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Case Report

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**Familial Branchial Fistula which was regarded  
as Branchio-Oto-Renal Syndrome**

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**ABSTRACT**

Branchio-oto-renal (BOR) syndrome is a rare disorder first reported by Melnick et al. in 1975. We describe two siblings with branchial fistulae who seemed to manifest BOR syndrome. When otolaryngologists treat patient with fistulae and auricular abnormalities, they should carry out a complete examination of hearing ability and try to discover renal diseases in cooperation with urologists. If they examine only the ear, nose and throat, they may overlook serious renal diseases in routine clinical practice.

**INTRODUCTION**

Congenital branchial fistula, a remnant of embryonal branchia, is frequently observed in routine clinical practice. Branchio-oto-renal (BOR) syndrome is a rare disorder with multiple branchial cervical fistulae, auricular abnormality, hearing impairment and renal deformity as reported by Melnick et al. in 1975<sup>1)</sup>. Reported cases of this syndrome have gradually increased since their report. We describe two siblings with branchial fistulae who seemed to manifest BOR syndrome.

**CASE REPORT**

**Case 1:** A 10-year-old boy

**Chief complaint:** Branchial fistula and related exudate in the left side of the neck.

**Past history:** The patient had been treated in the Department of Pediatrics for tics and short stature since March 1994.

**Present illness:** The patient had suffered from branchial fistula and continuous exudate from of the

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**Key words :** BOR syndrome, branchial fistula, hearing disorder, renal disease, Melnick-Fraser synd.

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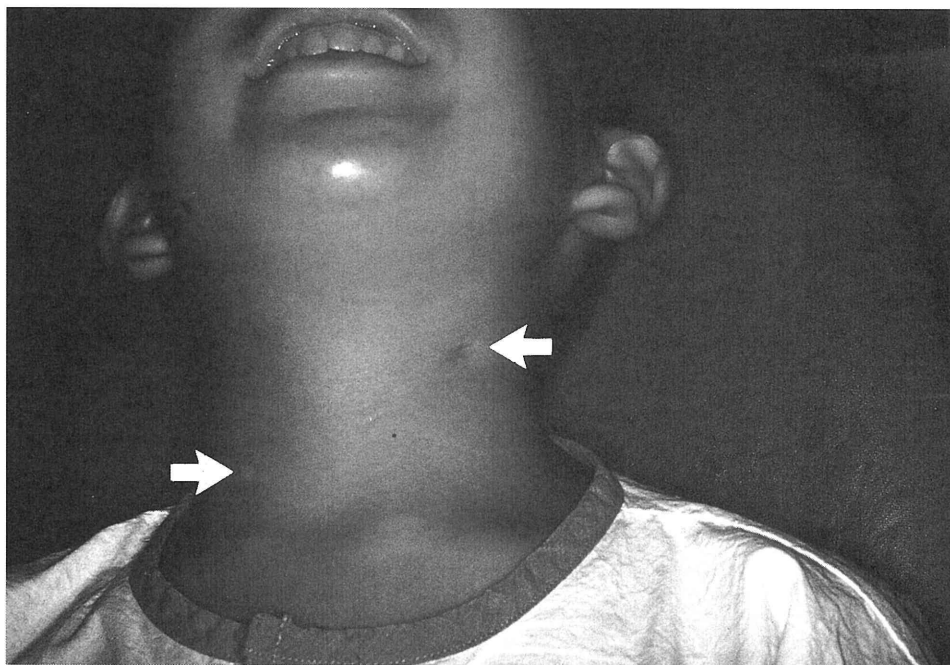


Fig. 1 Case 1 A 10-year-old boy

left side of the neck since birth. He was referred from the department of pediatrics to our department in March 1995 and admitted for excision of the branchial fistula in August 1995.

**Findings on admission:** The patient's general appearance was good except for his poor physical development (body weight: 28.5 kg, height: 127.3 cm). A fistula with clear exudate were observed at the level of the upper margin of the thyroid cartilage on the anterior margin of the left sternocleidomastoid muscle. A smooth-surfaced round skin mass about 0.5 cm in diameter was detected near the cricoid cartilage on the anterior margin of the right sternocleidomastoid muscle. He also had a left preauricular pit and had normal shaped auricle (Fig. 1).

**Examination results:** In spite of normal hearing ability, the patient showed no stapedial reflex in the acoustic impedance audiometric test. Although the results of urinalysis were normal, left ureteral deformity was revealed by intravenous pyelography. The left kidney showed mild hydronephrosis due to the ureteral stricture caused by entanglement of various vessels entangled with the left ureter (Fig. 2).

