Utility of Anti-endothelial Cell Autoantibodies as a Marker for Immune-mediated Vasculitis in Sudden Sensorineural Hearing Loss

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Mohammad Abd El-Kareem

ABSTRACT

Introduction

Sudden hearing loss is a sensorineural hearing impairment that develops over a period of a few hours to a few days and whose etiology can be found only in 10% to 15% of patients.

Several theories have been proposed regarding the development of sudden sensorineural hearing loss (SSNHL). There is considerable evidence suggesting that hearing can be influenced by immunity in the inner ear.

The pathogenesis of autoimmune hearing loss includes vasculitis of inner ear vessels, cross-reacting antibodies, or autoantibodies directed against inner ear antigenic epitopes.

The hypothesis that vascular damage might have a pathogenetic role in immune-mediated SSNHL is supported by labyrinthine fibrosis and cochlear ossification found in patients affected by SSNHL in conjunction with autoimmune disorders.

This work aimed to detect to what extent the vascular damage could have a role in the pathogenesis of SSNHL and to evaluate the role of anti-endothelial cell antibodies (AECA) as a serological marker of vasculitis in patients with SSNHL.

The present study included fifty patients with idiopathic SSNHL (ISSNHL). Thirty healthy subjects, age and sex matched, were included in the study as a control group.

Some immunological parameters, namely erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), AECA, anti-neutrophil cytoplasmic antibodies (ANCA) and anti-nuclear antibodies (ANA), were done for patients and control groups.

Results

ESR, CRP and AECA levels showed highly significant elevations in patients group as compared to controls. Thus these parameters could be of value in suspecting immune-mediated vasculitis in hearing loss. Correlation studies revealed a highly significant positive correlation between AECA levels and both of ESR and CRP, which indicates that the cause of rising of all these parameters is almost the same.

As regards ANCA and ANA, no positive cases were noticed among controls. In the patients group, 54% of patients were ANCA-positive and only 6.0% of patients were positive for ANA and thus differed significantly from normal controls.

AECA levels were significantly elevated in ANCA-positive patients. AECA levels showed a highly significant difference in patients with different degrees of hearing loss (HL). The results obtained by the receiver operating characteristic (ROC) curve indicated that AECA may provide a valuable tool for detecting inner ear vasculitis as a cause of SSNHL.

Conclusion

Vasculitis of the inner ear vessels may play a role in the pathogenesis of some cases of ISSNHL. It may occur with any age, sex and with any degree of HL. ESR and CRP should be taken in consideration as a routine screening test for such cases. AECA may represent a serological marker of immune-mediated vascular damage in SSNHL. It could be used early in the disease for proper early diagnosis and to identify a subset of patients whose immunosuppressant therapy may result in stabilization of and possibly improvement in hearing acuity.

Key words

Anti-endothelial cell antibodies; sudden sensorineural hearing loss; vasculitis; immune-mediated inner ear diseases.

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List of Abbreviations

A	
-AAV	: ANCA-associated vasculitis.
-Ab	: Antibody.
-aCL	: Anti-cardiolipin antibodies.
-ADCC	: Antibody-dependant cellular cytotoxicity.
-AECA	: Anti-endothelial cell antibodies.
-Ag	: Antigen.
-AHA	: Anti-heparin antibodies.
-AICA	: Anterior inferior cerebellar artery.
-AIDS	: Acquired immune deficiency syndrome.
-AIED	: Autoimmune inner ear disease.
-ANA	: Anti-nuclear Antibodies.
-ANCA	: Anti-neutrophil cytoplasmic Antibodies.
-Anti-GBM	: Anti-glomerular basement membrane antibodies.
-aPL	: Anti-phospholipid antibodies.
-APS	: Anti-phospholipid syndrome.
-AUC	: Area under the ROC curve.
B	
- β2-GPI	: β2-glycoprotein-I.
-B cells	: B lymphocytes.
-BD	: Behçet's disease.
-BM	: Basilar membrane.
C	
-CAM	: Cell adhesion molecule.
-*c*-ANCA	: Cytoplasmic anti-neutrophil cytoplasmic antibodies.
-CBC	: Complete Blood Count.
-CD11b	: Cluster of differentiation11b.
-CD95	: Cluster of differentiation 95 (=Fas).
-CDC	: Complement-dependent cytotoxicity.
-CF	: Correction factor.
-CHL	: Conductive hearing loss.
-Cl^-	: Chloride ions.
-cm	: Centimeter.
-cm^2	: Square centimeter.
-CRP	: C-reactive protein.
-CSF	: Cerebrospinal fluid.

