

Normal Pressure Hydrocephalus, Dementia and Kynurenic Acid

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Abstract

A female 49 years old patient with vestibular schwannoma developed normal pressure hydrocephalus. Patient complained about gait disturbance, urinary incontinence and memory impairment. Investigation of clinical parameter and measurement of kynurenic acid in the cerebrospinal fluid (CSF) and serum in patients with normal pressure hydrocephalus and in corresponding controls (CO; N=15) were performed. Within investigated parameters significant increase of protein and IgG levels in CSF were found in patient with normal pressure hydrocephalus. Furthermore, kynurenic acid was increased in the CSF by 60% and in the serum by 40%, comparing to CO subjects. Kynurenic acid level in CO was in the CSF and serum 2.77 ± 0.23 and 53.4 ± 4.0 nM, respectively. Three lumbar punctures were applied to patient with normal pressure hydrocephalus and clinical parameters partially normalized and lowering of kynurenic acid levels in CSF and serum were observed. Patient was improving after each lumbar puncture but the effect was transient, therefore permanent CSF shunting was recommended. After that a complete remission of symptoms occurred. Revealed data indicate a significant advantage of single punctures in management of treatment for normal pressure hydrocephalus. Increase of kynurenic acid in CSF represents interesting parameter. It is questionable if occurrence of cognition impairment and/or dementia in patients with normal pressure hydrocephalus might be related to an enhancement of kynurenic acid in the CNS.

Keywords: Hydrocephalus; Dementia; Cerebrospinal fluid; Serum; Kynurenic acid

Introduction

Hydrocephalus malresorptivus respectively normal pressure hydrocephalus usually is associated with a history of meningitis, meningeos carcinomatosa, subarachnoid hemorrhage, cerebral trauma or neurosurgical interventions. It has been reported that schwannomas, meningiomas and cavernous hemangioma can produce hydrocephalus malresorptivus due to hyper proteinorachia and obstruction of pacchionian granulation [1,2].

Kynurenic acid, a well-known antagonist of the glutamatergic and nicotine cholinergic neurotransmissions [3,4], has been suggested to be involved in the impairment of cognition [5]. Accumulated data demonstrate enhanced kynurenic acid levels in the CNS in various neuropsychiatric disorders with dementia and in the aging process [6-8].

Dementia and cognition impairment have been reported also by patients with normal pressure hydrocephalus [9,10].

During a period of two months a forty nine years aged female developed signs of progressing dementia, gait disturbance and urinary incontinence. Cerebral CT without application of contrast medium revealed moderate hydrocephalus. MRI investigation with contrast medium demonstrated a tumour of 1.5 cm in diameter at the left pontocerebellar angle. Because of progressing symptoms gait disturbances, urinary incontinence and cognitive decline this patient was referred to the department for neurology for further investigations. The aim of the study was the evaluation of clinical parameters and investigation of kynurenic acid levels in the CSF and serum of patient with hydrocephalus and in corresponding control subject.

Materials, Patients and Methods

Materials

Kynurenic acid was purchased from Sigma. All other chemicals used were of the highest commercially available purity.

Patients

Control subjects: Out of a larger series of patients who underwent lumbar puncture to exclude subarachnoid haemorrhage or to exclude viral or bacterial meningitis 15 individuals were selected as normal subjects. CSF samples from these patients did not contain erythrocytes and no abnormalities in neuroimaging and further clinical investigations, which included electroencephalography and transcranial Doppler-sonography, were found. Age of normal subjects ranged between 18 and 50 years; (37.9 \pm 2.7; N=15; W/M: 10/5).

Patient with hydrocephalus During a period of two months in 49 years old female gait disturbances and urinary incontinence occurred and signs of progressing dementia developed.

Methods

Biological parameters investigations: Lumbar puncture was carried out to obtain CSF for routine parameter determinations, i.e., cell count, protein content and detection of oligo-clonal IgG bands, autochthonic immunoglobulin production, IgG index and albumin content. Blood samples were taken for routine investigation of leukocyte count, IgG and IgM and albumin content. For neurochemical analyses samples of CSF and serum were collected immediately in 1 ml aliquots and stored at -40°C until analysed. CSF and serum was coded to make anonymous and the study was carried out according to Lower Austrian Ethical Regulations.

