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Main Article

Diagnostic tests for immunomediated hearing loss: a systematic review

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Abstract

Objective: To quantitatively evaluate the diagnostic accuracy of diagnostic tests for immunomediated hearing loss.

Data sources: We searched Medline and the Cochrane Database of Systematic Reviews for potentially relevant studies.

Study selection: Twenty-five studies met the inclusion criteria of this systematic review. The diagnosis of immunomediated hearing loss was based on the clinical presentation and the response to corticosteroid administration.

Data extraction: The following data were extracted from the selected studies and entered into a standardised database: population demographics; exclusion and inclusion criteria; diagnostic tests; sensitivity; specificity; the number of true positive, true negative, false positive and false negative values; therapy used, including dose and duration; and delay between symptom onset and therapy commencement.

Data synthesis: This systematic review combined data from 679 patients with immunomediated hearing loss, reported by 22 research teams. Substantial heterogeneity was found among the included studies; for this reason, summary sensitivity and specificity values were not computed.

Conclusions: The results of diagnostic tests for immunomediated hearing loss depend on many factors, and there is a risk of potential bias. This is the first time that such a systematic review has been presented; such a review is a more rigorous method of demonstrating the utility of the available diagnostic tests.

Key words: Autoimmunity; Inner Ear; Vestibular Disorders; Sensorineural Deafness

Introduction

Since the initial description by McCabe in 1979,[1] the number of published research articles on immunomediated hearing loss has increased year on year. Immunomediated inner-ear disease is now an accepted nosological entity within ENT practice.

The number of published papers runs into the hundreds, perhaps thousands, and keeping up with primary research is therefore a difficult task. Moreover, many of these studies give unclear, confusing or downright contradictory results; however, when taken together, a more consistent and clear picture may possibly emerge.

The methods used in traditional reviews are not transparent and their results are not reproducible, and therefore uncertainty remains. The lack of rigour and consequent bias of traditional reviews was exposed in the late 1980s, after which a more rigorous, systematic approach began to be employed.[2]

A systematic review is an overview of primary studies which contains an explicit statement of objectives, materials and methods, and which has been conducted according to explicit and reproducible methodology.[3]

Within the field of systematic reviews, a subgroup focuses on the accuracy of diagnostic tests. Systematic reviews and meta-analyses of studies which evaluate the accuracy of diagnostic tests are being published with increasing frequency in the medical literature.[4,5] The systematic analysis of publications focusing on immunomediated hearing loss is necessary in order to improve the criteria used to study this disease, as has been suggested.[6,7] The diagnosis of immunomediated hearing loss (mainly in its isolated forms) is difficult, being based on clinical history, response to therapy and exclusion of other pathology.[8–11] Various methodologies have been developed in order to evaluate different clinical protocols, diagnoses and therapy. The accuracy of diagnostic tests differs among studies. Therefore, a thorough evaluation of diagnostic tests is necessary to ensure that only accurate tests are used in practice.

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Diagnosis of immunomediated hearing loss was first established by McCabe on the basis of a defined clinical pattern and a positive response to dexamethasone and cyclophosphamide therapy.[1] Extensive hospital laboratory investigations were performed, which were negative except for a positive lymphocyte inhibition assay in some patients. The lymphocyte migration inhibition test has subsequently been replaced by the lymphocyte transformation test.[12,13]

Different studies, using diverse experimental models of autoimmune labyrinthitis,[14–19] have aimed to improve our understanding of the cellular and humoral responses occurring within the inner ear, by characterising the effects of: specific and non-specific antigens; local and systemic immunisation; circulating immune complexes; inner-ear autoantibodies; and human leukocyte antigen genes. Such investigations have led to the development of numerous diagnostic tests.

Type II collagen[20] and other antibodies such as anti-endothelial cells[21], sulphoglucuronosyl glycolipids autoantibodies[22], the major peripheral myelin protein P0[23], etc have been used as serological markers for IMIED.[24–30]

Harris and Sharp applied the Western blot technique to demonstrate specific antibodies to inner-ear antigens in animal immunised with heterologous inner-ear antigen and also in patients with sensorineural hearing loss.[31] On the basis of this approach, many antibodies of different molecular weights have been identified.[32–35]

As immunomediated hearing loss has a wide clinical spectrum, and as new immunopathological techniques are generally cumbersome, there have been several attempts to define a high-risk profile for immunomediated hearing loss. This profile usually considers clinical presentation and the results of non-specific serological tests (such as sedimentation rate and the levels of complement, immunoglobulins, C-reactive protein, etc) as well as specific immunological laboratory tests.[36–38]

Applying a systematic approach to the study of diagnostic tests used in immunomediated hearing loss may enable: objective appraisal of the evidence; enhanced precision of results, by creating pooled estimates; timely introduction of effective interventions; and generation of promising new research topics.

