Acta Clin Croat 2008; 47:205-210 Original Scientific Paper

TRANSCRANIAL SONOGRAPHY IN THE EVALUATION OF PINEAL LESIONS: TWO-YEAR FOLLOW UP STUDY

Mislav Budišić, Jelena Bošnjak, Arijana Lovrenčić-Huzjan, Maja Strineka, Raphael Bene, Dražen Ažman, Darko Bedek, Zlatko Trkanjec and Vida Demarin

University Department of Neurology, Sestre milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic of Croatia, Zagreb, Croatia

SUMMARY – We have recently reported that transcranial sonography (TCS) is a method competitive to magnetic resonance neuroimaging (MRI) in the evaluation of pineal gland lesions. The aim of the present is study was to assess the usefulness of TCS in a larger patient sample during a two-year follow up. Twenty patients with incidental pineal gland cyst (PGC) detected by MRI scan of the brain and 40 healthy controls without any previous documented data on a disease related to pineal gland were evaluated by TCS and compared with MRI scans. There were no statistically significant differences in PGC size measured by TCS by two observers (p=0.475), PGC size measured by TCS and MRI (first observer, p=0.453; and second observer, p=0.425), size of the pineal gland measured by TCS and MRI in control group (first observer, p=0.497; and second observer, p=0.370), and pineal gland size measured by TCS by two observers in control group (p=0.473). Study results suggested TCS to be a suitable method in the evaluation of pineal gland lesions. Although its resolution cannot match the MRI resolution, its repeatability and accuracy might add to its practical value. We suggest that the repeat MRI scan of such lesions might be replaced by clinical and TCS follow up.

Key words: *Pineal cysts – diagnosis; Pineal gland – diagnosis; Brain Diseases – diagnosis; Ultrasonography – Doppler – Transcranial*

Introduction

Pineal gland abnormalities with a reported prevalence of 0.6% to 5.8% are common and often asymptomatic findings in neuroimaging reports[1-5]. Both magnetic resonance imaging (MRI) and computed tomography (CT) scans have been demonstrated to have high sensitivity in detection; however, findings may often be atypical and non-pathognomonic. Therefore, definitive diagnosis of the lesions can only be established by histopathologic analysis[6-13].

Transcranial sonography (TCS) displays brain parenchyma echogenicity through the intact skull. It is a non-invasive, bed-side neuroimaging technique based on high-resolution ultrasound systems and phase array sector transducers. Although spatial resolution is lower than with other imaging modalities, the possibility of B-mode TCS to record brain parenchyma has been widely neglected. In combination with Doppler signal or power-based transcranial sonography, it generates intravascular color signals from the amplitude of the echo signal and enables evaluation of the cerebrovascular state of the patient as well[14-17]. Transcranial sonography has proved reliable and sensitive in detecting basal ganglia abnormalities, e.g., hyperechogenic nigral substance in Parkinson's disease, disrupted midline brainstem raphe in patients with unipolar depression, and lenticular nucleus in atypical parkinsonian syndromes[18-22]. Also, TCS has proved to be reliable in evaluation of the ventricular system of the brain[23].

Our study group has recently reported that TCS is a neuroimaging method competitive to MRI in the evaluation of pineal gland lesions, especially in adult age[24].

Correspondence to: *Mislav Budišić, MD,* University Department of Neurology, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: mislavbudisic@yahoo.co.uk
Received July 4, 2008, accepted November 17, 2008

The aim of the present study was to determine the usefulness of TCS in a larger patient sample during a two-year follow up.

Subjects and Methods

Patients

The study included 20 patients with incidental pineal gland cyst (PGC) detected by MRI scan and 40 healthy controls with no previously documented data on a disease related to pineal gland. Informed consent was obtained before entering the study. All patients underwent complete neurological or neuropediatric examination performed by two independent physicians blinded for the results of the other. Reasons for admission to our department included chronic headache in six patients, partial complex seizures in three patients, absence seizures in two patients, grand mal seizures in one patient, and headache and dizziness in eight patients. Inclusion criteria also included transcranial insolability with appropriate bilateral temporal bone windows. None of the patients had a history of symptoms specifically referable to PGC (signs of increased intracranial pressure, cerebrospinal fluid obstruction, or brainstem and cerebellar compression)[25,26]. All patients received optimal medical treatment if needed. For each patient, two sets of cranial MR images of the brain were reviewed. The latest available cranial MR images within 3 months were used to examine the region of interest. Fifteen patients were re-evaluated by TCS and MRI two years after the initial examination. Three patients underwent surgical treatment.