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Measurement of protein, albumin, IgG, IgM and white blood cell counts were carried out using routine laboratory methods. The ratio of CSF:serum IgG and ratio CSF:serum albumin and the IgG index were calculated [11]. For determination of oligoclonal IgG bands, aragose isoelectric focusing was performed, followed by transfer to cellulose nitrate membrane and double antibody avidin-biotin-peroxidase labelling [12].

Neuroradiological investigations: Routine clinical investigations of cranial computer tomography (CT), magnetic resonance tomography (MRT) and electroencephalography (EEG) and brainstem evoked-potentials (BAEP) were carried out.

Measurement of kynurenic acid: Measurement of kynurenic acid was performed as described by Kepplinger et al. [8]. Briefly, CSF and serum sample was mixed with 0.2 M HCl (vol/vol), proteins were precipitated by adding 50% TCA, and sample centrifuged (20 min, 14,000 rpm). The supernatant was applied to a Dowex 50W cation exchange column pre-washed with 0.1 M HCL. Subsequently, the column was washed with 1 ml 0.1 M HCL and 1 ml distilled water, and kynurenic acid was eluted with 2 ml distilled water and was quantitated

by high performance liquid chromatography (HPLC) system coupled with fluorescence detection.

Statistical analysis: All mean values are given \pm SEM. Analyses has been performed in duplicates or triplicates. For statistical significance the one-way ANOVA and the Student's t-test were applied. The levels for statistical significance were taken as $P < 0.05$.

Results

Clinical data

The electroencephalographic study demonstrated Theta-Delta activity predominantly in frontal, central and temporal regions indicating normal pressure hydrocephalus (EEG; Figure 1a).

Monaural brainstem evoked potentials indicated acoustic schwannoma (BAEP, Figure 2). Monaural acoustic threshold was 6 dB on the right side, 15 dB on the left side. Monaural brainstem evoked potentials (BAEP) showed on the left side an increase of interpeak latencies and reduction of amplitude of P I, P II, P III and P IV, typical for acoustic schwannoma.

MRI investigation demonstrated a tumour of 1.5 cm in diameter at the left pontocerebellar angle (Figure 3) visual able in all sequences and with strong contrast medium enhancement in T1 weighted images, typical for vestibular schwannoma.

MRI flair images revealed enlarged lateral ventricles with a small

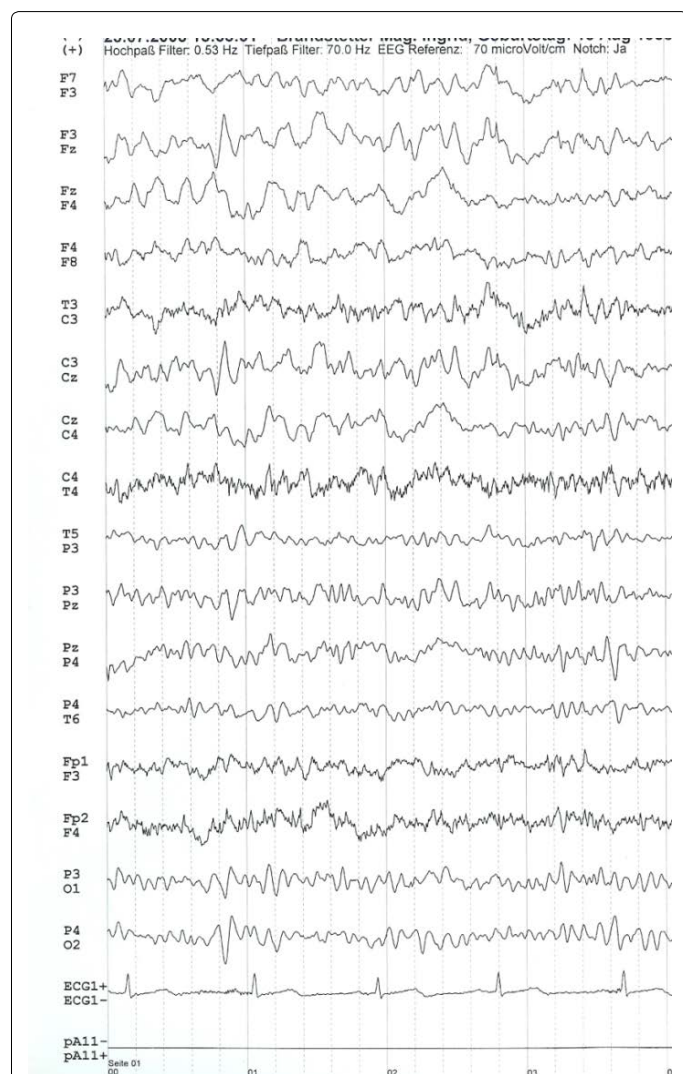


Figure 1a: Electroencephalographic (EEG) study demonstrating Theta-Delta activity predominantly in frontal, central and temporal regions indicating normal pressure hydrocephalus.

