RHEUMATOID ARTHRITIS AFFECTS BRAINSTEM AUDITORY EVOKED POTENTIAL

Shelja Deswal[1], Jyoti Yadav[2], Joginder Gulia[3], Harpreet Singh[4], Ashish Arvind[5]

Sr. Resident[1,5], Professor[2,3] , Senior Professor[4], Department of Physiology, Department of Physiology, Pt. B.D. Sharma, PGIMS, Rohtak-124001, India, Department of ENT, Pt. B.D. Sharma, PGIMS, Rohtak-124001, India, Department of Medicine, Pt. B.D. Sharma, PGIMS, Rohtak-124001, India, Department of Physiology, Department of Physiology, Pt. B.D. Sharma, PGIMS, Rohtak-124001, India

Abstract: **Background:** Rheumatoid arthritis is a chronic multisystem disease characterized by persistent inflammatory synovitis, usually involving peripheral joints in a symmetric distribution. Despite its predominant osteoarticular and periarticular manifestations, RA is a systemic disease often associated with cutaneous and organ-specific extra-articular manifestations. It has been seen that as many as 40% of patients may have extraarticular manifestations. It usually presents as polyarthritis affecting small or large joints. Brainstem auditory evoked potential recording can represent an objective, clinically useful and non-invasive procedure to stress the early impairment of both auditory nerves and brainstem function. **Aims and Objectives:** To study brainstem auditory evoked potential changes in rheumatoid arthritis patients **Material and Method:** Control (group 1) comprised of 25 healthy female subjects of age 30 to 50 years while study group (group 2) comprised of 25 female patients with RA of more than 5 years. Proven cases of RA (as per 1987 ACR criteria) underwent brainstem auditory evoked potentials. The recording was carried out by using RMS EMG EPMK2. Ear discharge, deafness, history of intake of ototoxic drugs, chronic hepatic, renal and respiratory diseases were excluded. **Result:** In left ear, the difference in absolute peak latency of wave IV of group 1 and 2 and the difference of wave V of group 1 and 2 were significant ($p<0.05$) while for rest of the waves it was insignificant ($p>0.05$). The differences in interpeak latencies (I-III, III-V, I-V) were insignificant ($p>0.05$). The difference in amplitude of I-Ia between group 1 and 2 was significant ($p<0.05$) but difference in amplitude of I-Va was insignificant ($p>0.05$). In right ear, difference in absolute peak latency of wave III of group 1 and 2 was significant ($p<0.05$) while for rest of the waves it was insignificant ($p>0.05$). The differences in interpeak latencies and amplitude were insignificant ($p>0.05$). **Conclusion:** Differences of absolute peak latency of wave IV and V in left ear and III in right ear were significant ($p<0.05$) when compared with control. The difference in amplitude of I-Ia was significant ($p<0.05$) in left ear when compared with control. Thus rheumatoid arthritis affects brainstem auditory evoked potential.

Key Words: Autoimmune inner ear disease, Brainstem auditory evoked potential, Rheumatoid arthritis

Author for correspondence: Dr. Shelja , Department of Physiology,Pt. B.D Sharma, PGIMS Rohtak – 124001.e-mail: docshelja27@gmail.com

Introduction:

Rheumatoid arthritis (RA), a chronic multisystem disease characterized by persistent inflammatory synovitis, usually involving peripheral joints in a symmetric distribution. The potential of the synovial inflammation to cause cartilage damage, bone erosions and subsequent changes in joint integrity is the hallmark of the disease. Onset is most frequent during the fourth and fifth decades of life with 80% of patients developing the disease between the age of 35 to 50 years.[1] Gene-environment interactions appear as the most plausible underlying cause of RA. Age, sex, smoking, shared epitope correlate with RA.[2] Rheumatoid arthritis is well known to affect many organ systems, including the auditory system. It can involve the incudo-malleolar and incudo-stapedial joints altering the ossicular mechanics in response to static air pressure modifications. These joints are true diarthroses and therefore subject to the same rheumatic lesions as any other articulation in the body.[3] Perisacular tissue surrounding the endolymphatic sac contains the necessary components for an immunological reaction. In addition, the inner ear is capable of producing an autoimmune response to sensitized cells that can enter the cochlea from the circulatory system through the spiral modiolar vein.[4] Sensorineural hearing loss (SNHL) is a collection of common auditory disorders resulting from dysfunction of the inner ear, auditory nerve, or the auditory processing pathway in the central nervous system. The inner ear has been thought of as an immune privileged organ for a long time. Andersen initiated a new era of inner ear immunology by describing intimate contact between the

lymphocytes and macrophages in the endolymphatic sac of guinea pigs. This association suggested that two cell types mediated the antigen-presenting process in the endolymphatic sac.[5] the presence of immunocompetent cells and phagocytized antigen within macrophages was also reported in the endolymphatic sac These findings revealed the specific role of the endolymphatic sac in antigen processing and immune activity in the inner ear.[6]