Material and methods

We searched Medline and the Cochrane Database of Systematic Reviews for potentially relevant studies.

In Medline, we applied the following search strategy: search ('hearing loss, sensorineural/diagnosis' [MeSH] OR 'hearing loss, sensorineural/immunology' [MeSH] OR 'hearing loss, sudden/diagnosis' [MeSH] OR 'hearing loss, sudden/immunology' [MeSH]) AND (autoimmune [all fields] OR 'autoimmune diseases' [MeSH] OR 'immune-mediated' OR 'immune-mediated' OR 'immuno-related' OR 'auto-immune' OR 'sensitivity and specificity' [MeSH]).

The references from all articles selected were scanned for potentially relevant articles that had not been identified by the original search. All articles related to those selected were scanned for potentially relevant articles, using Pubmed.

Two reviewers (DL and FGL) screened the titles and abstracts of all articles to independently identify relevant articles. Full copies of all selected articles were retrieved by the same two reviewers, who independently selected relevant articles which fulfilled the inclusion and exclusion criteria. Disagreements were resolved by discussion.

Studies published in English, Spanish, French, Italian and German were included; studies published in other languages were excluded.

Twenty-five articles were included in this study, according to the following criteria. The inclusion criteria were: clinical study (no animal models); high level of clinical suspicion (i.e. sensorineural hearing loss, sudden deafness, progressive, fluctuating, Ménière-like); response to corticosteroids; and a diagnostic test as the focus of study. The exclusion criteria were: infants as subjects; less than six subjects; studies of patients with a systemic autoimmune disease; and studies in which a cause of hearing loss other than idiopathic or suspected immunomediated hearing loss was identified.

Although we collected data obtained from cohorts of patients with sensorineural hearing loss of different aetiologies, we report here only data from patients with clinically suspected immunomediated hearing loss.

Two independent reviewers (DL and FGL) extracted the following data from the selected studies (either as reported, or collected from the reported data): population demographics; exclusion and inclusion criteria; diagnostic tests performed; sensitivity and specificity; the number of true positive, true negative, false positive and false negative results; therapy used, including doses and duration; and any delay between symptom onset and therapy commencement. These same reviewers then entered the data into a standardised database. For some studies the number of cases and controls differed from those

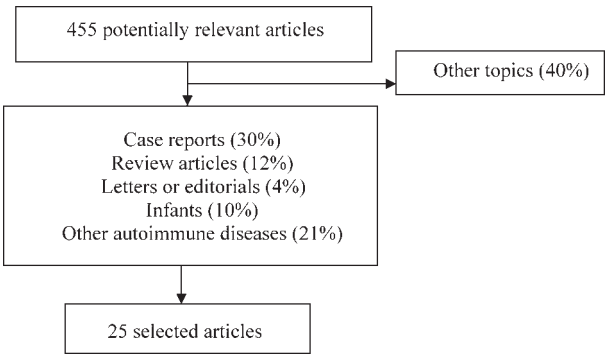

FIG. 1

Search results. The different exclusion criteria, and the percentage of articles presenting those exclusion criteria, are shown. Some articles presented several exclusion criteria (e.g. a case report about a systemic autoimmune disease).