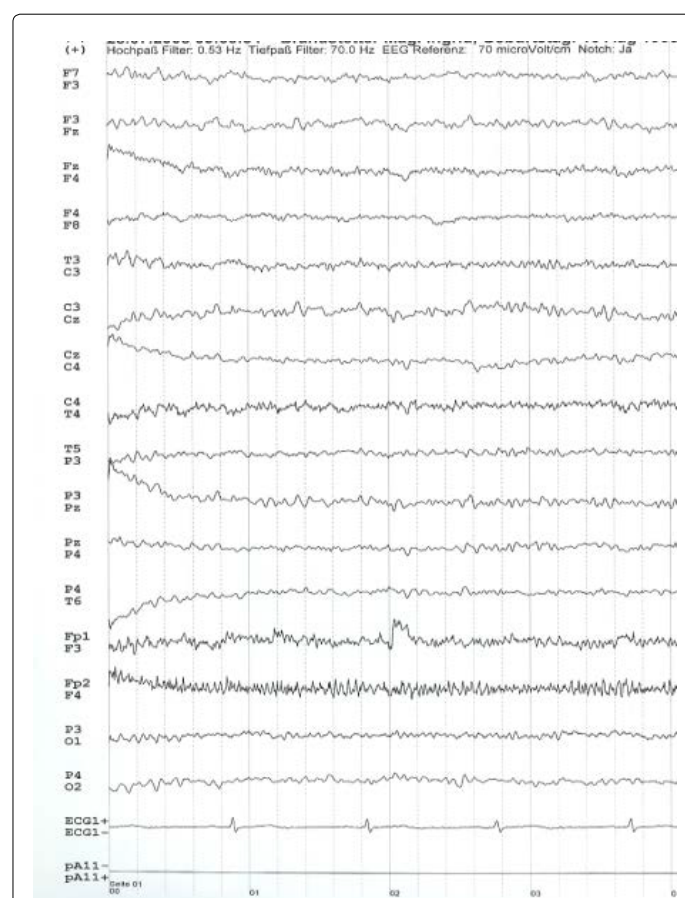
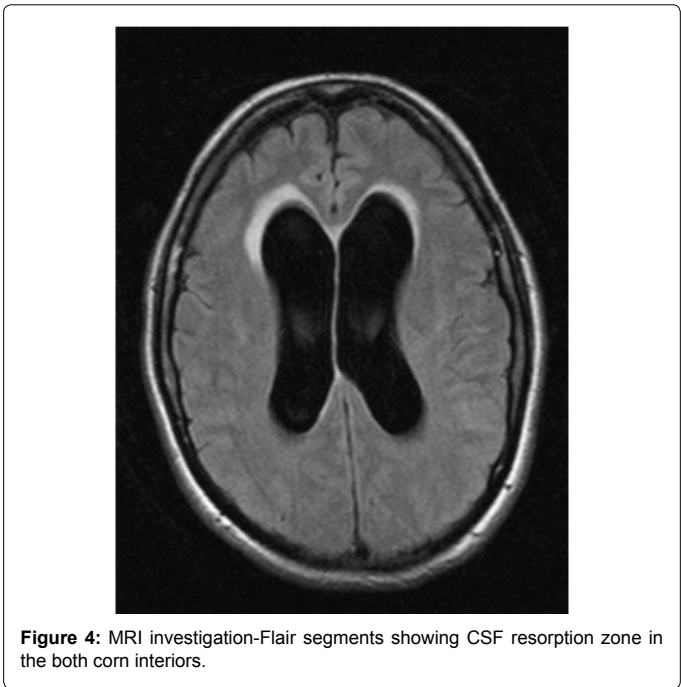
