Cephalalgia


The aim of this research was to study the prevalence of chronic headache (CH) and associated socio-cultural factors in Turkish immigrants and native Germans. Five hundred and twenty-three Turkish and German company employees were screened using a standard questionnaire. Those who suffered from headaches were also examined by a neurologist. Complete data were available for 471 (90%) subjects. Thirty-four participants (7.2%) had CH. Two independent factors for association with CH could be identified: overuse of acute headache medication (OR = 72.5; 95% CI 25.9-202.9), and being a first-generation Turkish immigrant compared with native Germans (OR = 4.4; 95% CI 1.4-13.7). In contrast, the factor associated with chronic headache was not increased in second-generation Turkish immigrants. Medication overuse was significantly more frequent in first-generation Turkish immigrants (21.6%) compared with second-generation Turkish immigrants (3.3%) and native Germans (3.6%; χ² = 38.0, P < 0.001). First-generation Turkish immigrants did not contact headache specialists at all, compared with 2.8% of second-generation Turkish immigrants and 8.8% of native Germans (χ² = 118.4, P < 0.001). Likewise no first-generation Turkish immigrant suffering from CH received headache preventive treatment, compared with 6.6% of native Germans (χ² = 19.1, P = 0.014). The data from this cross-sectional study reveal a high prevalence of chronic headache as well as a very low utilization of adequate medical care in first-generation Turkish immigrants in Germany. □ Chronic headache, cross-sectional study, epidemiology, German, Turkish

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Introduction

The term chronic headache (CH) usually describes migraine or tension-type headache that occurs on more than 14 days per month (1). Population-based studies suggest that CH is a common disorder and a growing health problem all over the world (2, 3, 5–7). Mechanisms and risk factors leading to the development of CH are still unclear. The majority of studies suggest the pivotal role of overuse of acute headache medication as the main risk factor in developing chronic headache (8, 9).

Several epidemiological surveys have suggested a low socio-economic status to be associated with a higher risk of CH as well (10). The aim of the current study was to investigate the influence of socio-cultural factors that could be involved in developing CH.

Turkish immigrants represent the largest non-German population within the Federal Republic of Germany. Due to significant language barriers and socio-cultural and religious differences the integration of first-generation immigrants is rarely achieved, subsequently leading to poor
socio-economic conditions and low-income households. Typically, the household income of first-generation immigrants is generated by low-income jobs in the service industry. We therefore studied over 500 subjects in a company that employs first-generation immigrants, second-generation immigrants and native Germans.

Methods

The study population comprised Turkish and German employees of a large company in Germany. We selected this company because besides the German employees, nearly half of the workers were Turkish immigrants and the vast majority of the employees, both Turkish and German, were living in the township. Our data collection took place during 2001 and 2002. Headache types (migraine, tension-type headache, chronic headache) were diagnosed according to the IHS (International Headache Society) criteria.

The study population comprised 523 subjects. All parts of the company structure (workers, trainees, administrators and managers), except those on the night shift, sick leave or vacation, were included in the study. All subjects were screened using a structured headache questionnaire as described previously (8, 11). Screening interviews were carried out face-to-face by medical students of Turkish origin, who were fluent in both German and Turkish. All subjects who reported having headaches during the previous year were examined by an experienced neurologist of Turkish origin, who also was fluent in both languages. Subjects who reported having headache on more than 14 days per month were considered as patients with CH.

Study participants were asked about their demographic and socio-cultural characteristics, including age, gender, origin, nationality, religion, education, current occupation and fluency in the German language. We also collected data on headache characteristics, and intake of acute and preventive headache medication. Subjects were also asked about their contacts with physicians (headache specialists) as well as with other non-medical therapists (acupuncture, Jacobson muscle relaxation and physiotherapy). Turkish subjects were asked whether they consulted a Hoca (Islamic priest) because of suffering from headaches.

Statistical analysis

We used logistic regression to assess the association of potential associated factors with CH. The origin of subjects ('ethnicity', the variable of interest) was divided into three groups: Turkish immigrants of the first generation and Turkish immigrants of the second generation (who had been born and raised in Germany) and native Germans. In order to control for possible confounders we included the following variables into the model: age (interval scaled, years), gender (male vs female), overuse of acute headache medication, education and occupation. Subjects who graduated from high school or university were considered as 'high education', otherwise as 'low education'. Occupation has been divided into 'high occupation' (executives) and 'low occupation' (subjects in training, workers and skilled workers).