Methods

TCS was performed blindly for the results of MRI scan, freehandedly, using the Aloka ProSound SSD-5500 device. The measurement was done twice by independent physicians blinded for the results of the other and for the results of MRI scans. The insonation was done through both temporal "bone windows" on intact skull with a 2 MHz sector transducer. The penetration depth was 14 cm and gain image was adopted individually. Upon identification of the butterfly-shaped structure of mesencephalic brainstem, the probe was tilted by 10 degrees up and the ventricular system was shown as anechoic, surrounded by a thin hyperechogenic margin. The distance between the two hyperechogenic margins was calculated as the diameter of the 3rd ventricle. Echogenicity of the pineal gland was observed in the dorsal part of the 3rd ventricle along diencephalic line. Although even a small change in angulation is likely to result in change of the value, two orthogonal direction measurements in the axial line on MRI scan were considered to match the semi-axial TCS results. The maximal width in laterolateral and anteroposterior line was measured. PGC was defined as every hypoechogenic area within hyperechogenic gland matrix or hypoechoic lesion with or without the septum surrounded by a thin echoic wall. Also, we performed quantitative measurement of normal gland area by encircling it and presenting it in cm^2.

MRI imaging was done with an Elscint Prestige 2T device equipped with a standard circular polarized coil. Scans are recorded in the sagittal, coronal and axial line with 5-mm slice thickness. Since TCS records were done in axial line, the measurement of PGC in two orthogonal directions in the same line on MRI scan was considered to match TCS results. The inclusion criteria on MRI scan included round or ovoid area of signal abnormality in the pineal recess, hypointense to white matter on T1-weighted images and isointense with cerebrospinal fluid on T2-weighted images. The lesion was internally homogeneous on T2-weighted images and no lobularity of the margin was present[8].

Statistics

The statistical package SPSS for Windows (version 6) was used on data analysis. For descriptive statistics, the continuous numeric variables were shown as mean values, standard deviations, minimum and maximum values. The difference between groups was calculated using the one-way analysis of variance (ANOVA), with the significance level set to $p<0.05$. Multiple regression analysis was used to isolate the significantly correlated sets of values.

Results

Control scans of 20 males and 20 females, mean age 29.4 (SD, 12.1) years, revealed a pea-like, uniformly hyperechogenic structure superior to mesencephalic line. The mean size of the gland detected by MRI was 6.73(±0.68) x 5.17(±0.64) mm. The mean TCS size was 6.71(±0.71) x 4.91(±0.64) mm (first observer) and 6.59(±0.69) x 4.78(±0.71) mm (second observer).

The median size of the gland area on TCS was 0.27 cm^2. In eight controls we found small hypoechogenic

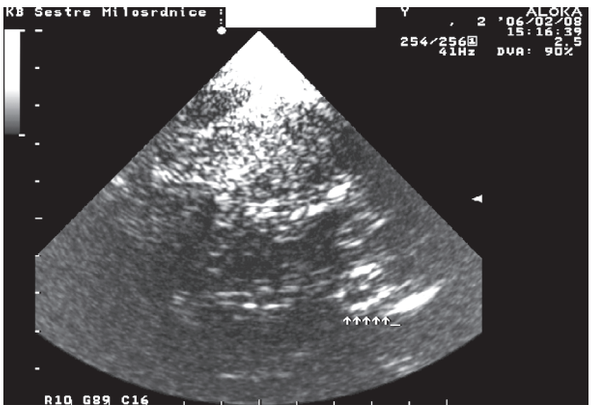

Fig. 1. An 18-year-old female patient with pineal cyst recorded on transcranial sonography.

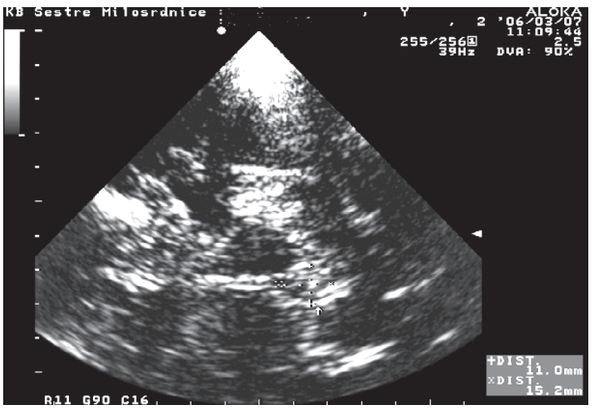

Fig. 2. Hypoechogenic cyst mass in a 10-year-old patient.