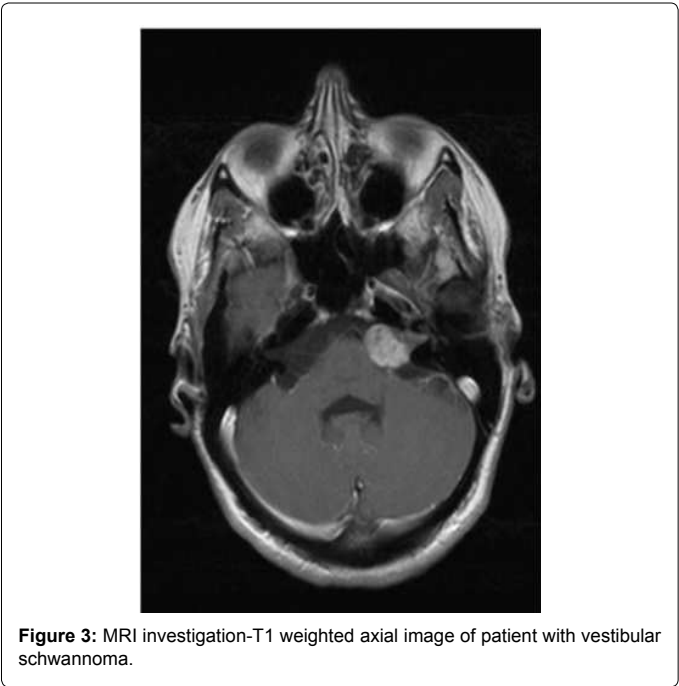
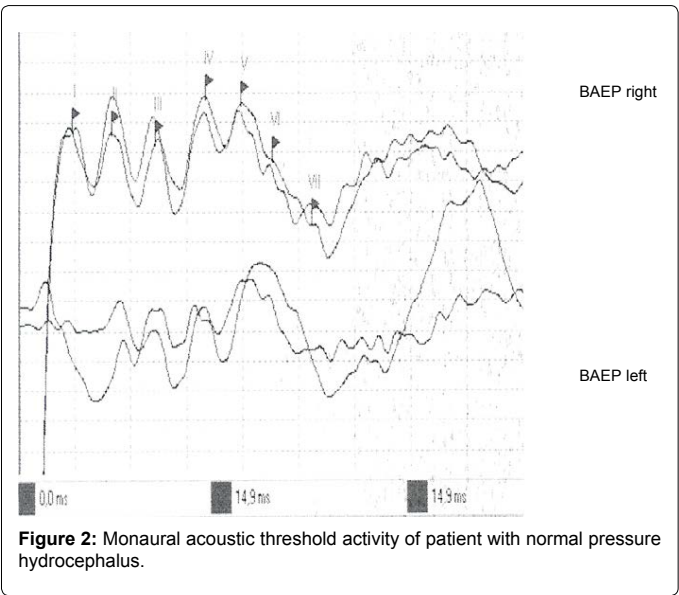