D	
-dB	: Decibel.
-DCs	: Deiters' cells (outer phalangeal cells).
-Dyne	: A unit of force.
E	
-EC	: Endothelial cell.
-ECs	: Endothelial cells.
-ELISA	: Enzyme-linked immunosorbent assay.
-ENT	: Ear, Nose and throat.
-ESR	: Erythrocyte Sedimentation Rate.
F	
-FACS	: Fluorescence-activated cell sorter analysis.
-Fas	: Apoptosis Stimulating Fragment (=CD95).
-FCS	: Fetal calf serum.
-FTA-ABS	: Fluorescent Treponemal Antibody Absorption.
G	
-GCA	: Giant Cell Arteritis.
-G-CSF	: Granulocyte colony-stimulating factor.
-GM-CSF	: Granulocyte macrophage colony-stimulating factor.
-GRO-α	: Growth-related oncogene alpha.
H	
-HBV	: Hepatitis B virus.
-HCV	: Hepatitis C virus.
-HDL-cholesterol	: High-density lipoprotein cholesterol.
-HIV	: Human Immunodeficiency Virus.
-HDMEC	: Human Dermal Microvascular Endothelial Cells.
-HL	: Hearing Loss.
-HLA I	: Human leucocyte antigen class I.
-HLA II	: Human leucocyte antigen class II.
-HRP	: Horseradish peroxidase enzyme.
-H.S.P.	: Henoch Schonlein purpura.
-HSP	: Heat shock proteins.
-HSP 60	: Heat shock protein 60.
-HSP 70	: Heat shock protein 70.
-HUVEC	: Human umbilical vein endothelial cells.
-Hz	: Hertz.
I	
-ICAM-1	: Intercellular adhesion molecule 1.

-ICSH	: International council for standardization in hematology.
-IgG, A, M	: Immunoglobulin G, A, M.
-IHCs	: Inner hair cells.
-IκBα	: Inhibitor-alpha for NFκB.
-IL	: Interleukin.
-IL-1	: Interleukin-1.
-IL-1β	: Interleukin-1β.
-IL-1RA	: Interleukin-1 receptor antagonist.
-IL-2	: Interleukin-2.
-IL-6	: Interleukin-6.
-IL-8	: Interleukin-8.
-IPC	: Inner phalangeal cell.
-IPSNHL	: Idiopathic progressive sensorineural hearing loss.
-ISSNHL	: Idiopathic sudden sensorineural hearing loss.
J	
-JNK	: c-Jun N-terminal kinase.
K	
-K^+	: Potassium ions.
-KD	: Kawasaki's disease.
-kDa	: Kilo Dalton.
-kHz	: Kilo Hertz.
-K-S test	: Kolmogorov-Smirnov test.
L	
-LDL-cholesterol	: Low-density lipoprotein cholesterol.
M	
-MAPK	: Mitogen-activated protein kinase.
-MCP-1	: Monocyte chemoattractant protein-1.
-MCTD	: Mixed connective tissue disease.
-mm	: Millimeter.
-mmol/l	: Millimole/liter.
-MPA	: Microscopic Polyangiitis.
-MPO	: Myeloperoxidase.
-MRI	: Magnetic resonance imaging.
-MS	: Mass spectrometry.
-MS/MS	: Tandem mass spectrometry.
-MW	: Molecular weight.
N	
-n	: Number of subjects.