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TABLE I

SELECTED ARTICLES

Authors	Year	Total pts (*n*)	Pt cases (*n*)	Female cases (%)	Clinical presentation	Diagnostic test
McCabe[1]	1979	18	6	NA	PSNHL	Lymphocyte inhibition assay
Brookes[39]	1985	64	28	NA	PSNHL SSNHL	Immune complex
Kempf & Hornig[40]	1987	33	24	NA	PSNHL	Anti-endothelial, anti-sarcolema, anti-smooth muscle
Hughes *et al.*[41]	1988	52	52	65.5	FSNHL	Lymphocyte transformation test
Helfgott *et al.*[42]	1991	18	9	NA	PSNHL	Type II collagen antibodies
Lejeune & Charachon[43]	1991	23	10	47.8	PSNHL FSNHL	Lymphocyte transformation & non-specific serologic test
Veldman *et al.*[44]	1993	46	20	NA	PSNHL SSNHL	Western blot
Cotter *et al.*[45]	1994	30	17	NA	PSNHL SSNHL	B19 human parvovirus antibodies
Kanzaki *et al.*[46]	1994	14	11	NA	PSNHL	Non-specific serologic test
Moscicki *et al.*[47]	1994	58	31	NA	PSNHL	Western blot 68 kDa
García-Berrocal *et al.*[48]	1995	31	19	NA	PSNHL SSNHL	Non-specific serologic test
Rauch *et al.*[49]	1995	30	30	47	FSNHL	Hsp 70 antibodies
Disher *et al.*[50]	1997	74	74	NA	PSNHL SSNHL	Western blot 68–70 kDa
Quaranta *et al.*[51]	1997	6	6	NA	PSNHL SSNHL	Immune complex, antinuclear, antimitochondrial
Yamawaki *et al.*[52]	1998	114	74	NA	PSNHL	Anti-SGLPG ELISA
Hirose *et al.*[53]	1999	34	24	NA	PSNHL SSNHL	Western blot, PCR
Zavod *et al.*[54]	2000	35	35	NA		MRI, HLA
Lunardi *et al.*[55]	2002	98	8	37.5	Cogan	Cogan peptide
Lorenz *et al.*[56]	2002	24	12	75	PSNHL	ELISPOT INF-g T cells
García-Berrocal *et al.*[57]	2002	81	59	NA	PSNHL SSNHL FSNHL	Hsp 70 ANAs, CD4
Cadoni *et al.*[58]	2002	32	25	NA	SSNHL	Anti-endothelial antibodies
Garcia Callejo *et al.*[59]	2003	51	30	NA	PSNHL SSNHL FSNHL	Western blot 68, 33, 35, 220 kDa
Mazlumzadeh *et al.*[60]	2003	15	10	NA	PSNHL SSNHL	PET
Loveman *et al.*[61†]	2004	23	13	NA	PSNHL	Anti 68 kDa antibodies
Zeitoun *et al.*[62†]	2005	63	28	NA	PSNHL SSNHL	Western blot 68, 72 kDa, ANAs, rheumatoid factor

Only patients not responding to therapy were considered as controls. [†]The presented numbers of cases and controls differ from those described by the authors, as only those patients responding to steroids were considered as cases. Pt = patient; NA = percentage could not be calculated; PSNHL = progressive sensorineural hearing loss; SSNHL = sudden sensorineural hearing loss; FSNHL = fluctuating sensorineural hearing loss; SGLPG = sulfoglucuronosyl lactosaminyl paragloboside; Hsp = heat shock protein; ELISA = enzyme-linked immunosorbent assay; PCR = polymerase chain reaction; MRI = magnetic resonance imaging; HLA = human leukocyte antigen; ELISASPOT = enzyme-linked immunosorbent spot; INF = interferon; ANA = antinuclear antibodies; PET = positron emission tomography

described by the authors, as only patients not reponding to therapy were considered as controls.

Discrepancies were checked and resolved by an independent reviewer (JRGB). We reviewed the data reported by each study and removed any studies containing duplicated data.

Statistical analysis was performed using Meta-DiSc (freeware) software, in order to allow meta-analysis of studies.[63] Summarised sensitivity and specificity results were not computed, because of the substantial heterogeneity among studies.

Results

Our search of the two databases identified a total of 455 potentially relevant articles, of which 25 fulfilled the inclusion criteria.[1,39–62] Seventy-six per cent of articles were excluded after reading the title and

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abstract. Another 18 per cent were excluded after reviewing the full article (Figure 1). One article was written in Chinese and was also excluded.

The systematic review considered 679 patients and 450 controls, studied by 22 research teams (Table I). Patients' ages at study entry had a mean value of 42.3 years and ranged from 11 to 84 years. The median duration of disease follow up across study cohorts was 5.1 years.

Substantial heterogeneity was found among the included articles. Cohorts were variously recruited from out-patient clinics, in-patient units or emergency departments, or were of 'mixed' provenance; however, in most studies, patients' sites of recruitment was not stated.

Patients' clinical characteristics varied among studies. Four per cent of the studies recruited patients with sudden deafness, 35 per cent recruited those with progressive deafness, 8 per cent recruited those with Ménière's disease, and 54 per cent recruited 'mixed' patients with sudden, progressive or fluctuating hearing loss.