Figure 1b: Normalization of EEG activities in the brain regions of patient with normal pressure hydrocephalus after lumbar puncture of 45 ml.

CSF resorption zones at both interior corns of the lateral ventricles (Figure 4). Cella media index was 3.25 indicating a hydrocephalus grade II (3.0-3.5).

Clinical parameters of blood and CSF are presented in Table 1 and showed normal cell count, but significantly increased protein concentration (hyper proteinorachia: 69.3 mg/dl; 202% of CO; $P<0.05$) and IgG levels in CSF (9.64 mg/dl; 342% of CO; $P<0.01$) (Table 1, 1st investigation) of patient with normal pressure hydrocephalus, comparing to corresponding control subjects. After the 1st investigation revealed parameters confirmed symptoms of normal pressure hydrocephalus.

After CSF puncture of 45 ml clinical features of normal pressure hydrocephalus disappeared and the EEG normalized (Figure 1b). Patient refused neurosurgery of the schwannoma but accepted



Biological parameters	Control subjects Age 18-50 years	After 1 st investigation	Patient with NPH after 2 nd investigation	After 3 rd investigation
Age (years)	37.9 ± 2.7	49	49	49
Number	(15)	(1)	(1)	(1)
W/M	10/5	1/0	1/0	1/0
Protein in serum, mg/dl	7.09 ± 0.12	7.8	7.0	6.4
Albumin in serum, mg/dl	4490 ± 10	4610	3940	3650
IgG serum, mg/dl	912.9 ± 48.5	1180	989	952
IgA serum, mg/dl	182.9 ± 21.7	167	128	124
IgM serum, mg/dl	101.51 ± 16.2	135	107	103
Number of leukocytes, 10 ⁶ /l	6.54 ± 0.49	9.1	6.8	7.7
Protein in CSF, mg/dl	34.25 ± 3.84	69.3* $P=0.0385$	56.0	47.0
Albumin in CSF, mg/dl	25.93 ± 3.69	52.8	47.2	41.0
IgG CSF, mg/dl	2.82 ± 0.43 ^a	9.64*** $P=0.001$	6.32	5.15
Ratio CSF:serum IgG	3.099 ± 0.464 ^a	8.17* $P=0.016$	6.39	5.41
Ratio CSF:serum albumin	5.803 ± 0.837	11.45	12.00	11.23
IgG index	0.5333 ± 0.0171	0.71* $P=0.021$	0.53	0.48
Cell count, × 10 ⁶ /l	5.37 ± 0.99	2	1	0
Oligoclonal IgG bands	Negative	Negative	Negative	Negative

Investigations: 1st, 2nd and 3rd are described in material and methods. Data represent mean ± SEM. Number (N) of subjects is given in parentheses. One-Way ANOVA analysis between four columns revealed significant differences. *P* indicates statistical difference in comparison to control subject. Statistical analysis: a, b indicates statistical significance at $P<0.05$

Table 1: Biological parameters of serum and CSF in patient with normal pressure hydrocephalus (NPH) and in corresponding control subjects.

gamma-knife intervention. Two months after gamma knife radiation schwannoma was slightly shrinking but the patient developed again signs of normal pressure hydrocephalus. Patient insisted to have done further a single puncture as a therapy (45 ml, 2nd investigation) instead

of recommended invasive continuous CSF pressure recording. After puncture the recovery lasted for 2 months and patient developed again the symptoms of normal pressure hydrocephalus. After following puncture of 45 ml CSF (3rd investigation) the recovery occurred also, but lasted only 10 days. CSF protein concentration remained less increased comparing to the control subjects, i.e. the level was 47.0 mg/dl (137 % of CO) and IgG value was 5.15 mg/dl (183% of CO, $P < 0.05$).

Cella media index after 2nd and 3rd CSF punctures was 2.9 and 2.5, respectively. Then patient was referred for permanent CSF shunting. Thereafter the patient completely recovered to her previous intellect duty for 10 years. One-way ANOVA analysis on columns selected between CO and three investigations revealed following significant differences: IgG in CSF ($F=6.7262$; $P=0.0049$); ratio CSF:serum IgG ($F=3.6699$; $P=0.0386$). Tendency for significance was observed for leucocyte in serum ($F=3.6711$; $P=0.0512$) and IgG index ($F=2.5394$; $P=0.0985$), using one-way ANOVA analysis.

No significant differences were seen for protein in serum ($F=1.59965$; $P=0.2349$); albumin in serum ($F=2.0752$; $P=0.1496$), IgG serum ($F=0.6659$; $P=0.5867$); IgA serum ($F=0.2736$; $P=0.8434$), IgM serum ($F=0.0900$; $P=0.9643$); protein in CSF ($F=2.4090$; $P=0.1105$) and albumin in CSF ($F=0.7190$; $P=0.5569$), using one-way ANOVA analysis.

Kynurenic acid level in CSF and serum of patient with normal pressure hydrocephalus was increased (160% of CO and 142% of CO, respectively) comparing to control subject (1st investigation, Table 2). During a period of therapeutic interventions significant lowering of kynurenic acid levels in the CSF and serum was observed (2nd and 3rd investigation, Table 2) and one-way ANOVA analysis of variance between columns revealed significant differences.

Levels of kynurenic acid in CSF and serum of control subjects correlated well with data previously published [8]. The age 49 years of patient with normal pressure hydrocephalus corresponded with the age of used control subjects (between 18-50 years).

Discussion

According to literature normal pressure hydrocephalus respectively hydrocephalus malresorptivus occurs in 2 to 10 % of patients with schwannoma at the cerebellopontine angle [1,2]. The probability for development of hydrocephalus depends on tumor size (>4 cm diameter) and development of hyper proteinorachia [2]. We believe that investigated patient developed hydrocephalus due to hyper proteinorachia and not due to presence of the tumor since schwannoma was small about 1.5 cm diameter. In good correlation with our interpretation, gamma knife treatment did not improve symptoms and did not normalize alterations of clinical parameters in this patient. Importantly, applications of three single punctures followed by

permanent CSF shunting improved symptoms and clinical parameters and patient returned to intellect professional life for 10 years. In the line with our observation a recovery of symptoms by permanent CSF shunting was reported by Fujimoto et al. [13], too.

