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Sudden Hearing Loss Associated with High Levels of Calcineurin Inhibitors after Liver Transplantation

Hearing impairment in patients after liver transplantation (OLT) has only been reported sporadically. However, potential ototoxic side effects may be related to immunosuppression. We report a series of 5 patients who developed sudden hearing loss after OLT and presented high levels of calcineurin inhibitors at the same time.

In 4/5 patients, sudden hearing loss was bilateral. Patients' main characteristics were very heterogeneous (e.g. age, time since OLT, underlying liver disease). Sudden hearing loss occurred under high levels of tacrolimus (n=3, mean serum levels at the time of hearing loss: 24 ng/ml) and cyclosporine A (n=2, 343 ng/ml), respectively. Further immunosuppression consisted of prednisolone (n=4) and azathioprine (n=1). There were no other risk factors such as administration of ototoxic drugs. Levels of immunosuppressants were rapidly corrected after the event. Nevertheless, in 4/5 patients hearing aids (3/4 bilateral) became necessary during follow-up. Furthermore, two patients suffer from tinnitus since the hearing loss.

In conclusion, high levels of calcineurin-inhibitors after OLT seem to be a risk factor for sudden hearing loss. In most cases, hearing loss was irreversible and resulted in need of a hearing aid. Neurotoxicity may be a probable mechanism. Further evaluations are necessary to allow a better understanding of the problem.

Key words:

liver transplantation, sudden hearing loss, immunosuppression, neurotoxicity syndromes, cyclosporine, tacrolimus

Akuter Hörverlust in Assoziation mit hohen Spiegel von Calcineurin-Inhibitoren nach Lebertransplantation

Beeinträchtigungen des Gehörs bei Patienten nach Lebertransplantation (LTx) sind bislang nur sporadisch beschrieben. Potentielle ototoxische Nebenwirkungen könnten in Zusammenhang mit der Immunsuppression stehen. Wir berichten über eine Serie von 5 Patienten, die alle einen akuten Hörverlust nach Lebertransplantation erlitten und zeitgleich hohe Spiegel von Calcineurin-Inhibitoren aufwiesen.

In 4/5 Patienten trat der Hörsturz beidseitig auf. Die Hauptcharakteristika der Patienten waren sehr heterogen (z.B. Alter, Verlauf nach LTx, zugrundeliegende Lebererkrankung). Die Hörstürze traten unter hohen Spiegel von Prograf (n=3, mittlerer Serumspiegel zum Zeitpunkt des Hörsturzes: 24 ng/ml) bzw. Cyclosporin A (n=2, 343 ng/ml) auf. Die weitere Immunsuppression bestand aus Prednisolon (n=4) und Azathioprin (n=1). Weitere Risikofaktoren wie

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Rifai K, Klempnauer J, Manns MP, Strassburg ChP (2006) Sudden Hearing Loss Associated with High Levels of Calcineurin Inhibitors after Liver Transplantation. Tx Med 18: 33-35

die Gabe ototoxischer Medikamente lagen nicht vor. Die Wirkspiegel der Immunsuppressiva wurden nach dem Ereignis rasch korrigiert. Trotzdem wurden bei 4/5 Patienten im weiteren Verlauf Hörgeräte (3/4 beidseitig) notwendig. Zusätzlich leiden zwei Patienten seit dem Ereignis unter Tinnitus.

Zusammengefaßt scheinen hohe Spiegel von Calcineurin-Inhibitoren nach Lebertransplantation einen Risikofaktor für einen akuten Hörverlust darzustellen. Der Hörverlust war meist irreversibel und zog ein Hörgerät nach sich. Neurotoxizität könnte ein möglicher Mechanismus sein. Weitere Untersuchungen sind notwendig, um das Problem besser beurteilen zu können.

Schlüsselwörter:

Lebertransplantation, akuter Hörverlust, Immunsuppression, Neurotoxizität, Cyclosporin, Tacrolimus

Abbreviations

CNI = calcineurin inhibitor
OLT = orthotopic liver transplantation

Introduction

Hearing loss is a frequent disorder that may have a significant impact on patients' quality of life [1]. With increasing long-term survival after liver transplantation (OLT), possible side effects of immunosuppression are gaining more clinical significance [2]. Many side effects of calcineurin inhibitors (CNI) have been well studied. Of these, cardiovascular and neurotoxic side effects could be involved in development of hearing loss after organ transplantation [3,4]. However, only little data is available on sudden hearing loss [5,6] or chronic hearing impairment [7,8] in patients after organ transplantation. We recently published the results of a systematic questionnaire regarding hearing impairment in patients after liver transplantation [9]. Here, we report a series of 5 patients who developed sudden hearing loss after liver transplantation that was associated with high serum levels of calcineurin inhibitors.

Materials and Methods

The main characteristics of the 5 patients with sudden hearing loss and high levels of CNI are shown in Table 1. Three of 5 patients were female (60%).