-Na^+	: Sodium ions.
-NFκB	: Nuclear factor kappa B (= Nuclear factor kappa-light-chain-enhancer of activated B cells).
-NK cells	: Natural Killer cells.
O	
-OD	: Optical density.
-OHCs	: Outer hair cells.
P	
-PAN	: Polyarteritis nodosa.
-*p*-ANCA	: Perinuclear anti-neutrophil cytoplasmic antibodies.
-PBMC	: Peripheral blood mononuclear cells.
-PBS	: Phosphate-buffered saline.
-PR3	: Proteinase-3.
-Prx2	: Peroxiredoxin2.
-PSD95	: Postsynaptic density 95.
-PTS	: Permanent threshold shift.
R	
-r	: Correlation coefficient.
-RF	: Rheumatoid factor.
-RIA	: Radioimmunoassay.
-ROC	: Receiver operating characteristic.
-RP	: Raynaud's phenomenon.
-RPM	: Round per minute.
-RPSNHL	: Rapidly-progressing sensorineural hearing loss.
S	
-SARS	: Severe acute respiratory syndrome.
-SD	: Standard Deviation.
-SHL	: Sudden hearing loss.
-SLE	: Systemic lupus erythematosus.
-SLEDAI	: SLE disease activity index.
-SMV	: Spiral modiolar vein.
-SNHL	: Sensorineural hearing loss.
-SSc	: Systemic sclerosis.
-SSNHL	: Sudden Sensorineural hearing loss.
T	
-T3	: Total Tri-iodothyronine.
-T4	: Total Thyroxine.
-TA	: Takayasu's Arteritis.

-T cells	: T lymphocytes.
-TF	: Tissue factor.
-TLR4	: Toll-like receptor 4.
-TMB	: 3,3′,5,5′-tetramethylbenzidine.
-TNF-α	: Tumor necrosis factor-alpha.
-TORCH	: Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex.
-TSH	: Thyroid-stimulating hormone.
-TTS	: Temporary threshold shift.
U	
-µl	: Microliter.
V	
-VCAM-1	: Vascular cell adhesion molecule 1.
-VDRL	: Venereal Disease Research Laboratory.
W	
-WB	: Western blot.
-WG	: Wegener's granulomatosis.

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INTRODUCTION AND AIM OF THE WORK

INTRODUCTION

Sudden sensorineural hearing loss is defined as hearing loss of 30 decibel (dB) or more over at least three contiguous audiometric frequencies that develops over a period of a few hours to 3 days and whose etiology can be found only in 10% to 15% of patients ***(Tebo et al., 2006)***.

Several theories have been proposed regarding the development of SSNHL. There is considerable evidence suggesting that hearing can be influenced by immunity in the inner ear. Immunity can protect against infections of the labyrinth, but immune response may also damage the delicate tissues of the inner ear ***(Geelan et al., 2009)***.

A number of systemic autoimmune disorders includes hearing loss and vertigo as parts of their constellation of symptoms such as *systemic lupus erythematosus* (SLE), *Cogan's syndrome*, *Wegener's granulomatosis* (WG) and *polyarteritis nodosa* (PAN) ***(Cadoni et al., 2003)***. It also appears that autoimmune damage can exist as an entity confined to the labyrinth. It is extremely important to recognize immune disorders of the inner ear because they are among the few forms of hearing loss that are currently amenable to medical treatment ***(Gross et al., 2008)***.

The pathogenesis of autoimmune hearing loss includes vasculitis of inner ear vessels, cross-reacting antibodies, or autoantibodies directed against inner ear antigenic epitopes ***(Bovo et al., 2009)***.

The hypothesis that vascular damage might have a pathogenetic role in immune-mediated SSNHL is supported by labyrinthine fibrosis and cochlear ossification found in patients affected by autoimmune disorders