The studies also varied in their inclusion and exclusion criteria. Most studies excluded patients with any other known causes of sensorineural hearing loss. A few did not report any exclusion criteria. Response to steroids was an inclusion criterion in only 20 per cent of studies, although all studies presented patients who have received a trial of steroid therapy. There is no reference standard for the diagnosis of immunomediated hearing loss. However, 9 per cent of studies used the test for 68 kDa protein as a reference in order to evaluate the sensitivity and specificity of their diagnostic test (Table II).

The delay between symptom onset and diagnostic testing was only evaluated in three studies; these reported a mean of 5.5 weeks and a range of one week to one year.

The most frequently employed therapy for immunomediated hearing loss was methylprednisolone 1 mg/kg per day for a minimum period of seven days, tapering off for another three to eight weeks, and usually continuing at a maintenance dose of 8 to 16 mg until clinical stabilisation. Other therapies also employed were: methotrexate (four patient cohorts), cyclophosphamide (two cohorts) and plasmapheresis (four cohorts).

Criteria for response to therapy were presented in 16 studies. Thirty-six per cent of the studies did not present any therapeutic response criteria (Table II).

Only five studies presented data on the duration of patient follow up. Of those that did, the mean value was 5.1 years and the range one month to 17 years.

Three hundred and forty-four patients underwent either Western blot or enzyme-linked immunosorbent assay analysis for the 68 kDa antigen. Other tests employed are presented in Table I.

Seven studies used a Western blot test to detect the 68 kDa antibody, whereas three used Western blotting on cochlear cell extracts to enable detection of different cochlear autoantibodies. Two studies evaluated the utility of diagnostic imaging (magnetic resonance and proton-emission tomography) in cases of immunomediated hearing loss.

The sensitivity and specificity of anti-68 kDa protein testing using Western blotting were respectively 0.48 (0.39–0.56 95 per cent confidence interval (CI)) and 0.57 (0.46–0.67 CI) (Figure 2). The sensitivity of other diagnostic tests was close to 0.4 (Average). The lowest sensitivity values were obtained for non-specific serological tests. The highest sensitivity and specificity values were obtained for analysis of Cogan peptide antibodies (which contributed to the characterisation of Cogan's syndrome). The lowest specificity values were obtained for the determination of human parvovirus B19 immunoglobulins, positron emission tomography, and non-specific serological and immunological tests (Figure 3).

TABLE II

INCLUSION, EXCLUSION AND THERAPY RESPONSE CRITERIA FOUND IN THE SELECTED ARTICLES

Criteria	Articles (%)
Inclusion (n=25*)	
Sensorineural hearing loss	67
Steroidal response	16
Test for 68 kDa protein	8
Other	9
Exclusion (n=12*)	
Known causes for hearing loss	67
No therapy	8
No diagnostic test	8
Other	18
Therapy response (n=16*)	
PTA >10 dB	31
PTA >15 dB	69
SA >12%	43
SA >15%	14
SA >20%	43

*Number of studies presenting this type of criteria. PTA = pure tone audiometry; SA = speech audiometry

Discussion

The diagnosis of autoimmune hearing loss described by Mc Cabe in 1979 was based on a defined clinical pattern and a positive response to dexamethasone and cyclophosphamide therapy.[1] In the last three decades, many case reports, aetiopathogenic hypotheses, animal experimental models, immunological testing techniques and therapeutic concepts have been presented.[6–11]

Experimental studies have illustrated that immunomediated and autoimmune pathology can affect the inner ear.[14–19] These experiments have led to the development of numerous diagnostic tests. However, most of these tests have not been widely taken up in clinical practice, and their results are often controversial. Therefore, the accuracy of such diagnostic tests needs to be evaluated.

