, an AI loses reliability after administration of intravenous immunoglobulin.

Antibody index serology for viral infections of the central nervous system

In acute HSV encephalitis (HSE) antibody tests have little use, but after 2 weeks anti-HSV antibodies can be detected in the majority of cases [11]. An AI is useful in situations where PCR has a lower positivity rate: after viral clearance due to treatment and in chronic HSE (Table 1). Chronic, relapsing HSE has been described and is difficult to distinguish from a form of autoimmune encephalitis triggered by HSV, characterized by the presence of antibodies against the N-methyl-D-aspartate (NMDA) receptor. An anti-NMDA receptor AI can aid in distinguishing between these conditions [12], guiding the decision to treat with antiviral or immunosuppressive drugs.

VZV CNS infection can result in a large spectrum of clinical syndromes, following primary infection or viral reactivation. A positive VZV AI can be found in up to 80% of cases and is a more powerful diagnostic tool than CSF PCR, with highly variable

Table 1
Clinical utility of antibody index serology for the diagnosis of viral infections of the central nervous system

Virus	Clinical manifestation of CNS infection	Performance of CSF PCR		Utility of antibody index serology	Reference
		Positivity rate	Limitations		
HSV 1/2	Acute HSV encephalitis (HSE)	96-98%	Significant decline after 7 days of antiviral therapy	Low sensitivity and little complementary value in the acute phase	[46]
	Chronic relapsing HSV encephalitis	Unknown	Significant decline after 7 days of antiviral therapy	Useful in patients receiving antiviral therapy and in chronic phases of encephalitis (>14 days)	[11]
	HSV-triggered autoimmune encephalitis	Low	In PCR-negative cases, it is difficult to distinguish from chronic relapsing HSVE	Intrathecal synthesis of anti-NMDAR antibodies after HSE supports the diagnosis	[12,47]
VZV	Encephalitis	26.5–80%	Highly variable, dependent on immune status, clinical manifestations and antiviral treatment	Intrathecal antibodies can be found in 80% and contribute to diagnosis Especially important in patients receiving antiviral therapy	[13,14]
	VZV Vasculopathy	30%	A negative PCR does not exclude the diagnosis	Positive in 93% of patients with VZV vasculopathy	[15]
CMV	Encephalitis	80–100%	Presence of CMV genome in CSF can occur in absence of symptomatic infection	CMV encephalitis occurs in a severely immunocompromised population where serological testing may be less reliable	[48]
Flaviviruses	Meningoencephalitis	Very low	Viral clearance occurs before or soon after onset of neurological symptoms, thus viral genome is no longer detectable in most patients upon presentation	In PCR-negative cases AI provides the highest level of evidence for diagnosing flavivirus encephalitis Cross reactivity with other Flaviviruses warrants specific attention	[9,18]
Enterovirus	Meningitis/ Encephalitis	95%	Detection is generally limited to species and not serotype-specific	Little complementary value	[21]
	Acute flaccid myelitis	EV-D68: 31% EV-A71: 3%	Explanatory mechanism for low sensitivity is unknown	Recommended in all cases	[23,24]
Measles virus	SSPE	Very low	Very low positivity rate due to lack of extracellular release of viral genome	Positive AI has been reported in 19% of SSPE cases and IgG antibodies in CSF have been reported in 88%	[26,27]
Influenza virus	Influenza-associated encephalitis/encephalopathy	16-21%	A negative PCR does not rule out the diagnosis	Due to low PCR positivity rate, AI has been proposed as part of the diagnostic algorithm	[28]

CMV, cytomegalovirus; HSV1/2, herpes simplex virus type 1 and 2; SSPE, subacute sclerosing panencephalitis; VZV, varicella zostervirus.

positivity rates (Table 1) [13,14]. VZV vasculopathy poses a particular diagnostic challenge. It occurs when VZV reactivates in cerebral arteries, which can result in ischaemic or haemorrhagic stroke. VZV DNA is detected in CSF of 30% of cases, whereas a positive AI is present in 93% [15].