irregularities (less than 2 mm) within the gland matrix, which were not considered pathologic. The mean age of our patients was 19.6 (SD, 10.1) years and the cyst size on TCS scan varied from 3.5x5 mm to 17x10 mm in diameter. PGC characteristics on the most recent MRI scan and TCS are shown in Table 1. No statistically significant differences were found between PGC size measured by TCS by first and second observer (p=0.475), PGC size measured by TCS and MRI (first observer, p=0.453; and second observer, p=0.425), size of the pineal gland measured by TCS and MRI in control group (first observer, p=0.497; and second observer, p=0.370) or pineal gland size measured by TCS by first and second observer in control group (p=0.473).

The mean 3rd ventricle diameter was 8.2 (7.3-9.1) mm and 8.0 (6.9-9.2) mm in the control group and PGC patients, respectively, which was not significantly different. The follow up imaging performed in 15 patients after two years did not demonstrate any difference in the size of lesions, thus confirming the diagnosis of benign PGC[5,10,12]. Meanwhile, three patients underwent surgical treatment and the diagnosis was verified by specimen histopathology. Control MRI and TCS scans performed after surgical treatment showed complete cyst delineation in each patient.

Discussion

Our findings showed the usefulness of TCS in the detection of pineal gland lesions. We confirmed that TCS findings corresponded to the findings of MRI both in the detection of PGC and pineal gland itself. Fur-

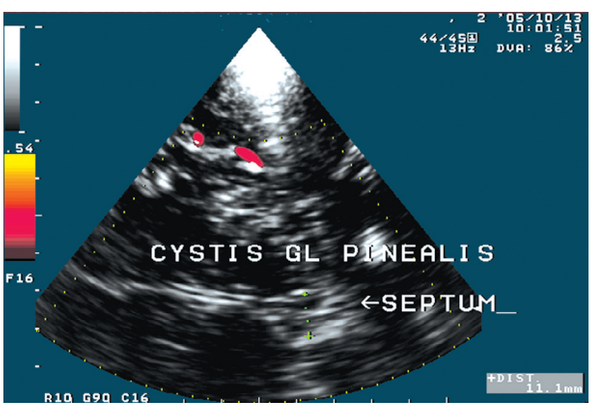

Fig. 3. Large septated pineal cyst on transcranial sonography.

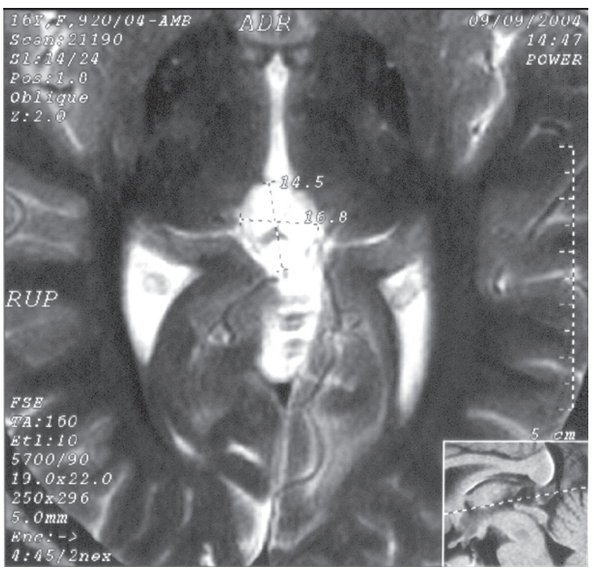

Fig. 4. The same lesion on magnetic resonance image.

thermore, TCS proved to be a useful and reliable neuroimaging technique in long term follow up of PGC. Also, the method showed high inter-observer reliability.

