Case Report

Sensorineural hearing loss in Bartter syndrome

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ABSTRACT

Background: Bartter syndrome is a rare inherited case characterized by autosomal recessive and has few different types. Diagnosis is established by laboratory findings, namely hypokalemic metabolic alkalosis, and normotensive. Hearing loss indicates Bartter syndrome type IV. **Purpose:** To report a case of Bartter syndrome with delayed speech. **Case report:** A seven years old girl with delayed speech and recurrent hypokalemia was referred to the Otolaryngology Head and Neck Surgery Department, Dr. Cipto Mangunkusumo Hospital, in order to evaluate the hearing level and treatment needed. Based on the Otoacoustic Emission (OAE), Brainstem Evoked Response Audiometry (BERA), and Auditory State Steady Response (ASSR), the diagnosis was profound bilateral sensorineural hearing loss and proceeded with hearing aid and also speech occupational therapy. **Clinical question:** Is there a relationship between Bartter syndrome and the incidence of hearing loss? **Review method:** Literature review through PubMed, Cochrane, and EBSCO, using keywords such as the impacts of Bartter syndrome on hearing loss, and sensorineural hearing loss in Bartter syndrome case. **Result:** Following screening of double publication and based on clinical questions over the past five years, only one relevant literature was found. **Conclusion:** Audiological assessment should be done in all Bartter syndrome's cases. Early intervention and timely audiological rehabilitation could improve the quality of life of such children.

Keywords: Bartter syndrome, sensorineural hearing loss.

ABSTRAK

Latar belakang: *Sindrom Bartter merupakan kasus jarang, yang diturunkan secara autosomal resesif dan terdiri atas beberapa tipe. Diagnosis ditegakkan berdasarkan temuan laboratorium yaitu hipokalemi, alkalosis metabolik dan tekanan darah normal. Adanya gangguan pendengaran merupakan sindrom Bartter tipe IV.* ***Tujuan:*** *melaporkan kasus Sindrom Bartter dengan keterlambatan bicara.* ***Kasus:*** *Dilaporkan satu kasus anak perempuan berusia tujuh tahun dengan gangguan bicara dan terdapat riwayat hipokalemia berulang yang dirujuk ke Departemen Telinga Hidung Tenggorok-Bedah Kepala Leher, Rumah Sakit Cipto Mangunkusumo untuk menilai ambang dengar serta tatalaksana selanjutnya. Berdasarkan hasil pemeriksaan* Otoacoustic Emission (OAE)*,* Brainstem Evoked Response Audiometry (BERA) *dan* Auditory State Steady Response (ASSR) *ditemukan tuli sensorineural sangat berat bilateral yang kemudian ditatalaksana dengan pemakaian Alat Bantu Dengar dan terapi wicara dan okupasi.* ***Pertanyaan klinis:*** *Apakah ada hubungan antara sindroma Bartter dengan insidens gangguan pendengaran?* ***Telaah literatur:*** *Pencarian literatur melalui, PubMed, Cochrane dan EBSCO dengan kata kunci hubungan gangguan pendengaran pada sindrom Bartter, gangguan pendengaran sensorineural pada sindrom Bartter.* ***Hasil:*** *Setelah dilakukan skrining yakni publikasi ganda dan sesuai pertanyaan klinis dari lima tahun terakhir hanya didapatkan satu literatur yang relevan.* ***Kesimpulan:*** *Pemeriksaan pendengaran harus dilakukan pada kasus dengan sindrom Bartter. Intervensi dini dan rehabilitasi audiologi yang tepat waktu dapat meningkatkan kualitas hidup anak dengan sindrom Bartter.*

Kata kunci: *sindroma Bartter, tuli sensorineural.*

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INTRODUCTION

Frederic C. Bartter in 1962 reported Bartter's syndrome (BS), a condition that results defects in excretion in the renal tubules and reabsorption of electrolytes. Typical clinical features of Bartter's syndrome include impaired renal excretion, hypokalemic metabolic alkalosis, hyperaldosteronism, normotension hyperreninemia. In 1995 a new type of BS in a family in Southern Israel was reported which combines features of BS and sensorineural hearing loss, known as type IV BS.[1,2]