Several flaviviruses are associated with CNS disease, including Japanese encephalitis virus, West-Nile virus, tick-borne encephalitis virus, yellow fever (17D vaccine) virus, dengue virus and Zika virus. In recent years, these viruses have demonstrated a major outbreak potential and several have become endemic in Europe [16].This emphasizes the need of preparedness and availability of diagnostic tools [17]. Because of the rapid viral clearance in most flavivirus infections, CSF PCR testing rarely confirms the diagnosis. In PCR-negative cases, demonstration of intrathecal antibody production is considered the best level of evidence for a diagnosis of flavivirus encephalitis [18]. The high degree of cross-reactivity warrants a careful approach including travel history and virus neutralization tests [19].

In non-polio enterovirus (EV) CNS infections, intrathecal antibody synthesis has been demonstrated from 48 hr after onset [20]. In EV meningoencephalitis CSF PCR is highly sensitive (>95%) and an AI has little utility [21]. Acute flaccid myelitis (AFM) has been associated with several enteroviruses, including EV-D68 and more rarely EV-A71 [22]. Detecting viral genome of EV-A71 and EV-D68 in CSF is challenging, with positivity rates of 3% and 31%, respectively [22,23]. A study from the USA reported presence of EV antibodies in CSF in 79% of cases and EV-D68 antibodies in 43% [24]. Therefore we propose that a positive AI supports neurological involvement in infections with these enteroviruses (Table 1).

Subacute sclerosing panencephalitis (SSPE) is a rare complication of measles. The diagnosis is challenging since it may occur up to 20 years after primary infection. CSF-PCR has little diagnostic utility because of very limited release of viral particles into the extracellular space [25]. In a retrospective study of 17 cases of SSPE 88% of cases had detectable anti-measles IgG in CSF [26]. Another study found a positive AI in 19% of SSPE cases [27]. In diagnostic specimens we received from two patients with SSPE, the measles AI was very high in several follow-up specimens, emphasizing the utility of an AI (Fig. 1).

Influenza-associated encephalitis/encephalopathy (IAE) is a complication of influenza infection in the paediatric population, although reports of IAE in adults have increased since the 2009 H1N1 Influenza A pandemic. As CSF PCR is positive in only 16% of cases, the diagnosis is generally presumptive, supported by influenza genome detection in respiratory samples [28]. We propose the demonstration of intrathecal antibody synthesis could strengthen the diagnosis, but future studies are necessary to evaluate the performance of AI in these patients.

Antibody index serology for viral infections of the eye

Differentiating between systemic disease and infectious disease as causes of uveitis is challenging and a timely diagnosis is essential to guide treatment, preventing progressive loss of vision. When the routine workup fails to find a diagnosis, anterior chamber paracentesis, a relatively safe procedure, can be performed [29]. Usually it yields small sample volumes, the choice of tests should therefore be carefully considered. A retrospective study on the relative

Table 2
Clinical utility of the Goldmann–Witmer coefficient (GWC) for the diagnosis of viral uveitis

Virus	Clinical manifestation	AH PCR Positivity Rate	Utility of GWC	Reference
Rubella virus	Rubella-associated uveitis and Fuchs uveitis syndrome	18–20%	Sensitivity 93-100%	[4,32,33]
HSV 1/2	Anterior Uveitis	54–74%	Sensitivity of 92%	[3,49]
	Acute Retinal Necrosis	79–100%[a]	Sensitivity of 57%[a]	[38–40]
VZV	Anterior Uveitis	75%	Sensitivity of 87.5% in patients with uveitis, especially useful in cases of herpes zoster ophthalmicus without cutaneous involvement (herpes zoster sine herpete)	[3]
	Acute Retinal Necrosis	79–100%[a]	Sensitivity of 57% [1]	[38–40]
	Progressive outer retinal necrosis	Up to 100%	Limited utility due to its exclusive occurrence in severely immunocompromised hosts	[41]
CMV	Anterior uveitis	35%	Unknown	[34]
	Fuchs uveitis syndrome	Unknown	Recommended to complement PCR testing	[31]
	Posner-Schlossman syndrome	26–52%	Recommended to complement PCR testing	[36,37]
	Retinitis	93–95%, decreasing to 48% after start of treatment	Limited utility due to its exclusive occurrence in severely immunocompromised hosts, sensitivity 21%	[43–45,50]

CMV, cytomegalovirus; HSV1/2, herpes simplex virus type 1 and 2; VZV, varicella zostervirus.
[a] Data describe combined sensitivity for either HSV or VZV.

contribution of aqueous humour (AH) PCR and GWC for the diagnosis of infectious uveitis found that in 48% of cases of suspected infectious uveitis the diagnosis was established by only GWC and not by PCR [3]. In another study of 152 patients with posterior uveitis, the combination of PCR and GWC provided a diagnosis in 29% of cases. In 66% of these cases, the diagnosis was based only on a positive GWC [30].