We calculated crude and multivariable-adjusted odds ratios (OR) and their corresponding 95% confidence intervals (CI). We used a stepwise selection procedure to identify the most important multivariable adjusted associated factors for chronic status of headache using a P-value of ≤0.02 as inclusion or exclusion criteria. All analyses were performed using SPSS (version 11.0).

Results

We screened 523 subjects. Complete sets of data were available from 471 (90%) subjects. There were 246 women and 225 men, with a mean age of 29.7 ± 6.3 years; 222 (47%) subjects were German natives and 249 (53%) were Turkish immigrants.

Demographic, socio-economic and clinical characteristics of the studied population are shown in Tables 1–3. Overall, 45% of subjects reported having headache in the previous year. Thirty-four subjects (7.2%) fulfilled the criteria of CH, and 21 (4.5%) subjects overused the acute headache medication. Seventeen subjects overused analgesics and four subjects overused ergots.

A comparison of demographic and socio-economic features of the studied population revealed that the group of first-generation immigrants was on average older and comprised subjects with a lower socio-economic status, while the sub-population of the Turkish immigrants of the second generation did not differ from the group of German natives.

The stepwise selection procedures identified two main factors associated with CH: 'overuse of acute headache medication' and 'ethnicity' of the studied population. Subjects who overused acute headache medication had a higher prevalence of CH (OR = 72.5; 95% CI 25.9–202.9). CH was more than four times more likely (OR = 4.4; 95% CI 1.4–13.7) among Turkish immigrants than among German natives. The prevalence of chronic headache was not
Table 1 Demographic and socio-economic characteristics of the studied population

<table>
<thead>
<tr>
<th></th>
<th>German natives (n = 194)</th>
<th>First-generation Turkish immigrants (n = 97)</th>
<th>Second-generation Turkish immigrants (n = 180)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>28.6 ± 5.9</td>
<td>36.5 ± 5.4*</td>
<td>27.3 ± 4.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Females</td>
<td>43.3%</td>
<td>33%*</td>
<td>49.4%</td>
<td>0.34</td>
</tr>
<tr>
<td>'Low' education</td>
<td>82.5%</td>
<td>97.9%*</td>
<td>83.3%</td>
<td>0.01</td>
</tr>
<tr>
<td>'Low' occupation</td>
<td>88.1%</td>
<td>100%*</td>
<td>92.2%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Significant.

Table 2 One-year prevalence of clinically confirmed headache conditions among 471 German employees by ethno-cultural origin

<table>
<thead>
<tr>
<th></th>
<th>German natives (n = 194)</th>
<th>First-generation Turkish immigrants (n = 97)</th>
<th>Second-generation Turkish immigrants (n = 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>30 (15.5%)</td>
<td>15 (15.5%)</td>
<td>29 (16.1%)</td>
</tr>
<tr>
<td>Tension-type headache</td>
<td>45 (23.2%)</td>
<td>46 (47.4%)</td>
<td>45 (25.0%)</td>
</tr>
<tr>
<td>CH</td>
<td>7 (3.6%)</td>
<td>23 (23.7%)</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td>Overuse of acute headache drugs</td>
<td>3 (1.5%)</td>
<td>16 (16.5%)</td>
<td>2 (1.1%)</td>
</tr>
</tbody>
</table>

Table 3 Crude and adjusted odds-ratio for the relation of ethnicity to chronic headache

<table>
<thead>
<tr>
<th>Variable of interest 'ethnicity'</th>
<th>OR 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>German natives</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>First-generation Turkish immigrants</td>
<td>8.3</td>
<td>3.4-20.1</td>
</tr>
<tr>
<td>Second-generation Turkish immigrants</td>
<td>0.6</td>
<td>0.2-2.1</td>
</tr>
<tr>
<td>Adjusted for age, gender, education and occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>German natives</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>First-generation Turkish immigrants</td>
<td>4.7</td>
<td>1.7-12.5</td>
</tr>
<tr>
<td>Second-generation Turkish immigrants</td>
<td>0.69</td>
<td>0.2-2.5</td>
</tr>
<tr>
<td>Adjusted for age, gender, education, occupation and overuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>German natives</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>First-generation Turkish immigrants</td>
<td>4.4</td>
<td>1.4-13.7</td>
</tr>
<tr>
<td>Second-generation Turkish immigrants</td>
<td>0.6</td>
<td>0.2-2.1</td>
</tr>
</tbody>
</table>

Increased in Turkish immigrants of the second generation. All other evaluated variables were not included in the final models. Use of a backward elimination procedure yielded the same final model.