**Operative findings:** On August 9, 1995, excision of the left branchial fistula was performed under general anesthesia. The branchial fistula was approximately 3 mm in diameter at its orifice, tapering off distally. The fistula had two fine branches midway which spread in an anterior direction. The main fistula extended medially in a posterosuperior direction, from the anterior margin of the sternocleidomastoid muscle to the left wall of the mesopharynx via the posteroinferior part of the stylohyoid muscle. The approximately 3 cm main fistula was ligated and resected at the level of the stylohyoid muscle.

**Histopathological findings:** The fistula was lined with squamous epithelia and a number of lymphoid tissues had accumulated in the subepithelial connective tissue (Fig. 3).

#### Case 2: A five-year-old girl

**Chief complaint:** Bilateral branchial cervical fistulae and related exudate in the neck.

**Past history:** Not remarkable.

**Present illness:** The patient had been suffering from continuous exudate from bilateral cervical fistulae and binaural fistulae since birth. This patient was the younger sister of the first patient and



Fig. 2 Case 1 Intravenous pyelography after 15 minutes

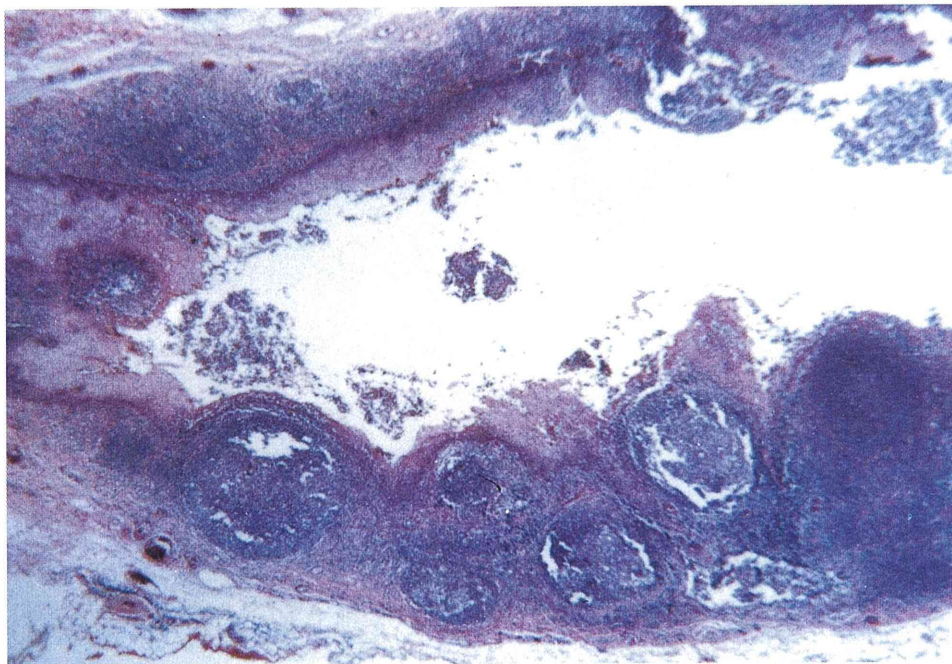


Fig. 3 Case 1 Hematoxylin-eosin stain  $\times 4$

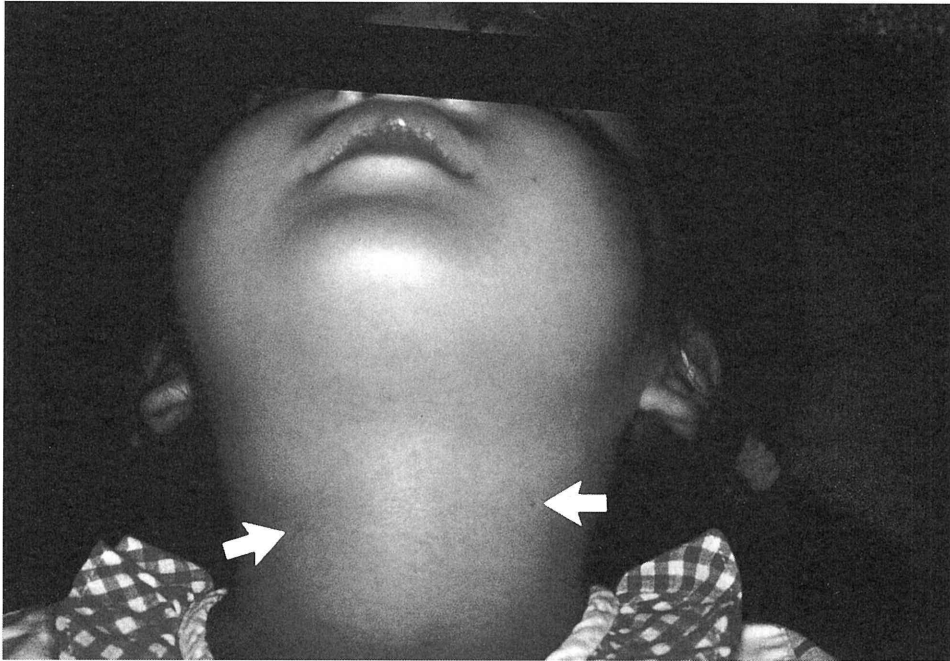


Fig. 4 Case 2 A 5-year-old girl

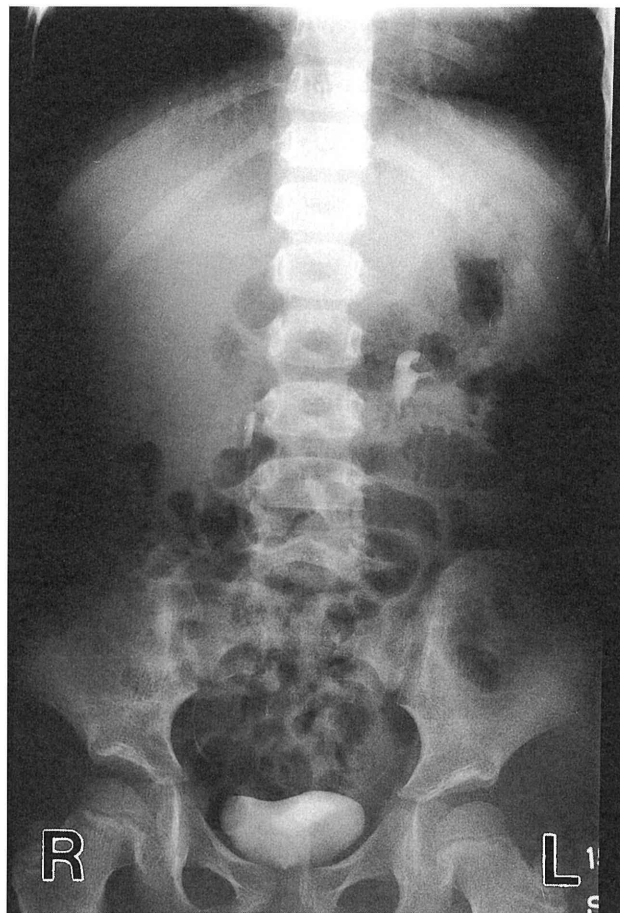


Fig. 5 Case 2 Intravenous pyelography after 15 minutes

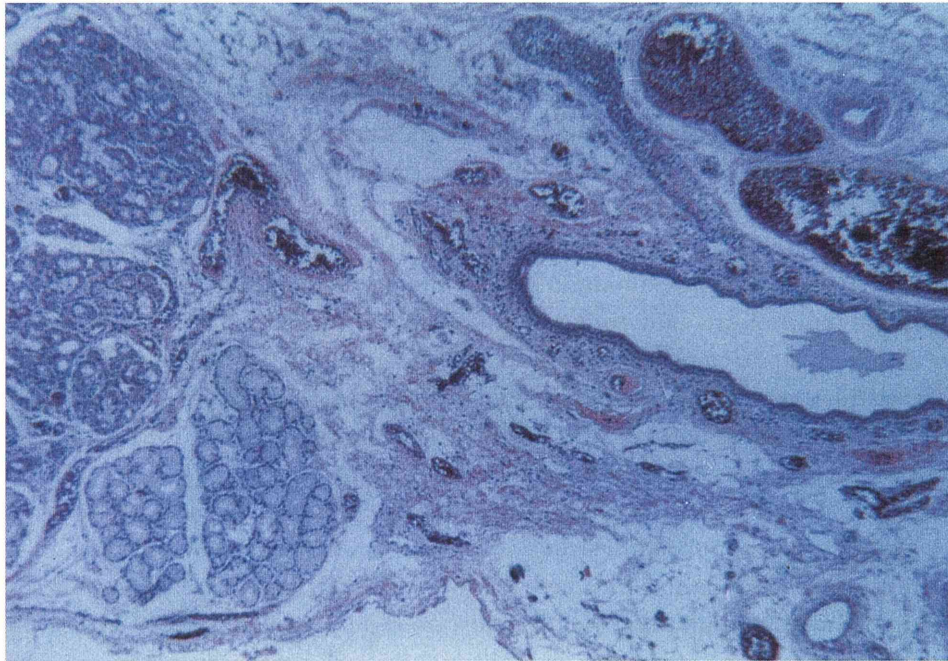


Fig. 6 Case 2 Hematoxylin-eosin stain  $\times 2$

both of them first visited our department in March 1995.

**Findings on admission:** She weighed 15 kg with a 100-cm frame and had a good general appearance. The fistulae and their clear exudate were observed at approximately the mid-levels of the anterior margins of the bilateral sternocleidomastoid muscles. The left lesion was approximately 1 cm higher than the right lesion. In addition to these abnormalities, the patient suffered from bilateral preauricular pits but had normal shaped auricle (Fig. 4).

