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Sensorineural hearing loss post use of Streptomycin in an abdominal tuberculosis patient

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ABSTRACT

Extrapulmonary tuberculosis involves 11-16% of all patients of tuberculosis out of which 3 to 4% belong to abdominal tuberculosis. Despite its known reported ototoxic effects, streptomycin is still in use today because it is the best and most effective aminoglycoside antibiotic against TB. In humans, the ototoxic effect of aminoglycosides is reported to be sensorineural hearing loss which is usually permanent as the cochlear hair cells do not regenerate. Here we report a case of sensorineural hearing loss developed post use of streptomycin in a 58 year old female abdominal tuberculosis patient.

INTRODUCTION

Abdominal tuberculosis is one of the most common types of extra-pulmonary tuberculosis, comprising of tuberculosis of gastrointestinal tract, peritoneum, omentum, mysentery and its lymph nodes and other abdominal organs such as liver, spleen and pancreas. The extrapulmonary tuberculosis involves 11-16% of all patients of tuberculosis out of which 3 to 4% belong to abdominal tuberculosis. [1] The diagnosis of abdominal TB is difficult to make owing to the non-specific presentation of symptoms and signs. Also, it can mimic many diseases and conditions such as malignancy, bacterial infectious disease, and inflammatory disease. [2]

Aminoglycoside antibiotics are the first ototoxic agents to highlight the problem of drug-induced hearing and vestibular loss. It has long been known that the major irreversible toxicity of aminoglycosides is ototoxicity. Aminoglycosides have variable cochleotoxicity and vestibulotoxicity. Among them, streptomycin and gentamicin are primarily vestibulotoxic, while amikacin, neomycin, dihydrostreptomycin, and kanamicin are primarily cochleotoxic.[3] Cochlear damage can lead to permanent hearing loss, while vestibular damage results in dizziness, ataxia, and/or nystagmus. Because it is possible to physiologically compensate for vestibular damage, cochleotoxicity is generally considered to be a far graver problem. In humans, the ototoxic effect of these aminoglycosides is reported as a sensorineural hearing loss, which is usually permanent as the cochlear hairs do not regenerate. This observation first came to light shortly after the discovery of streptomycin, the first antibacterial agent to be effectively used against TB. The ototoxic side effects of streptomycin gained attention, when a substantial number of TB patients under streptomycin were found to develop irreversible cochlear and vestibular dysfunction. De Lima et al. (2006) reported on high frequency sensorineural hearing loss in 75% of TB patients they evaluated in their study. [4] Despite its known reported ototoxic effects, streptomycin is still in use today because it is the best and most effective aminoglycoside antibiotic against TB.

Here we report a case of sensorineural hearing loss developed post use of streptomycin in an abdominal tuberculosis patient.

CASE PRESENTATION

A 58 year old female admitted in the emergency with complaints of nausea, vomiting, generalized weakness and ataxia for last 13-15 days. Three months back she had presented with abdominal pain, distension and swelling in the left leg. Whole abdomen ultrasonography (USG) conferred 7 cm left adnexal space occupying lesion (SOL) and 6 cm right adnexal SOL. Venous Doppler study of bilateral lower limbs and pelvis showed deep venous thrombosis in external iliac vein, common femoral