Prevalence of medication overuse was higher in Turkish immigrants of the first generation (21.6%) than in Turkish immigrants of the second generation (3.3%) and in Germans (3.6%; $\chi^2 = 38.0$, $P < 0.001$). The first generation of Turkish immigrants did not contact headache specialists at all ($\chi^2 = 2.8\%$ of Turkish immigrants of the second generation and 8.8% of German patients; $\chi^2 = 118.4$, $P < 0.001$) and none of them received headache preventive treatment ($\chi^2 = 6.6\%$ of German patients; $\chi^2 = 19.1$, $P = 0.014$). Twenty-three German headache sufferers (12%), but none of the Turkish headache patients, consulted a headache specialist. Thirteen subjects out of the total population (2.8%) received headache preventive therapy. All these subjects were German. In contrast, none of the Turkish subjects had medical headache prevention. Overall, 40 headache sufferers used non-medical treatment options, such as acupuncture, Jacobson muscle relaxation or physiotherapy. Subjects of Turkish origin of the first generation used non-medical treatment options more frequently than German headache sufferers (28.4% vs 4.5%);
Discussion

Using a cross-sectional design, we studied a mixed sample of German natives and Turkish immigrants in Germany to evaluate possible socio-economic and cultural factors associated with chronic headache.

We found the 1-year prevalence of headache to be 45%, which is basically lower than in most population-based studies (12–14). Some others, however, have reported comparable results (15). In our study, the lower prevalence could be explained by the fact that we investigated employed subjects, who probably are healthier than subjects of a population-based sample. The prevalence of chronic headache of 7.2% observed in our study was higher than in previous reports (2–7). Subgroup analysis suggests that this was due to a very high frequency (23.7%) in the subgroup of the first generation of Turkish immigrants. The prevalence of CH in the subgroup of Turkish immigrants of the second generation (2.2%), however, was similar to that in German natives (3.6%) and comparable with previous studies. The 1-year prevalence of migraine and tension type headache in both subgroups of Turkish immigrants observed in our study is in line with results of the Turkish Headache Epidemiology Study Group’ (17).

The main finding of our study is that we were able to identify two factors associated with chronic headache: overuse of acute headache medication and being a Turkish immigrant of the first generation. Overuse of acute headache medication is well known as probably the strongest risk factor associated with chronic headache. Many cross-sectional studies demonstrated a coexistence of medication overuse in the majority of patients with chronic headache (2–6). Moreover, recent prospective studies clearly demonstrated that critically frequent use of acute headache drugs is a main risk factor for de novo development of chronic headache (8, 9, 16). In parallel with these reports the majority of subjects in our population overused analgesics. Interestingly, none of the studied patients overused triptans. This fact might indirectly indicate that triptans probably have not yet been introduced to this patient population. This is in line with another observation, that only 23 headache sufferers (all of them Germans) contacted a headache specialist and only 13 patients received headache preventive treatment. These observations clearly suggest a lack of adequate headache care in the studied population, especially in the subgroup of Turkish immigrants of the first generation.

We understand that the very high odds ratio for overuse of acute headache medication can be caused by comparison of subjects with chronic headache with subjects without any headache and therefore not taking any painkillers at all. We therefore analysed the subpopulation of subjects with headache and found a lower odds ratio for medication overuse, which is comparable with a previous study by our group (8).

A group of Turkish immigrants of the first generation had a fourfold increased prevalence rate of having CH. This finding could be explained by the following: Turkish immigrants of the first generation had poor knowledge of German language, were less educated and had a lower socio-economic status. Probably these factors were responsible for poor access to health care facilities. The rate of consultations with headache specialists was the lowest in this group. Consequently, Turkish headache sufferers did not use headache preventive medication but rather ineffective non-medical treatment options. Turkish immigrants of the first generation often consulted a Hoca to treat their headache. Magic conceptions of aetiology and pathogenesis of diseases have a broad acceptance in this population. Hocas are authorities to be consulted for treatment. In ritual acts they intend to stave off noxious influences and to strengthen the healing power with sacred formulas and through powerful objects. In contrast, the subpopulation of second-generation Turkish immigrants, who grew up in Germany, did not differ from the subgroup of German natives with regard to socio-economic characteristics. Probably therefore, the prevalence of CH in Turkish immigrants of the second generation was comparable with that in German natives.