For the first time we demonstrate that in our patient with normal pressure hydrocephalus kynurenic acid levels in CSF and serum were moderately increased. An enhancement of kynurenic acid in CSF of patients with hydrocephalus represent significant finding since there are many neurological disorders demonstrating correlation between increased kynurenic acid in CNS and occurrences of dementia and/or cognition impairment, i.e., in Alzheimer, HIV-1 infection/AIDS, Schizophrenia even aging [3-8]. Whereas an enhancement of kynurenic acid levels in the serum can increase the cardiovascular disease risk factor [14].

Interestingly, due to lumbar punctures the volumes of ventricles was lowered and importantly lowering of kynurenic acid levels in CSF was found and these changes were accompanied by improvement of cognition. Revealed data suggest influence of CSF flow on lumbar CSF protein concentration since after the single puncture parameters lowered, too. In addition, lowering of ratio CSF:serum IgG value after punctures suggest altered blood-CSF barrier permeability due to high protein levels in the CSF.

Notable is also the effect of lumbar punctures to lower kynurenic acid levels in the serum in patient with normal pressure hydrocephalus. The mechanism of lowering of kynurenic acid levels in the serum after puncture is not known yet, but this effect might relate to the lowering of cardiovascular disease risk factor which has been also described in hydrocephalus [14,15].

Conclusion

We believe that impairment of cognition and dementia in patients with normal pressure hydrocephalus could be associated with an enhancement of kynurenic acid in CSF, respectively in the brain. Study on kynurenic acid levels in CSF and serum in patients with hydrocephalus will be further elaborated.

Acknowledgement

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Ethical Considerations

The procedures of the research proposal from Berthold Kepplinger have been approved by Lower Austrian Ethical Regulations. Research was based on voluntary participation and oral and/or written informed consent with the Institution Neurological Departments (head at the time period of investigation: Prim. MD. Berthold Kepplinger, MSc) Landeskrankenhaus Mauer and Amstetten and patients.

Biological parameters	Control subjects (CO) Age 18-50 years	After 1 st investigation	Patient with NPH after 2 nd investigation	After 3 rd investigation
Age (years)	37.9 ± 2.7	49	49	49
Number	(15)	(1)	(1)	(1)
W/M	10/5	1/0	1/0	1/0
Kynurenic acid in CSF (nM)	2.769 ± 0.225 ^a (100%)	4.44 ^b , $P=0.0854$ (160.3% of CO)	3.75 ^{P=0.3901} (135.4% of CO)	1.2 ^{*b} , $P=0.0248$ (18.1% of CO)
Kynurenic acid in serum (nM)	53.37 ± 3.99 ^a (100%)	75.85 ^{P=0.1812} (142.1% of CO)	23.83 ^{P=0.0858} (44.7% of CO)	19.3 ^b , $P=0.0514$ (36.2% of CO)

Investigations: 1st, 2nd and 3rd are described in Material and Methods. Data represent mean ± SEM. Number (N) of subjects is given in parentheses. *P* indicates statistical difference in comparison to control subject. Statistical analysis: a, b indicates statistical significance at $P < 0.05$

One-Way ANOVA analysis on columns selected between CO and three investigations revealed significant differences of kynurenic acid in the CSF ($F=3.7419$; $P=0.0364$)

One-Way ANOVA analysis on columns selected between CO and three interventions revealed significant differences of kynurenic acid in the serum ($F=3.4039$; $P=0.0476$)

Table 2: Kynurenic acid levels in the CSF and serum of patient with normal pressure hydrocephalus (NPH) and in control subjects (CO).

Conflict of Interest

The authors declare no conflict of interest. The idea for the article was conceived by Berthold Kepplinger and Halina Baran. The investigations were performed by Berthold Kepplinger, Jochen Reuss, Roman Sobota and Pavol Kalina. The data were analyzed by Berthold Kepplinger, Brenda Sednitzky-Semler and Halina Baran. The article was written by Halina Baran and Berthold Kepplinger.

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