Patients' age at OLT was highly variable (17-58 years). The type of underlying liver disease was heterogenous as well (one patient with hepatitis C cirrhosis, autoimmune hepatitis, malignant hemangioendothelioma, primary sclerosing cholangitis and progressive familial intrahepatic cholestasis). Two of 5 patients were retransplanted (40%). At the time of sudden hearing loss, OLT dated back 0-5 years. Follow-up since OLT was 1-17 years. Thus, all these basic patient data were heterogenous and of no avail. In all patients, repeated audiometric evaluations were performed to confirm the diagnosis and the extent of hearing loss. Risk factors for hearing loss such as ototoxic drugs (e.g. aminoglycoside antibiotics, loop diuretics, salicylates) were noted.

Results

In 4/5 patients, sudden hearing loss was bilateral (see Table 2). Hearing loss developed under high levels of Tacrolimus (n=3, mean serum level at the time of sudden hearing loss: 24 ng/ml) respectively cyclosporine A (n=2, 343 ng/ml). Further immunosuppression consisted of prednisolone (n=4) und azathioprin (n=1). Other risk factors such as administration of ototoxic drugs (e.g. aminoglycosides) were not present. Despite immediate dose correction, no full recovery of hearing was achieved. In 4 of 5 patients, hearing aids have become necessary during follow-up. In 3 of these 4 patients, hearing aids are bilateral. Furthermore, 2 patients suffer from tinnitus since the episode of sudden hearing loss. Mean audiometrically measured hearing loss is actually at -93±17 dB (Min-Max: 80-120 dB) on the right ear and -78±42 dB (Min-Max: 10-120 dB) on the left ear.

Discussion

This is the first clinical report of 5 adults who developed sudden hearing loss after liver transplantation that was very probably associated with high levels of immunosuppression. Severe sensorineural hearing loss was confirmed by repeated audiograms. In none of the patients, an association with other known risk factors such as ototoxic drugs was found. The association of sudden hearing loss and high levels of CNI has already been reported for cyclosporine and tacrolimus in 2 cases af-

Tab. 1: Main characteristics of patients with sudden hearing loss and high levels of calcineurin inhibitors

Patient	Sex	Age at OLT	Indication for OLT	Date of OLT	Date of hearing loss
1	m	33 y.	Hepatitis C cirrhosis	1985	1990
2	w	28 y.	Autoimmun-hepatitis	1993	1993
3	w	58 / 58 y.	Hemangio-endothelioma	1996 / 1996	1996
4	w	24 / 26 y.	PSC	1999 / 2001	2000
5	m	17 y.	PFIC	2001	2002

Abbreviations: OLT = Orthotopic liver transplantation; PSC = Primary sclerosing cholangitis; PFIC = Progressive familial intrahepatic cholestasis

Tab. 2: Hearing loss and immunosuppression

Patient	Hearing loss	Hearing loss right / left	Serum level of CNI	Other immunosuppressants	Hearing outcome
1	Bilateral	-100 / -80 dB	Cyclosporine 378 ng/ml	Prednisolone	Hearing aid, tinnitus, bilateral
2	Bilateral	-120 / -120 dB	Tacrolimus 27 ng/ml	Prednisolone	Hearing aid, bilateral
3	Bilateral	-80 / -100 dB	Cyclosporine 308 ng/ml	Prednisolone	Hearing aid, unilateral
4	Unilateral	-85 / -10 dB	Tacrolimus 26 ng/ml	Azathioprine	Tinnitus, unilateral
5	Bilateral	-80 / -80 dB	Tacrolimus 19 ng/ml	Prednisolone	Hearing aid, bilateral

Abbreviation: CNI = Calcineurin inhibitor

ter kidney respectively after kidney-pancreas transplantation [5,6]. Recently, the first reports of CNI-related chronic hearing impairment were published [7-9]. In most previously published cases, hearing loss was halted or even recovered after dose correction. However, despite immediate dose correction, no hearing recovery could be achieved in most of our patients. Four of 5 patients are still in need of a hearing aid and 2 patients suffer from tinnitus. In accordance to the literature, other immunosuppressants did not play an important role in our patients.

A dose-dependent toxicity is often found in CNI-related neurotoxicity. Other severe cerebral manifestations of CNI-related neurotoxicity have already been described (e.g. blindness, seizures). They are probably caused by a disturbance of the blood-brain barrier [10]. Thus, hearing loss may be caused by a disturbance of the barrier between

blood and inner ear [11]. Nevertheless, one cannot rule out that hearing loss is related to cardiovascular side effects of CNI [3]. These cardiovascular side effects could be caused by direct mechanisms such as inner ear vasculopathy or indirect mechanisms such as arterial hypertension.

In conclusion, we identified 5 adults with severe sudden hearing loss associated with high levels of calcineurin-inhibitors after liver transplantation. Almost all of them developed chronic hearing impairment despite dose correction of CNI. Dose-dependent neurotoxicity may be hypothesized as the probable mechanism. Up to now, hearing impairment was not in the focus of clinical care for patients after liver transplantation. Hearing loss should be added to the list of important side effects of immunosuppressants. Further evaluations are necessary to allow a better understanding of the problem.

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