With further development of diagnostic tools for neuroimaging, the rate of incidental detection of pineal cysts in asymptomatic subjects has increased. The great

Table 1. Data on transcranial sonography (TCS) and magnetic resonance imaging (MRI) findings in patients with pineal gland cyst

Case no.	Age (yrs)	Sex (M/F)	TCS size (mm)*	MRI size (mm)	MRI shape	TCS findings
1	28	M	7.2x5.9	7.9x6.1	ovoid cyst	hypoechogenic cyst mass
2	8	F	8.3x8.8	8.0x9.0	small septated ovoid cyst	hypoechogenic septated cyst
3	17	F	14.8x11.0	17.0x10.0	ovoid cyst with thin wall and septum	largerly hypoechogenic separated cyst with uniform hyperechogenic cyst wall and communication with third ventricle
4	33	F	12.0x8.0	12.0x7.5	lobulated cystic mass	hyperechogenic gland with multifocal hypoechogenic areas
5	8	F	10.8x6.2	9.0x6.1	ovoid cyst	poor insonation due to restlessness
6	3	M	5.9x3.5	5.0x3.5	small ovoid cyst	small hypoechogenic sidewise located oval cyst
7	21	F	5.6x9.9	6.0x8.6	round partly septated cyst	hyperechogenic matrix with small hypoechogenic areas
8	16	M	11.6x7.8	11.1x7.8	large homogeneous cystic mass	hyperechogenic gland with increased width
9	17	F	4.9x7.0	5.2x7.0	sidewise located oval cyst	hypoechogenic uniform eccentric lesion
10	9	F	12.0x9.8	12.0x9.0	ovoid cyst with peripheral calcifications	large hypoechogenic cyst with marked hyperechogenic wall
11	15	M	10.8x9.1	12.0x11.0	large septated cyst	hypoechogenic septated cyst
12	12	M	10.2x7.4	11.0x7.0	oval cyst with thin wall	uniformly hypoechogenic cyst mass
13	40	F	10.6x9.6	11.0x9.0	round septated cyst	trigonal hypoechogenicity within hyperechogenic gland matrix
14	28	M	8.5x7.2	9.1x7.9	ovoid cyst	small central hypoechogenic area within gland area
15	19	F	6.2x4.0	6.0x4.0	small ovoid cyst	small hypoechogenic oval cyst
16	31	F	8.5x5.3	8.4x5.0	round partly septated cyst	hypoechogenic septated cyst
17	18	M	11.1x9.2	13.2x9.2	large septated cyst	hyperechogenic gland with multifocal hypoechogenic areas
18	29	M	7.2x6.9	8.3x7.0	small ovoid cyst	small hypoechogenic oval cyst
19	9	M	6.6x6.2	7.0x6.1	round cystic mass	hyperechogenic gland with increased width
20	21	F	9.6x8.8	9.5x8.6	lobulated cystic mass	hyperechogenic gland with multifocal hypoechogenic areas

* mean size calculated by two independent physicians

majority of these findings reveal no clinical symptoms but some patients may develop signs of intracranial hypertension or tectal dysfunction with compression and distortion of the adjacent nervous structures[25]. MRI scan of a cystic configuration in the pineal region is usually associated with non-neoplastic pineal lesions rather than a tumor, however, the analysis does not allow for cystic pineal tumors to be distinguished from benign glial cysts with certainty. Because of the common occurrence of cystic formations in the pineal region on MRI brain imaging, it seems to be important to establish differential diagnosis and decide whether these patients need neurosurgical intervention, especially if definite clinical symptoms exist. The documented characteristics of benign pineal cyst on MRI scan include dimension less or equal to 20 mm, absence of expansive effect, a signal similar to that of cerebrospinal fluid, and absence of cyst growth. The true nature of the entity can only be disclosed by performing histopathologic analysis[6]. At this point, it is doubtful whether TCS can help in this discrimination between benign and malignant lesions but this study has shown that TCS is a method competitive to MRI in the detection of morphological abnormalities of the pineal region. On T2-weighted images, this lesion was identified as a high-intensity area with smooth margins and was homogeneous in nature, which was shown on TCS scan as hypoechogenic with echogenicity similar to that within the ventricular system. Cystic hypoechogenicity on TCS was often surrounded by hyperechoic gland wall as the result of the gland calcification. The degree of calcification in the pineal region invariably increases with age and corpora aranacea or brain sand is a constant feature of older age brain. Therefore, on TCS the pineal cystic lesions may vary from hypo- to hyperechogenic with anechoic areas as the result of cyst size and compression by the residual pineal tissue.

Although being variably visualized on TCS and hyperechogenicity can mimic small hypoechogenic lesion within it, the increased width and enlarged encircled area of the pineal region in laterolateral and/or anteroposterior projection seems to be a constant feature. Comparing MRI and TCS scans of major hypoechoic lesions revealed better morphology evaluation on TCS, and the septum of cavum or communication with ventricular system can be easily recorded on TCS. Also, in hypoechogenic lesions the uniform cyst wall with maximum thickness of about 2 mm seems to match the criteria for the differential diagnosis between pineal cyst and pineocytoma on MRI scan[10].