In conclusion, our data suggest that inadequate medical care due to language barriers or socio-cultural differences leads to a higher rate of chronic headache. Turkish headache sufferers often do not realize that excessive or frequent self-treatment may perpetuate or exacerbate their headaches. Most of the Turkish headache sufferers of the first generation do not seek medical advice. The opportunity for diagnosis and adequate medical intervention to halt the cycle is often missed. Physicians need to screen
CH patients for medication overuse. Turkish headache patients must be informed about the risks of analgesic overuse and rebound headache.

Acknowledgement

This study was supported by the Ministry of Health in Nordrhein-Westfalen, Germany.

References

Clozapine with amisulpride for refractory schizophrenia.


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[Indexed for MEDLINE]
pression and to a discontinuation of, or a change in, medication. With subsequent improvement in the patient’s condition that may hinder the diagnosis of hepatotoxicity and explain the scarcity of reports, despite its continuous use.

In experimental animals, citalopram was found to induce a fatty liver. A metabolite generated through its first-pass metabolism has been suggested to be responsible for the liver toxicity (2). Taken together, these findings and the absence of hypersensitivity features suggest that a metabolically mediated mechanism is feasible.

Cross-hepatotoxicity has been reported with tricyclic antidepressants (3). Citalopram possesses a chemical structure unrelated to that of other antidepressants, which is consistent with the lack of cross-reactivity observed in this patient.

Cross-reference

References

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Is Multiple Cavernoma a Developmental Defect in Schizophrenia?

To the Editor: The neurodevelopmental hypothesis of schizophrenia suggests that the interaction between genetic and environmental events during critical periods of neuronal growth in utero may adversely affect neuronal architecture in adulthood (1). Multiple cavernoma (multiple cavernous hemangioma) is a developmental defect of small blood vessels that causes diffuse heme-vascularizing of vessel spaces in the brain (2). This results in sedimentation, thrombosis, and calcification, which can be seen on magnetic resonance imaging (MRI).

Here we present a case of schizophrenia with obsessive-compulsive symptoms in a woman with familial bilaterally diffuse cavernoma.

Ms. A., an 18-year-old unmarried woman, was admitted to our ward with psychosis and obsessive-compulsive symptoms. She had ego-dystonic mental obsessions (she reported having “ugly thoughts” about others) and an ego-syntonic delusion that others could read these thoughts. She reported an extensive family history. Her mother had a meningioma, and her brother and uncle suffered from cavernous hemangioma (cavernoma). Her brother also suffered from epilepsy. There was no family history of schizophrenia or obsessive-compulsive disorder.

During high school, she was socially withdrawn and preferred to stay at home. One year before her admission, she developed paranoid delusions about her classmates but was not treated.

On admission, results of Ms. A’s neurological and dilated ophthalmoscopic examinations were normal. A computerized tomography scan showed two suspected enhance-

ments. Subsequent MRI demonstrated multiple cerebral cavernomas bilaterally, with typical “rings” visible on T2 imaging. Cavernomas were most abundant in the temporal and frontal regions. Her EEG was normal. An exacerbation of her paranoid thoughts during the first hospital week did not respond to 5 weeks of risperidone treatment (maximum dose=6 mg/day). At that time, she was switched to olanzapine, 20 mg/day, with a remission of her psychosis within 3 weeks. The addition of sertraline, 50 mg/day, relieved her obsessive-compulsive symptoms after an additional 4 weeks.

Familial cavernoma is an autosomal dominant disorder with incomplete penetrance (3). The 7q locus might harbor the causative gene (4). Common clinical signs of multiple cavernoma include neurological deficits, seizures, and hemorrhage (2), although these were not present in this patient. It is possible that this patient’s schizophrenia was causally linked to the developmental effects of her hereditary diffuse brain vessel malformation. Alternatively, this could represent an incidental and extremely rare comorbidity. (We found no such cases in the literature.)

References
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Clozapine With Amisulpride for Refractory Schizophrenia

To the Editor: Only sparse data exist regarding combination treatments of clozapine with other psychiatric medications or ECT (1). Here we report on seven patients who received combined application of clozapine and amisulpride. Amisulpride is not marketed in the United States. It acts primarily on dopaminergic D2 and D3 receptors of the limbic system. Because of its lower induction of extrapyramidal symptoms and its better efficacy against negative symptoms (compared to typical neuroleptics), it is grouped among the atypical neuroleptics.