**Examination results:** In spite of normal hearing ability, there was no stapedial reflex on the acoustic impedance audiometric test. Although the results of urinalysis were normal, intravenous pyelography disclosed ill-defined kidney calices, especially on the right side, probably due to horseshoe kidneys (Fig. 5).

**Operative findings:** On August 9th 1995, the bilateral cervical fistulae were excised under general anesthesia. The left fistula had a maximum diameter of 2 mm. Several funicular branches had developed midway along the fistula. The left fistula was 10 mm in length and extended toward the anterior cervical fascia. The right fistula, which was 13 mm in length and had a diameter of over 3 mm, spread toward the anterior part of the sternocleidomastoid muscle and reached the external margin of the anterior cervical muscles. The distal end of the fistula was tangled and coiled.

**Histopathological findings:** Salivary glands and their channels were observed along both fistulae (Fig. 6).

**Family history:** Their father, who has a left cervical fistula, has showed no symptoms of kidney or other diseases.

## DISCUSSION

There have been 83 reported cases of lateral cervical fistula in Japan, 44 males and 38 females. Of the 83, 36 patients had a familial background. Bilateral lesions were detected in 49 cases and unilateral lesions were detected in 22 cases. The incidence of right cervical fistula was slightly higher than that of left lesions.

Salivary gland tissue was detected in 3 of these cases. The operative and histopathological findings of the second case reported in this study showed a definite aberration of the salivary gland entering into the lateral cervical fistula. Generally the major salivary glands originate in the epithelium of the primordial oral cavity and the sublingual and minor salivary glands remain in the oral cavity. The parotid gland and submandibular gland move toward their specified positions. According to Youngs et al.