Bartter's syndrome type IV is associated with an autosomal recessive mutation in the BSND gene, which is located on chromosome 1p31 and encodes the Barttin protein. The Barttin protein is an essential chloride channels subunit of the *ClC-Ka* and *ClC-Kb* in the tubular segment extending from the thick segment of the ascending Henle arch to the cortical collectivus ducts of the kidneys, whereas in the inner ear it is found in potassium-secreted epithelial cells. With regard to hearing loss, recent studies have shown that sensorineural hearing loss in infantile BS is caused by loss of outer hair cells in the cochlea and decreased mechanoelectrical transduction currents of internal hair cells due to decreased endocochlear potential.[1–3] Disorders of the outer hair cells as thoroughly are major factor of deafness in type IV Bartter's Syndrome.[4]

Neonates can be born with polyhydramnios, prematurity and poor growth. One variant of antenatal BS has symptoms of transient hyperkalemia and acidosis. Older children may experience symptoms of chronic hypokalemia such as constipation, muscle cramps, nocturia, vomiting, weakness and poor growth. [2,3] Patients with BS are often diagnosed in a differential manner with Gitelman Syndrome (GS) which tends to have milder symptoms. Gitelman syndrome is caused by a parallel inactivation mutation in the SLC12A3 gene coding for the thiazide-sensitive sodium chloride co-transporter (NCC) in DCT. [1–3,5,6]

Bartter's syndrome is rare and its prevalence were varies. In the United States, the exact incidence is unknown but in Costa Rica, the frequency of neonatal Bartter syndrome is about 1.2 cases per 100,000 live births and higher in preterm births. In Kuwait, the prevalence in the general population is 1.7 cases per 100,000 people while in Sweden the incidence is 1.2 cases per 1 million.[5] This report aims to provide better understanding of speech delay due to sensorineural hearing loss in the presence of electrolyte disturbances.

CASE REPORT

A seven year old girl was consulted from the Paediatric's Nephrology Division with delayed speech. The patient was only able to say one or two meaningful words and did not respond when being called nor with loud sounds stimulation. The symptoms were recognized when she was already three years old. She then proceeded with routine speech therapy for one year periods but unfortunately the resulting speech development was not significant. The patient had history of seizures and weakness and often complained of nausea, vomiting, and excessive urinating. She also had general weakness and had been

experiencing muscle stiffness since 2015. Blood tests showed low potassium level that did not improve despite of therapy.

History of birth was spontaneous with gestational age of 40 weeks, birth weight was 3800 grams with no history of asphyxia and oxygen supplementation, and also no history of jaundice. She also had delayed motoric development, with history of head lifting at 6 months and walking at 4 years of age. Head circumference was measured 48 cm (microcephaly) with bilateral protruding ears.

Laboratory examination showed anaemia (Hb 10.1 g / dL) and metabolic alkalosis (pH 7.511, HCO3 33.2 mmol/L, base excess 10 mmol/L) with abnormal urinalysis (erythrocyte 12-14 / TBSA, blood +3). Serial laboratory results showed recurrent low potassium level at 2.67 mEq / L - 3.2 mEq / L. The results of renal ultrasound examination showed the kidneys and urinary tract were within normal limits. The Intelligence Quotient (IQ) test could not be performed because the patient was not cooperative during the examination.

Audiological examination performed at the ORL-HNS Audiology Division, Otolaryngology-HNS Departement, Cipto Mangunkusumo Hospital showed disrupted emission outer hair cells in both ears. The results of ABR examination with click stimulus showed that the V wave was detected at 70 dB, while 500 Hz Tone burst stimulus, the V wave was not detected up to 80 dB in both ears (Figure 1). ASSR examination results showed bilateral severe sensorineural hearing loss, in the right ear 77.5 dB and 87.5 dB in the left ear. (Figure 2)

The patient was then suggested using hearing aids, commencing speech and occupation therapy. Genetic testing was also planned. Furthermore, the parents were also coached about proper parenting and the importance of education for patient's development. In the latest evaluation, the child had used a hearing aid device on one ear but had not shown any significant development in hearing and speaking because he could not attend speech therapy due to the Covid-19 pandemic situation.