Brainstem auditory evoked potential is a sensitive and specific method to diagnose retrococohlear hearing loss, demyelination and other diseases of brain stem. BAEP are potentials recorded from ear and vertex in response to a brief auditory stimulation to assess the conduction through auditory pathway upto midbrain. Sound is converted into an electrical impulse and passes from cochlea to auditory cortex through the following pathway: spiral ganglion in cochlea→ventral and dorsal cochlear nuclei in brainstem→superior olivary nucleus in pons→lateral leminiscus in midbrain→inferior colliculus in midbrain→medial geniculate body in thalamus and ultimately to auditory area in cerebral cortex. The normal brainstem auditory evoked response (BAER) consist of 5 or more vertex positive and vertex negative waves arising within 10ms of auditory stimulus. They are labelled by using Roman numerical (I, II, III, IV, V).[7]

Material and Methods:

The study was conducted in the Department of Physiology in collaboration with departments of Medicine and ENT Pt. B.D. Sharma PGIMS, Rohtak in 50 females of age group 30-50 years.

Control (group 1) comprised of 25 healthy female subjects of age 30 to 50 years while study group (group 2) comprised of 25 female patients with RA of more than 5 years. Proven cases of RA (as per 1987 ACR criteria) underwent brainstem auditory evoked potentials. The recording was carried out by using RMS EMG EPMK2.

Inclusion criteria:

Patients of rheumatoid arthritis with disease duration of more than five years as per 1987 ACR criteria were included in the study.

Exclusion criteria:

History of intake of drugs with known ototoxicity, subjects with history of ear discharge and deafness, renal diseases, hepatic diseases, chronic respiratory diseases, diabetes mellitus, uncontrolled hypertension, pregnant or lactating mothers.

An informed consent was taken from the patients to participate in the study and brainstem auditory evoked potential was performed. The study was well within the ethical norms and permission was taken from ethical committee.

Result:

In left ear, the difference in absolute peak latency of wave IV of group 1 and 2 and the difference of wave V of group 1 and 2 were significant ($p<0.05$) while for rest of the waves it was insignificant ($p>0.05$). The differences in interpeak latencies (I-III, III-V, I-V) were insignificant ($p>0.05$). The difference in amplitude of I-Ia between group 1 and 2 was significant ($p<0.05$) but difference in amplitude of I-Va was insignificant ($p>0.05$).

Table 1: Comparison of mean values of latency, interpeak latency and amplitude of BAEP waves of left ear between group I and group II

Parameters	Group I (Mean ± SD)	Group II (Mean ± SD)	p value
Wave I(ms)	1.55±0.08	1.79±0.26	>0.05
Wave II(ms)	2.73±0.20	3.02±0.31	>0.05
Wave III(ms)	3.64±0.25	4.16±0.38	>0.05
Wave IV(ms)	4.85±0.33	5.30±0.38	<0.05
Wave V(ms)	5.62±0.25	6.06±0.58	<0.05
Interpeak latency I-III(ms)	2.09±0.24	2.36±0.46	>0.05
Interpeak latency III-V(ms)	4.15±0.36	4.27±0.63	>0.05
Interpeak latency I-V(ms)	2.06±0.34	1.90±0.48	>0.05
Amplitude I-Ia(µv)	0.43±0.24	0.32±0.23	<0.05
Amplitude V-Va(µv)	0.47±0.27	0.40±0.33	>0.05

In right ear, difference in absolute peak latency of wave III of group 1 and 2 was significant ($p<0.05$) while for rest of the waves it was insignificant ($p>0.05$). The differences in interpeak latencies and amplitude were insignificant ($p>0.05$).

Table 2: Comparison of mean values of latency, interpeak latency and amplitude of BAEP waves of right ear between group I and II

Parameters	Group I (Mean ± SD)	Group II (Mean ± SD)	p value
Wave I (ms)	1.52±0.17	1.68±0.22	>0.05
Wave II (ms)	2.63±0.29	2.88±0.37	>0.05
Wave III (ms)	3.51±0.29	3.94±0.38	<0.05
Wave IV (ms)	4.61±0.35	5.14±0.39	>0.05
Wave V (ms)	5.46±0.27	6.10±0.65	>0.05
Interpeak latency I-III (ms)	1.98±0.26	2.25±0.39	>0.05
Interpeak latency III-V (ms)	3.94±0.40	4.41±0.62	>0.05
Interpeak latency I-V (ms)	1.95±0.37	2.16±0.64	>0.05
Amplitude I-Ia (µv)	0.28±0.16	0.32±0.58	>0.05
Amplitude V-Va (µv)	0.35±0.26	0.43±0.46	>0.05

Discussion:

Rheumatoid arthritis is a systemic disease characterized by chronic inflammation of the synovial joints damage and loss of function.[8] The main risk factors for the disease include genetic susceptibility, sex, age, smoking, infectious agents, hormonal, dietary, socioeconomic and ethnic factors.[9] The cytokines and inflammatory mediators are produced at the site of disease. Tissue residing and infiltrating cells secrete proinflammatory cytokines in situ, which are likely to have a critical role in amplifying and maintaining the inflammation. The migration of inflammatory cells into the tissue is an important component of disease, specifically because adhesion molecules not only facilitate tissue infiltration, but also affect cell activation and cell-cell and cell-matrix interactions.[10] The "Bermuda triangle" of genetic, environmental factors and autoimmunity triggers the onset and perpetuation of synovitis underlying RA reactions which ultimately lead to the development of synovitis, joint damage and structural bone damage.[11] RA is characterized by joint swelling and leukocyte recruitment into synovial tissue. Within the peripheral blood and synovial fluid of patients with rheumatoid arthritis there are many soluble mediators that function together to create an inflammatory environment ultimately responsible for the synovial pannus formation and subsequent joint destruction. One such group of soluble mediators present in the peripheral blood and synovial fluid of rheumatoid arthritis patients are soluble adhesion molecules. Soluble adhesion molecules are commonly formed as the result of cell surface adhesion molecule shedding due to cell stimulation, but may also be the result of de novo synthesis of truncated soluble forms of adhesion molecules.[12] Synovial membrane becomes hyperplastic, there is an increased number of both synoviocytes and is infilterated with immune and inflammatory cells particularly macrophages, B and T-lymhocytes, plasma cells and dendritic cells and increased levels of cytokines are present.[13] Autoreactivity also plays a major role in the pathogenesis.The major RA-relevant autoantigens compromise Binding immunoglobulin protein (BiP), citrulline, Heterogenous Nuclear Ribonucleoprotein-A2 (hnRNP), p205, IgG, collagen and the shared HLA-DR epitope. The massive influx of T cells into the arthritic joint is accompanied by the anergization of over 90% of T cells. RA affected immune system is not able to completely downregulate the inflammation and the local tissue damage/repair.[14]

Harris[15, 16] and Harris et al [17] showed that inner ear can generate a local immune response after either lolcal or systemic immunization of antigen. These immune responses depend on the presence of an intact endolymphatic sac. Cells that mediate the labrinthitis enter the scala tympani via the spiral modiolar vein. The ensuing labryinthitis results in physiologic dysfunction, loss of sensory cells and ultimately fibrosis and osteoneogenesis within the

cochlea. The incudo-malleolar and incudo-stapedial joints are synovial in type. These joints are affected by rheumatoid changes. Autoimmune injury to the ear can involve the auricle, external auditory canal, middle ear and the inner ear. When the inner ear is involved the condition is termed autoimmune inner ear disease (AIED).

The classic definition of Autoimmune Inner Ear Disease (AIED) as provided by McCabe[18] is that of rapidly progressive (over weeks to months) bilateral SNHL that responds to the administration of immunosuppressive agents.

In left ear, in our study, insignificant ($p>0.05$) change was observed in absolute peak latency of waves I, II and III of BAEP when the controls (group I) were compared with RA patients (group II). In latency of wave IV and wave V there was significant ($p<0.05$) increase when controls were compared with RA patients. The interpeak latencies of left ear in rheumatoid arthritis patients (group II) showed no significant ($p>0.05$) change when compared with controls. There was significant ($p<0.05$) change in amplitude of I-I_a in left ear when controls were compared with RA patients. There was an insignificant ($p>0.05$) change in amplitude of V-V_a when controls were compared with RA patients (group II).

In right ear, in our study, insignificant ($p>0.05$) change was observed in absolute peak latency of waves I, II, IV and V of BAEP when the controls (group I) were compared with RA patients (group II). In latency of wave III, there was significant ($p<0.05$) change when controls were compared with RA patients. There was no significant ($p>0.05$) change in interpeak latencies I-III, III-V and I-V when controls were compared with RA patients in right ear. There was no significant ($p>0.05$) change in amplitude of I-Ia and V-Va when controls were compared with RA patients in right ear.

Salvinelli et al found similar result of wave I latency in their study. They evaluated the prevalence and features of hearing impairment in 28 RA patients. Auditory brainstem responses (ABRs) were recorded using 105 dB click stimulation. There was statistically significant increase in the wave I latency of ABRs in RA patients compared to controls.[19]

Conclusion:

We can conclude that Rheumatoid Arthritis causes an increase in latencies of the waves of brainstem auditory evoked potentials. Thus, rheumatoid arthritis could interfere directly with neurotransmission in the auditory pathway or indirectly by altering certain processes that modulate brainstem auditory activity.

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