The main limiting factor for this method is the need of appropriate temporal bone windows. Previous reports show that around 10% of individuals might be found ineligible for this approach.

In conclusion, our results suggest that TCS is a neuroimaging method competitive to MRI in the evaluation of pineal gland lesions, especially in adult age. We suggest that repeat MRI scans or control scans after surgical treatment of such lesions might be replaced by clinical and TCS follow up.

TCS is an easy bedside method of two-dimensional black and white brain imaging with spatial resolution lower than other imaging modalities but with the ability to display echogenic changes of pineal lesions. Additional efforts are needed to evaluate the utility of this approach.

References

1. HARRER JU, KLOTZSCH C, OERTEL M, MOLLER-HARTMANN W. Sonographic detection and follow up of an atypical pineal cyst: a comparison with magnetic resonance imaging. J Neurosurg 2005;103:564-6.
2. MAMOURIAN AC, TOWFIGHI J. Pineal cysts: MR imaging. Am J Neuroradiol 1986;7:1081-6.
3. SAWAMURA Y, IKEDA J, OZAWA M, MINOSHIMA Y, SAITO H, ABE H. Magnetic resonance images reveal a high incidence of asymptomatic pineal cysts in young women. Neurosurgery 1995;37:11-5.
4. GOLZARIAN J, BALERIAUX D, BANK WO, MATOS C, FLAMENT-DURAND J. Pineal cyst: normal or pathological? Neuroradiology 1993;35:251-3.
5. PETITCOLIN V, GARCIER JM, MOHAMMEDI R, RAVEL A, MOFID R, VIALLET JF, VANNEUVILLE G, BOYER L. Prevalence and morphology of pineal cysts discovered at pituitary MRI: review of 1844 examinations. J Radiol 2002;83:141-5.
6. ENGEL U, GOTTSCHALK S, NIEHAUS L, *et al.* Cystic lesions of the pineal region: MRI and pathology. Neuroradiology 2000;42:399-402.
7. SATOH H, UOZUMI T, KIYA K, KURISU K, ARITA K, SUMIDA M, IKAWA F. MRI of pineal region tumours: relationship between tumours and adjacent structures. Neuroradiology 1995;37:624-30.
8. TAMAKI N, SHIRATAKI K, LIN TK, MASUMURA M, KATAYAMA S, MATSUMOTO S. Cysts of the pineal gland: a new clinical entity to be distinguished from tumors of the pineal region. Childs Nerv Syst 1989;5:172 -6.
9. STEVEN DA, MCGINN GJ, MCCLARTY BM. A choroid plexus papilloma arising from an incidental pineal cyst. Am J Neuroradiol 1996;17:939-42.