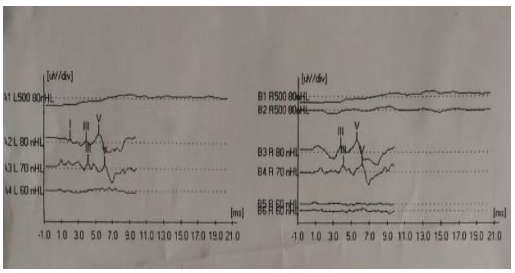

Figure 1. ABR result

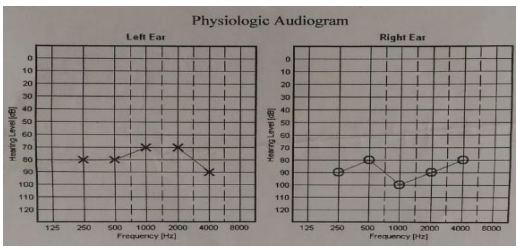

Figure 2. ASSR result

CLINICAL QUESTION

Is there a relationship between Bartter syndrome and the incidence of hearing loss?

REVIEW METHODS

The literature search was conducted on Cochrane, PubMed, and Google Scholar based on clinical questions: "Is there a relationship between Bartter's syndrome and the incidence of hearing loss?" in the last five years periods. Keywords used in search method were "hearing loss in Bartter's syndrome" and "sensorineural hearing loss in Bartter's syndrome". Ten studies were obtained and then proceeded with screening for duplication and abstract reading. Two relevant literatures were obtained. The search was extended to last ten years but there was no other relevant study obtained.

RESULT

Case report by Kumar et al[6] was the only study we found relevant with our clinical question. This study described 2 years old patient with Bartter syndrome and delayed speech. This child could not even say mono-syllabic words. No other family member had similar illness and there was no history of parental consanguinity in the patient's family. On audiometric assessment 120db tones of various frequencies were introduced by head phone which did not elicit response including eye blink or head turning, suggesting severe to profound hearing loss. Appraisal was done using guidance from Roever and Ocke Reis[7] and presented in table 1.

Table 1. Study Appraisal

Did the study address a clearly focused question/issue?	yes
Is the study design appropriate for answering the research question?	no
Was the study well defined protocol?	no
Are both the setting and the subject's representative with regard to the population to which the findings will be referred?	yes
Is the researcher's perspective clearly described and taken into account?	yes
Are the methods for collecting data clearly described?	no
Are the methods for analyzing the data likely to be valid and reliable? Are quality control measures used?	no
Was the analysis repeated by more than one researcher to ensure reliability?	no
Are the results credible, and if so, are they relevant for practice? Are results easy to understand?	no
It was clinically relevant outcomes?	yes
Are the conclusions drawn justified by the results?	yes
Are the findings of the study transferable to other settings?	yes

DISCUSSION

The cause of Bartter syndrome is a disruption in the sodium-potassium-chloride co-transporter (NKCC2) or the renal outer medullary K channel (ROMK) affecting the transport of sodium, potassium and chloride in the thick segments of the ascending branch of the Henle circle affecting the metabolism of reabsorbed sodium and potassium released.[2]

There are five types of Bartter's syndrome but those related to hearing loss are type IV, consisting of two subtypes, namely types IVa and IVb. Mutation of the BSND gene in type IVa causes interference with the Barttin protein, whereas in type IVb the CLCNKA and CLCNKB genes affect the synthesis of CLC-Ka and CLC-Kb proteins.[2,6]

Mutations in the BSND gene cause type IVa BS and result in impairment of Barttin insertion in the plasma membrane of CLC-Kb and CLC-Ka channels in the Henle's loop as well as in the inner ear, which interfere with epithelial salt transport. On the contrary, type IVb is a digenic disorder with mutations in both CLCNKA and CLCNKB genes, which can lead to impairment in the functioning of two chloride channels and as a result, severe salt wasting and deafness.[2]

Barttin protein is an essential subunit of the ClC-Ka and ClC-Kb chloride channels and is expressed in tubular segments spanning from the thick ascending limb to cortical collecting ducts in the kidney, whereas in

the inner ear, it is expressed in potassium-secreting epithelial cells.[8]