vein and superficial femoral vein on left side. Extensive pelvic and bilateral inguinal lymphadenopathy was inferred. Whole abdomen CT showed extensive retroperitoneal and bilateral pelvic as well as inguinal adenopathy. Left pelvic vessels were found compressed with venous outflow compromise, leading to left leg swelling and edema. Sapheno-femoral junction was found dilated. CEA, CA19-9, CA125, APTT, PT and INR were within normal limits. Treatment was started with enoxaparin 60mg BD. She was advised adnexal mass evaluation with blood test with tumour markers which were found normal. Inj Dalteparin sodium 11,000 IU once daily was recommended subcutaneously for one month followed by 8000IU once daily from 2nd to the 6th month. Biopsy was taken from the lymph node which was found insufficient. CT guided biopsy was performed followed by small biopsies of the left pelvic lymph node. Reports conferred necrotizing lymphadenitis with presence of few acid fast bacilli. She was started on anti-tubercular regimen consisting of 1 tab/day ethambutol hydrochloride 800 mg and isoniazid 300 mg, 2 tabs/day pyrazinamide 750 mg and 1 cap/day rifampicin 450 mg. After 1 week, she developed flu-like syndrome and skin manifestations. Rifampicin was discontinued on account of the patient being allergic to it. Inj Streptomycin in the dose of 15mg/kg was added to the above regimen. This regimen continued for two months before the patient was admitted with complaints of nausea, severe vomiting, weakness, ataxia for last 13-15 days.

The videonystagmography of vestibular function was done. Patient exhibited normal saccade system as all values were within normal range. No abnormal spontaneous nystagmus beats were observed. No abnormal nystagmus in the gaze system was observed. Smooth pursuit test, also known as pendulum tracking test showed 86% gain on the left and 88% gain on the right with side difference zero which was normal. Patient exhibited normal response in optokinetic test. The caloric test showed 100% canal paresis on the right side on estimation of nystagmus intensity by speed of slow phase thus suggesting a right peripheral vestibular lesion i.e. poor gain of vestibulo ocular reflex at low frequencies of vestibular stimulation in the right lateral semicircular canals. The non-caloric and occulomotor tests were normal. No abnormality in the central vestibulo ocular system was observed. Evidence of poor vestibulo ocular reflex in all six semicircular canals was observed in video head impulse test (VHIT) suggesting a bilateral vestibulopathy at high frequencies of vestibular stimulation.

Cervical vestibular evoked myogenic potential (VEMP) test showed mild abnormal vestibulo-collic reflex and saccular function on the right. However patient had perforation in the right ear due to which adequate amount of sound may not have reached the oval window on the right side causing a comparatively lesser stimulation of the right saccule. This hypoactive response on the right side was attributed to the conductive deafness in this ear rather than a saccular lesion. The visual vertical test was within normal limits with normal otolithic functions. Tone audiogram suggested moderate to profound degree of sensorineural hearing loss in the right ear and mild to severe degree of sensorineural hearing loss in the left one.

Streptomycin was discontinued owing to its probable propensity to cause ototoxicity. Patient was continued on the other drugs of the regimen

This adverse event was reported under Pharmacovigilance Programme of India (PvPI) [Report ID: 2017-22841]. Naranjo's algorithm [5] gave a score of 8 which categorizes the causality of the event as "probable". No rechallenge was attempted by the physician, after the withdrawal of the medication. Assessment of severity based on Hartwig and Seigel's severity assessment scale [6], conferred it to be a "severe" adverse drug reaction with a grade of level 6.

The temporal relationship between streptomycin and this incidence of sensorineural hearing loss was thus established.

DISCUSSION

Aminoglycosides are a well-known and successful class of antibiotics. The initial isolation of streptomycin from *Streptomyces griseus* provided the long-sought treatment for tuberculosis and an effective antibiotic against gram-negative bacteria. Ototoxicity refers to medication-caused auditory and/or vestibular system dysfunction those results in hearing loss or disequilibrium. In addition to their potent antimicrobial efficacy, all aminoglycosides can cause toxic side effects to the kidneys and inner ear. While damage inflicted by aminoglycosides on the kidney is usually reversible, damage to the inner ear is permanent. Within the inner ear, streptomycin preferably damages the vestibular organ. Modification of streptomycin to dihydrostreptomycin, however, resulted in a shift of ototoxic damage from the vestibular organ to the cochlea. Ototoxic side effects occur within days or weeks after systemic application and are often bilateral in presentation.[7] Screening, identification and monitoring for ototoxic hearing loss allows one to counsel patients and their families, to possibly stop ototoxic drugs or to adjust the treatment regimen, to provide and to rehabilitate hearing.[8] Developing countries often lack resources to implement effective screening and monitoring for ototoxicity; research needs to be directed at practical and cost-effective screening tools. [9]