The value of antibody indexes for viral uveitis is well established for herpes viruses and rubella virus (Table 2). These infections present with various clinical manifestations, resulting from the interplay between viral pathogenic factors and the host immune response. Considering the physiological delay of the humoral immune response, intraocular antibody synthesis becomes a more relevant diagnostic marker as time from symptom onset to testing increases.

Anterior uveitis

Fuchs uveitis syndrome (FUS) is a chronic, low-grade form of anterior uveitis, accounting for 1–6% of all cases of uveitis. Although the pathogenesis remains unclear, there are strong associations with Rubella virus (in Europe and the United States) and cytomegalovirus (CMV) (in East Asia) [31]. Studies from The Netherlands and Germany have demonstrated intraocular rubella antibody synthesis in 93–100% of cases, whereas Rubella virus genome could only be detected 18–20% [4,30,32,33]. GWC is therefore the preferred diagnostic tool. A retrospective study by Groen-Hakan [33] demonstrated that, unlike common assumption, not all cases of rubella virus associated uveitis (RVAU) present with FUS. Irrespective of the clinical manifestation, the GWC has excellent sensitivity for RVAU (97%) [33].

The GWC is also an important test for herpetic anterior uveitis, with reported sensitivities of 92% for HSV uveitis and 87.5% for VZV uveitis (Table 2) [3]. In recent years, CMV anterior uveitis in the immunocompetent host has gained attention due to publication of several case series [34]. Although the contribution of the GWC in this population is unclear, a French study showed that AH-PCR has limited utility, with a positivity rate of only 35% [34]. Finally, another herpes virus that deserves mention is EBV. EBV DNA is found in AH of up to 17% of patients with uveitis, but also in 7% of non-uveitis controls [35]. A positive EBV GWC is frequently found in combination with positive GWC or PCR results for other pathogens [35]. The role of EBV as an ocular pathogen remains unclear and a positive GWC should be interpreted with care [35].

Another form of anterior uveitis is Posner–Schlossman syndrome, characterized by recurring episodes of anterior uveitis with elevated intraocular pressure. Through the demonstration of intraocular antibody synthesis, CMV was identified as the main etiological agent [36]. PCR on AH is complementary for the diagnosis, but studies have reported low positivity rates (26–52%) [37].

Posterior uveitis

Acute retinal necrosis (ARN) and progressive outer retinal necrosis (PORN) are two forms of necrotizing herpetic retinopathy that can rapidly lead to loss of vision. Most cases are caused by VZV or HSV. Diagnostic criteria for ARN were defined by the American Uveitis Society in 1994, but did not include microbiological tests. New diagnostic criteria have been proposed, including demonstration of either viral genome or intraocular antibody production against these viruses [38]. In a study of 28 patients with ARN, a positive GWC for VZV or HSV was found in 57% of cases [39], but most cases are diagnosed by PCR (79–100%) [40]. The GWC is therefore mostly useful in PCR-negative cases. PORN, primarily associated with VZV, occurs in severely immunocompromised patients and is characterized by limited signs of inflammation [41]. Like other serological tests, the GWC has limited utility in this population.

The same applies to CMV retinitis, which occurs in the setting of severely impaired T-cell function. The positivity rate of AH-PCR is 93.5–95% in AIDS patients with CMV retinitis, decreasing to 48% after antiviral therapy [42–44]. A study on uveitis in immunocompromised patients showed 21% GWC positivity in CMV retinitis [45].

Conclusion

Although antibody indexes are not novel to the repertoire of serological techniques, their niche continues to expand. In viral encephalitis and viral uveitis, the calculation of an antibody index substantially increases the chance of identifying the infectious agent. Further standardization of this method is required to improve its routine application.

Transparency declaration

We declare that this manuscript has not been published previously, is not under consideration for publication by another journal and that its publication is approved by all authors. The authors

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Author contributions

All authors contributed substantially to (1) the conception the review, (2) drafting or revising and (3) final approval of the version to be submitted. Validation of data in Fig. 1: SB, CHG. Data curation for Fig. 1: SB, MvS, CHG. Supervision: EY, CHG, JvK.

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