We found significant heterogeneity among the selected studies, regarding such factors as: subjects; delay between onset of active disease and diagnostic testing; diagnostic tests; reference standards (e.g. Western blot, clinical response to corticosteroids, or none); and treatment response criteria (although

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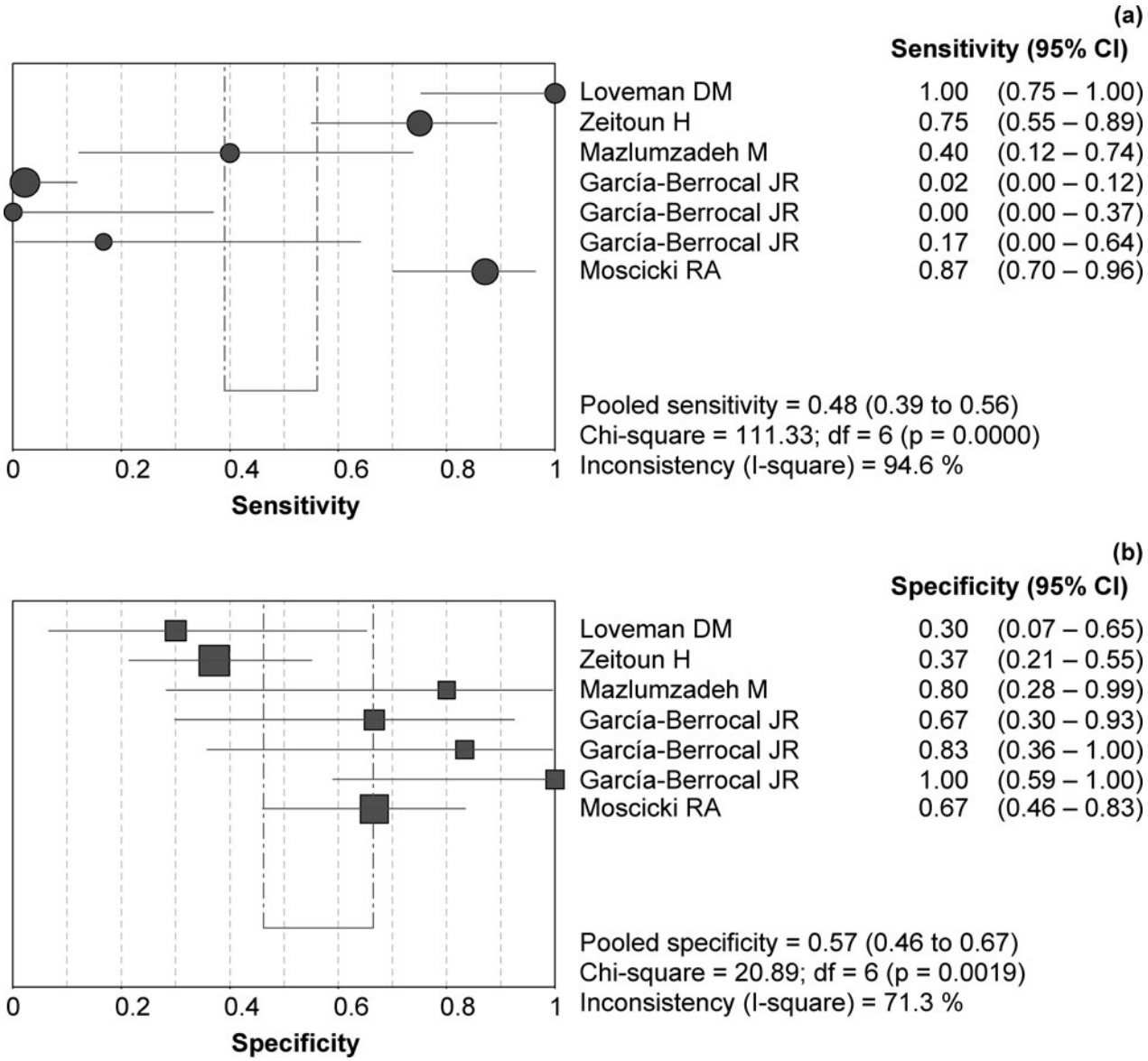

FIG. 2
(a) Sensitivity and (b) specificity of the Western blot test for 68 kDa protein. CI = confidence intervals

comparison of clinical responses to immunosupressants is very difficult, as different parameters were used to assess hearing recovery). Although variability does not necessarily lead to biased estimates of test performance, it may limit the applicability of results.[64]