The sensory function of the inner ear becomes impaired in type IVa and IVb BS. In type IVa, Barttin mutations impair potassium secretion in the stria vascularis and the vestibular labyrinth, whereas in type IVb mutations occur in both chloride channels impairing their normal function in the inner ear.[2]

With regard to hearing loss, the latest studies showed that sensorineural hearing loss in infantile BS is caused by the loss of outer hair cells and by a decrease in the mechanoelectrical transduction current of inner hair cells due to a drop in the endocochlear potential.[6]

Mutations that only occur in the CLC-Kb subunit, such as those in Bartter's syndrome type III, do not result in sensorineural hearing loss. A recent experimental study by Nomura et al., quoted by Cunha et al.[2] revealed that the retention of mutant forms of barttin in the ER is one of the underlying mechanisms responsible for the development of type IVa BS. These investigators reported that the treatment of MDCK cells with 17-allylamino-17-demethoxygeldanamycin (17-AAG), an Hsp90 inhibitor, enhanced the plasma membrane expression of mutant barttin (R8L and G47R), generating hypokalemia, metabolic alkalosis, and hearing loss.[2]

Bartter syndrome is characterized by hypercalciuria and nephrocalcinosis, and may be associated with maternal polyhydramnios, premature birth and low birth weight, and early onset of symptoms, including vomiting, polydipsia, dehydration with hypotension, muscle weakness, paresthesias, and developmental delay.[5] Some infants can have an appearance typical of BS, including a prominent forehead, triangular face with drooping mouth, large eyes, and pinnae.[2,6]

Here, it is reported a case of seven year old girl with Bartter syndrome. Our patient has several clinical features that were in accordance with Bartter syndrome, namely seizures, muscles weakness, growth impairment, speech deficiency, sensorineural hearing loss, intellectual impairment, and also physical phenotypic features including protruding ear. All these clinical features, according to Fulchiero et al.[1] are found in the majority of patients with type IV Bartter's syndrome. The patient also had repeated hypokalemia and metabolic alkalosis, which was also consistent with this syndrome.[1] This case was similar with the rare case presented by Kumar et al.[6]

The results of OAE, BERA and ASSR examinations showed bilateral severe sensorineural hearing loss. Cunha et al.[2] suggested that sensorineural hearing loss associated with Bartter syndrome type IV was caused by defects in the Barttin subunits of the ClC-Ka and CIC-Kb channels. Genetic testing had not been performed on this patient but the clinical presentation was in accordance with type IV Bartter syndrome. Behavioral and emotional disorders in patients could be a form of emotional expression that could not be conveyed verbally because of speech impediments.

According to research conducted by Kontorinis G et al.[9], sensorineural deafness in patients with type IV Bartter syndrome is a congenital abnormality, bilateral and not associated with inner ear malformations. Management of hearing loss in Bartter syndrome should be carried out as a comprehensive diagnostic evaluation covering all aspects of development. This includes examining speech and language in addition to nonlinguistic areas (general and manual motor skills, cognitive development. and intellectual) and social interactions. But most importantly, every child with a speech delay disorder must first be tested or screened for hearing loss before carrying out the tests that have been mentioned. The hearing test is very important, growth with hearing loss could risk of speech impairment in children.[6,10,11]

This was what happened in our patient. She previously had undergone physiotherapy and speech therapy for 3 years, but because there was no significant progress, she was then referred for a hearing examination and was found to have severe sensorineural hearing loss. The golden period of children's brain development takes place in the first 2 years of life. If hearing loss was not managed in this golden period, no sensory input in the form of sound could make the child able to talk, or develop cognitive, personal and social function.

After about one year using unilateral hearing aid, patient can now babbling but unfortunately because of current pandemic situation, she could not attend speech and occupation therapy which might escalate the result.

Vomiting, polydipsia, polyurea, dehydration and developmental delay could be a symptom of metabolic syndromes in children, such as Bartter syndrome. Audiological assessment should be performed in all cases of Bartter syndrome. Early intervention and timely audiological rehabilitation could improve the quality of life of such children.

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