<sup>2)</sup>, unlike normal salivary glands, heterotopic salivary glands developing in the anterior region of neck originate in the branchia. The findings obtained in the second case supported their hypothesis.

The histologically typical findings obtained in the first case including either squamous epithelium or columnar ciliated epithelium and wall composed of a number of lymphoid tissues with germ centers, referred to as lymphoepithelial cyst, and characteristic of this disease. The circumference of the fistula observed in the first case was irregular, probably because of frequent inflammation, while the circumference of noninflammatory fistulae is nearly elliptical in shape. Inflammation may induce the proliferation of germ centers of lymphoid tissues.

Some reported cases of branchial fistulae seem to include cases of BOR syndrome because of their complications with auricular abnormalities such as hearing disorders, aural fistulae and microtia. BOR syndrome is an autosomal dominant hereditary disease. Of seven BOR cases reported in Japan<sup>3~8)</sup> five showed familial abnormalities including hearing disorders and auricular deformities. As for the two patients reported here, no specific findings suggesting kidney diseases were obtained until they underwent thorough preoperative urological examinations (Table 1).

Researchers have pointed out various etiological factors related to BOR syndrome. According to the conventional theory, there is a certain histological relation between the internal ear and the kidney which can be confirmed by common susceptibility to toxic substances including cisplatin and the high incidence of common syndromes including Alport's syndrome. The results of animal experiments have also suggested the existence of a common antigen existing in cochlear vessels and kidney glomerules.