Testing for 68 kDa Bloch DB et al identified the 68 kDa protein as heat shock protein 70 (hsp70) but later other proteins of 68 kDa such as the choline-transporter like protein 2 have been identified as the target of antibody-induced hearing loss. Therefore, the nature of the 68 kDa protein is not yet completely elucidated protein is not useful in excluding disease, since the sensitivity of this test is low. While nearly all studies suggested poor diagnostic performance for this test, the exact test performance varied substantially. Variability may be attributed to the type of assay used,[65,66] but also to differences in: duration of symptoms before testing; therapy at the time of testing; and test thresholds. (The selected cut-off value designating a positive result may also affect the sensitivity and specificity.)[4,5,64] Furthermore, the sensitivity and specificity of the 68 kDa protein test was greater in some studies researching patients suspected of having only the target condition. This feature has been described as spectrum bias,[67,68] and the results of such studies of highly selected patient populations lack generalisability.[64] There is also a potential bias in studies in which the 'gold standard' test is performed only on subjects who have already tested positive for the diagnostic test in question.[69] Finally, treatment with immunosuppressive drugs at the time of testing might influence the antibody response and could therefore also account for discrepancies in test performance. Titres may also fluctuate with the course of the disease, making appraisal of a positive or negative result even more difficult.

Heterogeneity resulting from all these sources is probably unavoidable and reflects actual clinical

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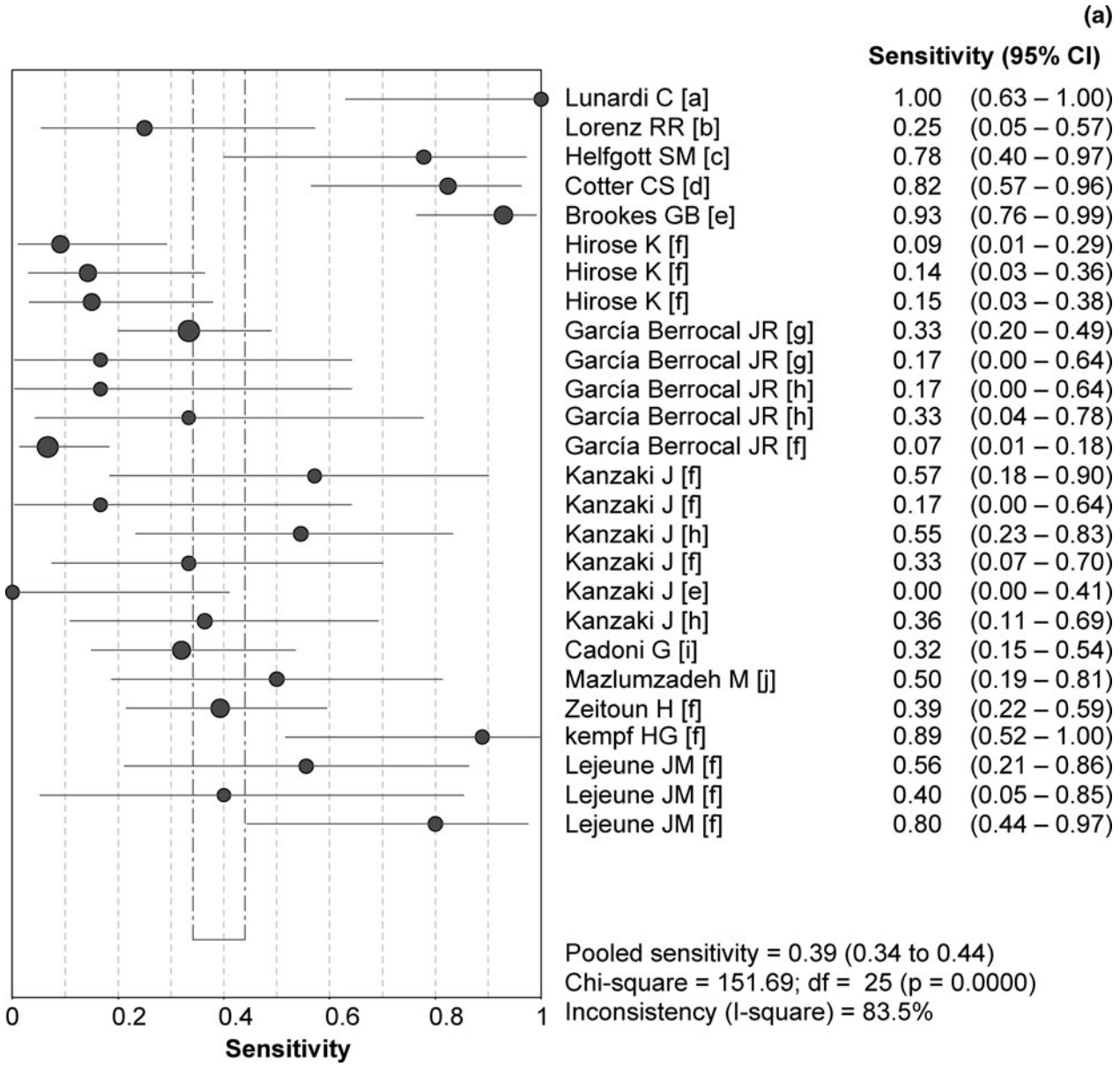