Symptoms of cochleotoxicity include hearing loss and/or tinnitus, while those of vestibulotoxicity consist of disequilibrium and dizziness. Unfortunately, these symptoms usually remain undetected till the acute phase of severe infection and diagnosis is thus delayed. The vestibular component of balance is located in the vestibule, located near the cochlea, within the inner ear. Movement of fluid through the three semi-circular canals, as well as the maculae of the saccule and utricle, stimulates hair cells which in turn create signals in the vestibular nerve. This nerve runs with the cochlear nerve as the vestibulo-cochlear or eighth cranial nerve, to the brainstem and from there to the cortex, where signals are interpreted as movement and acceleration. The injectable anti-TB drugs selectively destroy the basal hair cells of the basilar membrane, which are required for high frequency hearing. This occurs by reacting with transition metal ions to produce reactive oxygen species which in turn damages the cells through an oxidative process. [10] Hearing loss in those treated with aminoglycosides and polypeptides usually starts with high-frequency loss initially, with later progression to the frequencies more associated with speech communication. Damage is usually permanent. These drugs can also destroy the vestibular hair cells.

The present case described a patient reporting with abdominal pain, distension and swelling in the left leg. A battery of diagnostic investigations corroborated it to be abdominal tuberculosis. The patient was placed on ethambutol hydrochloride, isoniazid, rifampicin and pyrazinamide. Owing to the patient's allergic tendency towards rifampicin, the very drug was discontinued and the patient was placed on injection

streptomycin in place of rifampicin in the above regimen thereafter. Months after the start of this new regimen, patient reported with the symptoms of acute vestibulotoxicity.

Videonystagmography (VNG) of vestibular function was performed in this patient. VNG is a technology for testing inner ear and central motor functions as a part of vestibular assessment. VNG involves the use of infrared goggles to trace eye movements during visual stimulation and positional changes. [11] It is a series of tests used to determine the causes of a patient's dizziness or balance disorders. As a part of VNG, our patient was subjected to saccade test. This test evaluates the saccade system which is one of the faculties for gaze stabilization function of the vestibular system. Under ideal conditions of the visual and vestibular systems, the eyes should be able to accomplish this by one single fast eye movement with an exact, very accurate and very precise refixation of the eyes on the visual target as the target jumps from one point in the visual field to the other. Latency, velocity and precision of this eye movement are measured by this test which was within normal range in our patient's case. She was subjected to spontaneous nystagmus test which records any eye movement with eyes open in complete darkness as well as with optic fixation both in horizontal as well as with vertical axis. No abnormal nystagmus beats were observed in our patient. In the gaze nystagmus test, the VNG apparatus documents eye movements while the eyes fixate the gaze at different fixed points in the visual fields. No abnormal nystagmus in any of the eye positions were reported in this case. In the smooth pursuit test (also known as Pendulum Tracking Test), the VNG system measures the gain of the left cycle (movement from end of rightward movement of the target to end of leftward movement of the target) and that of the right cycle (movement from end of leftward movement of the target to end of rightward movement of target) and calculates the difference in gain between the two gains. In normal case, the gain should be above 90% and the side difference less than 10. Values above 80% are usually considered normal. Our patient showed 86% gain on left and 88% gain on the right with side difference 0, which was normal. In the optokinetic test, the patient's ability of gaze stabilization is assessed when the entire visual field moves at different speeds in different directions. Movement of the complete visual field is expected to develop nystagmus beats such that there is no blurring of image movement on the retina. The velocity of the slow phase of the generated nystagmus is compared with the velocity of the projection patterns and the relation between them is calculated as gain. The gain should be ideally 100% indicating the velocity of the eye movement to be equal to the velocity at which the visual field is moving. However gain values above 75% are considered normal. Our patient exhibited average gain of 75% on the left and 80% on the right side, which confirms normal optokinetic system. In caloric test, the VNG apparatus evaluates the intensity of the nystagmus generated by a standard caloric stimulation of both ears. The nystagmus here generated is measured by speed of slow phase velocity (SPV) in degrees/sec as well as by culmination frequency in number of beats in 30 seconds when the nystagmus is more pronounced. The intensity of the nystagmus generated is calculated first while the recording of nystagmus is done without optic fixation and later with optic fixation and the change in the intensity of nystagmus in the period in between these two phases is calculated and documented as the fixation index. The percentage of canal paresis (normal range 0 to 20%) and the percentage of directional preponderance (normal range 0 to 30%) are also calculated. Fixation index is normally less than 50%. Our patient showed 100% canal paresis on the right side with other parameters in normal range suggesting severe right peripheral vestibular lesion. The cervical vestibular evoked myogenic potential (cVEMP) reported mild abnormality of vestibule-collic reflex and the saccular function on the right side. The VEMP evaluates the structural and functional integrity of the vestibule-collic reflex which comprises of the saccule, inferior vestibular nerve, lateral vestibular nucleus, median longitudinal fasciculus and the nucleus of accessory nerve (11th cranial nerve), accessory nerve and the nerve to sternomastoid. A defect in any one of them is liable to present abnormal VEMP findings, but it is usually the saccule that is defective in abnormality of the VEMP test. However, in this particular patient there was a perforation in the right ear due to which adequate amount of sound may not have reached the oval window on the right side causing a comparatively lesser stimulation of the right saccule. The hypoactive response on the right side hence appears to be due to the conductive deafness in this ear rather than a saccular lesion in the right side.