The internal ear and kidney develop during the same embryonal period. The optic pit, the primordium of the internal ear, is formed in the fourth embryonal week. The pronephros also appears in this period. The mesonephros, which functions as a transient kidney before the formation of permanent kidneys appears at the end of the fourth embryonal week, corresponding with the period during which the first of three pairs of branchial arches become distinctly protuberant. In the fifth embryonal week, the second and third branchial arches develop over the fourth branchial arch and the ectodermal depression called the cervical sinus is formed. This phenomenon coincides with the development of the metanephros which is the precursor form of the permanent kidneys. Abnormalities are caused as a result of failures of the intercellular development process and space arrangement which are regulated by genetically programmed proteins existing on the cell surface. If proteins common to the development of both are impaired, they would probably cause differentiation typical of BOR syndrome.

Although in 1989 Haan et al.<sup>9)</sup> reported the inherent rearrangement on the 8q chromosome in those with a family history of BOR syndrome, it has not yet been confirmed whether this abnormality is peculiar to BOR syndrome or not.

Kidney disease due to BOR syndrome is usually asymptomatic and thus overlooked clinically. Fraser et al.<sup>10)</sup> reported that approximately 6% of the patients with BOR syndrome suffered from serious renal abnormalities. Two of the reported cases of BOR syndrome in Japan, were detected due to renal insufficiency. Serious renal disorder was reported in a one-month-old boy suffering from growth disorder, anemia and bleeding tendency<sup>4)</sup>. These symptoms were caused by bilateral renal hypoplasia. A final diagnosis BOR syndrome was established on the base of characteristic apparent deformities, abdominal ultrasound and computed tomography, and auditory brainstem response (ABR). In some cases the possibility exists that family members may have died of renal diseases. When otolaryngologists treat patient with fistulae and auricular abnormalities, they must investigate family history, carry out a com-

Table 1 Reported cases of BOR syndrome in Japan

reporter-year	age-sex	branchial	auricular abnormalities	hearing disorder	renal abnormalities	family history	surgical treatment	others
Ichimura (1985)	10 years·F	bilateral	binaural fistulae	binaural mixed type	left renal hypoplasia	not remarkable	reconstruction of ossicular chain	
Ichimura (1985)	54 years·F	bilateral	binaural fistulae	binaural mixed type	normal	father and older sister		
Jinno (1987)	1 month·M	bilateral	right auricular hypoplasia, narrowed right ear canal, left accessory auricle	binaural	bilateral renal hypoplasia	not remarkable		right facial paralysis, micrognathia
Ishidoya (1989)	5 years·M	unknown	bilateral auricular hypoplasia	binaural	right renal hypoplasia	mother	prevention of vesicoureteral reflux (VUR)	cleft palate
Yoshida (1991)	2 years·M	bilateral	binaural fistulae	left	normal	father	excision of bilateral branchial	
Yokokoji (1995)	8 years·F	bilateral	binaural fistulae, right cupped protruding ear, right accessory auricle	binaural mixed type	normal	father	excision of bilateral branchial fistula and binaural pits	
Iwasaki (1995)	23 years·F	bilateral	left auricular hypoplasia, left meatal atresia	right mixed type left deafness	bilateral renal hypoplasia	father	excision of bilateral branchial fistula	
Case 1	10 years·M	unilateral (left)	left preauricular pit	not remarkable (disappearance of stapedial reflex)	abnormal ureter	father and younger sister	excision of unilateral branchial fistula	tic, short stature
Case 2	5 years·F	bilateral	binaural fistulae	not remarkable (disappearance of stapedial reflex)	bilateral renal hypoplasia (suspected of horseshoe kidney)	father and older brother	excision of bilateral branchial fistula	

plete examination of hearing ability and try to discover renal diseases in cooperation with urologists. If they observe only the ear and nose and throat, branchial fistulae and auricular abnormalities, they may overlook serious renal diseases in routine clinical practice.

Although the first patient reported in this study had a history of tonic tics and short stature, his growth hormone secretion was normal. He grew to 39.2 kg and 140.0 cm by June 1997. His body weight was within  $-1SD$  and his height within  $-2SD$  of the Japanese averages. He has been treated in the department of pediatrics for approximately three years with Chinese herbal medicine, and there has been a lull in his tics. These symptoms are supposed to bear no definite relation to lateral fistula.

Generally bilateral branchial fistulae are symmetrically observed at the same level. The second case in this study, however, had bilateral cervical fistulae at definitely different levels. This phenomenon seemed to be caused by the asymmetrical development of the branchial arches. In the second case the branchial fistula on the left side of the neck was approximately 1 cm higher than that on the right side. Although the brother had a cervical fistula only on his left side, a mass on the right side occasionally produced exudate at age 2 or 3. Therefore the right lesion was probably a cyst which was an incomplete lateral cervical fistula. In the first case the location of the left fistula was approximately 7 cm higher than that on the right.