FIG. 3

(a) Sensitivity and (b) specificity of other diagnostic tests: [a] Cogan peptide; [b] increased frequencies of γ interferon producing T cells; [c] type II collagen antibodies; [d] human parvovirus B19 immunoglobulins; [e] immune complex; [f] different serological tests, such as erythrocyte sedimentation rate, complement 3 and 4 levels, and C-reactive protein; [g] lymphocyte subsets; [h] tissue non-specific antibodies (antinuclear antibodies); [i] anti-endothelial cell autoantibodies; [j] positron emission tomography. CI = confidence intervals

practice. Our study had the methodological disadvantage of using data from heterogeneous populations in which there were no common inclusion criteria and (in most cases) no blinded interpretation of test results.

Many difficulties are encountered when a systematic review of diagnostic tests is performed. Papers are not easily identified as studies of diagnostic test accuracy, and the lack of information in the abstract makes it difficult to assess eligibility for inclusion in a systematic review. Systematic reviews of diagnostic tests may be subject to publication bias – bad results are less often published. (We should be aware that the majority of studies that failed to show a diagnostic value for the 68 kDa protein test may have remained unpublished. If this is so, the true diagnostic performance of anti-68kDa antibody analysis may be even worse than that demonstrated by this review.)

This study had other limitations that need to be considered. There is not a true gold standard diagnostic test for immunomediated hearing loss. When we include response to steroids as a required criteria in the diagnosis of immunomediated hearing loss, we are aware that spontaneous recovery in hearing, as seen in Ménière's disease, may be mistaken for a positive response to corticosteroids.[61] On the other hand, immunomediated hearing loss with a more aggressive course may not respond to

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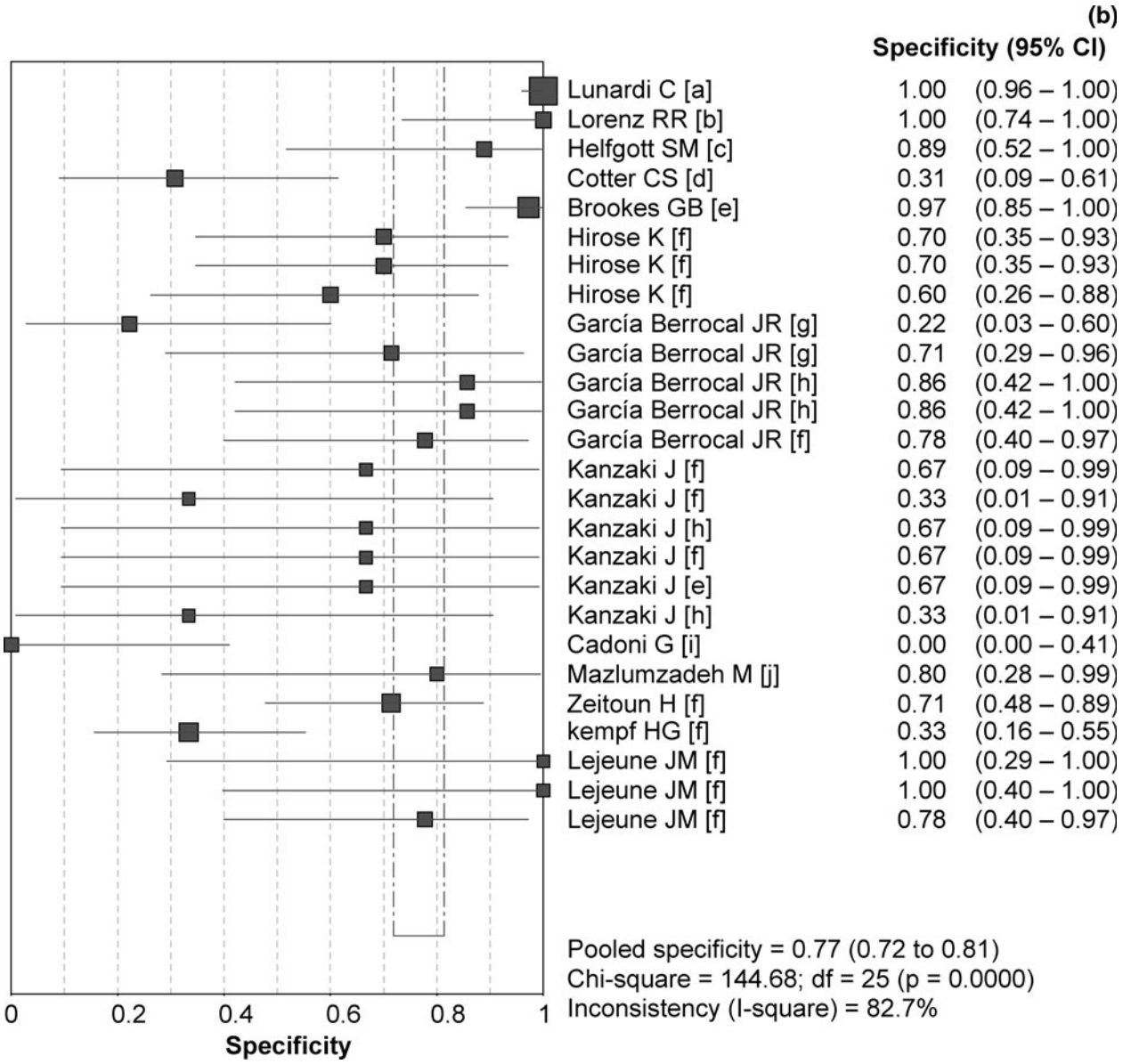