The visual vertical test was performed to detect abnormal subjective tilt. In normal persons, the ability to perceive verticality is quite good which is dependent on input from visual, vestibular and somatosensory systems. It also depends on a functioning central nervous system. The otolithic organs in the vestibular system sense gravity. Both the utricle and saccule contribute to the sense of verticality. After injury to the otoliths, or to the nerve that transmits impulses from the otoliths and other parts the ear to the brain, judgment of vertical may be altered. However, our patient exhibited normal otolithic functions. Pure tone audiometry is the standard behavioral assessment used to identify hearing threshold levels of an individual, enabling determination of the degree, type and configuration of a hearing loss. The results of pure tone audiometry are recorded on a chart or form called an audiogram. Tone audiogram suggested moderate to profound degree of sensorineural hearing loss in the right ear and mild to severe degree of sensorineural hearing loss in the left one.

Aminoglycosides appear to generate free radicals within the inner ear, with subsequent permanent damage to sensory cells and neurons, resulting in permanent hearing loss. Histopathologic studies have shown that outer hair cells are more sensitive to ototoxic injury than are inner hair cells. [3] In animal models, histological findings resemble apoptotic cell death rather than necrosis. In cases of aminoglycoside ototoxicity, a variety of free-radical species, including both oxygen and nitrogen free-radical species were detected in the inner ears, which are believed to initiate the apoptotic cascade. There appears to be a lack of association between aminoglycoside doses or serum concentration and vestibulotoxicity, so even if levels are normal, damage may still occur.

CONCLUSION

Significant proportion of patients being undergoing tuberculosis treatment is developing hearing loss, a significant adverse event that can impair their quality of life. The continued use of aminoglycosides has aroused a desire to understand the mechanism of ototoxicity and to develop strategies to reduce the ototoxic potential of these drugs. Clinicians must carry out a risk assessment whereby the risk of hearing loss is weighed against the risk of treatment failure from stopping or not using such ototoxic drugs. It is highly recommended that the patients and their families are kept aware of the ototoxic potential of these drugs.

More research is needed to allow comparisons between patients, and interventions to reduce the incidence of drug-induced hearing loss need further investigation. Focused pharmacovigilance and proper sensitization regarding potential adverse effects should be warranted.

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