10. BARBORIAK DP, LEE L, PROVENZALE JM. Serial MR imaging of pineal cysts: implications for natural history and follow-up. Am J Radiol 2001;176:737-43.
11. FLEEGE MA, MILLER GM, FLETCHER GP, FAIN JS, SCHEITHAUER BW. Benign glial cysts of the pineal gland: unusual imaging characteristics with histologic correlation. Am J Neuroradiol 1994;15:1796-7.
12. KOROGI Y, TAKAHASHI M, USHIO Y. MRI of pineal region tumors. J Neurooncol 2001;54:251-6.
13. HAYASHIDA Y, HIRAI T, KOROGI Y, KOICHI M, MARUYAMA N, YAMURA M, YAMASHITA Y. Pineal cystic germinoma with syncytiotrophoblastic giant cells mimicking MR imaging findings of a pineal cyst. Am J Neuroradiol 2004;25:1538-40.
14. ALEXANDROV A, DEMARIN V. Insonation techniques and diagnostic criteria for transcranial doppler sonography. Acta Clin Croat 1999;38:97-108.
15. LOVRENCIC-HUZJAN A. The role of ultrasound in diagnosing nonatherosclerotic vasculopathies of the nervous system. Acta Clin Croat 1998;37:68-72.
16. RUNDEK T, DEMARIN V, LOVRENCIC M. Transcranial Doppler diagnostic criteria in the evaluation of arteriovenous malformations. Neurol Croat 1991;40:259-67.
17. SEIDEL G, CANGÛR H, ALBERS T, MEYER-WIETHE K. Transcranial sonographic monitoring of hemorrhagic transformation in patients with acute middle cerebral artery infarction. J Neuroimaging 2005;15:326-30.
18. BECKER G, SEUFERT J, BOGHDAN U, REICHMANN H, REINERS K. Degeneration of substantia nigra in chronic Parkinson's disease visualized by transcranial color-coded real-time sonography. Neurology 1995;45:182-4.
19. BERG D, BECKER G, ZEILER B, *et al.* Vulnerability of the nigrostriatal system as detected by transcranial ultrasound. Neurology 1999;53:1026-31.
20. WALTER U, NIEHAUS L, PROBST T, BENECKE R, MEYER BU, DRESSLER D. Brain parenchyma sonography discriminates Parkinson's disease and atypical parkinsonian syndromes. Neurology 2003;60:74-7.
21. BUDIŠIĆ M, LOVRENČIĆ-HUZJAN A, TRKANJEC Z, LISAK M, KESIĆ M, VUKOVIĆ V, DEMARIN V. Transcranial sonography can discriminate Parkinson's disease from other movement disorders. Acta Clin Croat 2005;44:259-63.
22. BECKER G, BECKER T, STRUCK M, LINDNER A, BURZER K, RETZ W, BOGDAHN U, BECKMANN R. Reduced echogenicity of brainstem raphe specific to unipolar depression: a transcranial color-coded real-time sonography study. Biol Psychiatry 1995;38:180-4.
23. SEIDL G, KAPS M, GERRIETS T, HUTZELMANN A. Evaluation of ventricular system in adults by transcranial duplex sonography. J Neuroimaging 1995;5:105-8.
24. BUDIŠIĆ M, BOŠNJAK J, LOVRENČIĆ-HUZJAN A, MIKULA I, BEDEK D, DEMARIN V. Pineal gland cyst evaluated by transcranial sonography. Eur J Neurol 2008;3:229-33.
25. FETELL MR, BRUCE JN, BURKE AM, *et al.* Non-neoplastic pineal cysts. Neurology 1991;41:1034-40.
26. PERES MF, ZUKERMAN E, PORTO PP, BRANDT RA. Headaches and pineal cyst: a (more than) coincidental relationship? Headache 2004;44:929-30.

Sažetak

TRANSKRANIJSKA SONOGRAFIJA U PROCJENI OŠTEĆENJA PINEALNE ŽLIJEZDE

M. Budišić, J. Bošnjak, A. Lovrenčić-Huzjan, M. Strineka, R. Bene, D. Ažman, D. Bedek, Z. Trkanjec i *V. Demarin*

Naša prethodna studija je pokazala da je transkranijska sonografija (TCS) moždanog parenhima kompetitivna metodi magnetske rezonancije (MRI) u procjeni pinealne žlijezde. Cilj ove studije bio je pokazati mogućnosti TCS u bilježenju signala pinealne žlijezde i njene cistične morfologije te pokazati korelaciju sa snimkama MRI na većem broju bolesnika kroz dvije godine praćenja. U studiju je bilo uključeno 20 bolesnika s novootkrivenom cistom pinealne žlijezde na MRI i 40 kontrolnih osoba. Snimanje TCS je provelo dvoje neovisnih istraživača na uređaju Aloka SSD-5500 i bez uvida u rezultate MRI. Pinealna cista je označena kao svaka hipoehogena struktura unutar hiperehogene zone žljezdanog tkiva ili hipoehogena lezija sa septumom ili bez njega, okružena tankom ehogenom linijom. Širine žlijezde i lezije su izmjerene u latero-lateralnoj i antero-posteriornoj projekciji te uspoređene s rezultatima snimaka MRI. Podaci su obrađeni analizom ANOVA. Rezultati nisu pokazali statistički značajnu razliku između rezultata dvoje istraživača na TCS (p=0,475), veličine ciste mjerene pomoću TCS i MRI (prvi istraživač, p=0,453; drugi istraživač, p=0,425) i veličine pinealne žlijezde mjerene pomoću TCS u kontrolnoj skupini (p=0,473). Rezultati studije pokazuju mogućnosti TCS u otkrivanju pinealne regije uz dobru korelaciju s rezultatima MRI i značajnu podudarnost u rezultatima između dvoje neovisnih ispitivača. TCS se pokazala kao metoda kompetitivna metodi MRI u evaluaciji pinealnih cista, te ukazuje na mogućnost praćenja bolesnika kliničkim pregledom i pomoću TCS.

Ključne riječi: Pinealne ciste – djagnostika; Pinealna žlijezda – djagnostika; Bolesti mozga – djagnostika; Ultrazvuk – Doppler – transkranijski