FIG. 3
Continued

corticosteroids, although it may or may not respond to other immunosuppressive therapy.[61] However, most authors accept that the gold standard for diagnosis of immunomediated hearing loss is based on clinical presentation and response to corticosteroid administration.[6,53,70–72]

Cyclophosphamide remains a therapeutic alternative for patients whose disease becomes refractory to prednisone or who cannot be weaned off steroids. Methotrexate showed no effectiveness in a recent, multicentre trial.[73] Other drugs such as etanercept have been used only rarely, and have toxicity and economic considerations.[74,75]

Another limitation of our study was that patients were classified according to the clinical setting, as suffering progressive, fluctuant or sudden deafness. Whether all patients with immunomediated hearing loss share the same underlying pathophysiology is still unknown. Such complex presentations might reflect a multifactor pathogenic aetiology with overlapping mechanisms, and we therefore cannot completely exclude the possibility that some of these patients may have been misclassified. We have considered them all as different manifestations of immunomediated hearing loss.

Finally, we did not search for unpublished data or studies published in languages other than English, Spanish, German, French or Italian.

Poor reporting also limited our ability to explore the effect of study design upon results. The methodological weaknesses in the primary studies constitute a weakness in our systematic review.

Our review clarifies that there is a great discrepancy in the criteria being used, and that the results of diagnostic tests for immunomediated hearing loss depend on many factors and potential biases.

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Nevertheless, this is the first time that a systematic review (a more rigorous procedure to demonstrate the utility of the available tests) has been presented.

- **Humoral and cellular immune reactions have been implicated in the development of certain types of cochleovestibular dysfunction**
- **The medical literature contains numerous studies describing laboratory tests suggesting an immunological basis for inner-ear disorders**
- **The application of a systematic approach to the study of the diagnostic tests applied in immunemediated inner-ear disease may provide an objective appraisal of the evidence for the existence of these conditions**
- **This approach could limit health care costs by preventing unnecessary testing, and by allowing more rigorous evaluation of the effectiveness of different interventions**

Many of these diagnostic tests have given controversial results. In addition, primary immunomediated hearing loss is a rare disorder, occurring less frequently than sudden sensorineural hearing loss. The application of low sensitivity tests to a population with low disease prevalence will result in low negative and positive predictive values, with a high cost. Hence, it is important to know the accuracy of these tests, since they may not be cost-effective.

There is increasing interest in synthesising information on the diagnostic tests used in autoimmune diseases. A comprehensive, multicentre study may represent a powerful means of rigorously evaluating the various diagnostic tests used for immunomediated hearing loss. Such an approach could limit healthcare costs by preventing unnecessary testing. Such a comprehensive study would need to clearly define the study population, the response criteria and the point at which the diagnostic test is performed, as we propose and as this study evinces.

Acknowledgement

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