BOR syndrome comprises various branchiogenic abnormalities including branchial fistulae and external auditory deformities, hearing disorders due to abnormalities of the internal and middle ear and renal abnormalities. Patients with BOR syndrome manifest some of these abnormalities in combined form because of their mild phenotypic expression. According to Fraser's statistical analysis conducted on 133 patients with BOR syndrome, 89% have hearing disorders. Although the two patients treated in this department showed no hearing disorder, their symptoms and signs, such as the morphological kidney abnormalities were classified into the category of BOR syndrome. Previously reported cases included those with delayed hearing disorders. Consequently it is necessary for us to follow up the clinical courses of these patients, paying special attention not only to renal function but also to hearing activity.

#### ACKNOWLEDGMENT

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We thank Professor Fumihisa Hiraide (the Department of Otolaryngology, Tokyo Medical University, Japan) for his advice. We announce the sad news that Professor Hiraide passed away. We hope he will find peace in the next world.

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## BOR 症候群と思われる家族性の側頸瘻症例

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先天性側頸瘻は胎生期の鰓性器官の遺残として有名であり、日常の臨床でも遭遇することは決して稀ではない。Melnick らが 1975 年に多発性奇形の 1 つの型として側頸瘻・耳介部異常・難聴・腎奇形を持ったものを報告してから Branchio-oto-renal syndrome (以下 BOR 症候群と略す) と呼ばれ、近年徐々に報告例が増えている。今回私どもは家族発生の側頸瘻症例を経験し、またそれが BOR 症候群を呈したものと思われるのでここに報告する。

最初の症例は 10 歳の男児。チックと低身長のため平成 6 年 3 月より東京警察病院小児科受診中であった。生下時より左側頸部に瘻孔と浸出液を見ており平成 7 年 3 月小児科より耳鼻科紹介受診となった。左側頸瘻と診断を受け、同年 8 月側頸瘻摘出術となった。

尿検査では異常はなかったが、経静脈腎盂造影で左尿管の尿路奇形が発見された。左尿管に異所性血管が巻きついて狭窄を起こしており、そのため左の腎臓は水腎症気味となっていた。その他の体表奇形としては、左耳前部に瘻孔が存在した。

次の症例は 5 歳女児。生下時より両側頸部瘻孔からの浸出液、両側耳瘻孔が見られた。この児は最初の症例の妹で兄と共に平成 7 年 3 月耳鼻科初診となった。平成 7 年 8 月 9 日、全身麻酔下に側頸瘻摘出術を行った。

尿検査では異常はなかったが、経静脈腎盂造影で両側腎杯、特に右側の描出が不良でおそらく馬蹄腎と思われる所見がみられた。

BOR 症候群は遺伝疾患であり、遺伝形式は常染色体優性である。BOR 症候群は本邦では 7 例の報告があるが、そのうち家族に難聴や耳介奇形などの異常が見られたものは 5 例である。自験例も、今回の手術入院で泌尿器科の精査を受けるまでは、特に腎疾患を疑うような所見はなかった。

BOR 症候群の腎障害は無症候性が多いので、看過される傾向にあるのは否定できない。本邦での報告例のうち腎機能不全から 2 例が発見されている。側頸瘻および耳介部異常があった場合には、家族歴の聴取、難聴の精査はもちろん、泌尿器科の協力を得て腎疾患の発見に努めるべきと考える。そうしないと日々の臨床の場で漫然と側頸瘻や耳介部異常といった耳鼻咽喉科の範囲のみ診察し、重篤な腎障害が隠れているを見落とすことになりかねない。

BOR 症候群は、側頸瘻と耳瘻孔や外耳奇形などの鰓原性奇形に内耳から中耳にかけての奇形による難聴及び腎奇形を伴うものをさすが、形質発現が弱く、このうちのいくつかの組み合わせをとるものが多い。自験例は腎の形態異常があり、難聴を呈してはいないが、BOR 症候群の範疇と考えここに報告した。経過を追うごとに難聴の進行をみた例も報告されているので、腎機能とともに今後も経過をみていきたい。

なお本論文の要旨は 1996 年 1 月に神戸で開催された頭頸部外科学会にて発表した。