Seven patients (four men and three women) with a paranoid-hallucinatory (N=3) or schizoaffective psychosis (diagnosed according to DSM-III-R) gave written informed consent to be treated with clozapine combined with amisulpride. Their mean age was 41.3 years (SD=7.9, range=32-54). In the preceding 12-72 months, each had received neuroleptics from at least three different classes (butyrophenone, thiothixene, and phenothiazine); in four cases, ECT was also applied. Since no significant improvement had occurred, all patients had been given monotherapy with clozapine; the average length of treatment was 3 weeks (range=8-52). With
clozapine (an average dose of 293 mg/day), there was also no significant clinical improvement.

We then decided to administer amisulpride additionally to these patients. Treatment success was monitored with the Clinical Global Impression Scale (CGI) and the Brief Psychiatric Rating Scale (BPRS). The average dose of amisulpride was 543 mg/day (SD = 223, range = 200–800); comedication included lithium in two cases and lorazepam in three. The addition of amisulpride to clozapine was followed by a decrease in the mean BPRS total score from 50.1 (SD = 3.9) to 45.9 (SD = 4.6) after a 17-day period (Wilcoxon test: Z = −2.02, p < 0.05) and to 33.7 (SD = 9.3) after an average of 9.7 months (Wilcoxon test: Z = −2.20, p < 0.03). Global severity of the disease (CGI score) decreased from 6.7 (SD = 0.5) to 4.8 (SD = 1.1) points (Wilcoxon test: Z = −2.20, p < 0.03). Treatment response was rated as at least good (CGI score ≤ 2) in six of seven cases.

A 12-channel ECG was carried out before initiation of amisulpride (baseline) and 17 days later, on average. QTc times were evaluated as described elsewhere (2). There were no significant changes in ECG time intervals after the addition of amisulpride to clozapine; the mean resting heart rate and mean QTc time both remained unchanged (heart rate: 95.9 bpm versus 93.6 bpm; QTc: 339 msec versus 331 msec). The maximal QTc time was 410 msec. Mean clozapine plasma levels did not differ significantly compared to baseline (the average difference was −28.3 ng/ml).

Even though we could not definitively dismiss that monotherapy with clozapine might otherwise have led in some cases to an improvement in psychosis over long-term treatment (3), our preliminary data suggest that combined clozapine and amisulpride significantly improves schizophrenia symptoms after a relatively short time. The mechanisms underlying this remain unclear. The dopamine D2 and D3 receptor-blocking effects of amisulpride might complement the receptor binding profile of clozapine effectively, and such a combined receptor interaction might trigger an improvement in psychotic symptoms.

References

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Antidepressants and Premature Labor

To the Editor: Gregory E. Simon, M.D., M.P.H., and colleagues (1) neglected to include important issues in their report. The risk factors for premature labor include low socio-economic status, previous occurrence of premature labor, gestational bleeding, and uterine irritations (2). Failure to consider obstetrical health presents the possibility that these factors occurred more commonly in the group exposed to selective serotonin reuptake inhibitors (SSRIs) and were responsible for the higher rate of prematurity.

The study included women who delivered between January 1996 and December 1998. The rates of preterm delivery over the interval 1975 to 1995 increased by 3.6% among blacks and by 22.3% among whites, which indicates the presence of period effects (3). SSRI use was more common than tricyclic antidepressant use in the latter years of the study by Dr. Simon et al. (1966-1998). Therefore, a twofold increase in the rates of preterm labor cannot be specifically attributed to SSRIs exposure.

Depressive symptoms were not assessed directly. Some women in both antidepressant treatment groups and the control group will remain depressed or have subthreshold symptoms. Either the active (state) effects of depression or the residual (trait) effects (changes in maternal physiology that remain even when the mother is asymptomatic) could affect pregnancy outcome negatively. Positive outcomes attributed to an SSRI may be related to either unmitigating depression or the interaction of depression with SSRI exposure. To propose that negative outcomes are not due to depression because they occurred differentially across the two antidepressant-treated groups is valid only if symptom levels in both groups were equivalent.

Potentially toxic exposures have specific considerations during pregnancy that are not reported: the dose, the timing of the dose during gestation, and the changes in dose across the pregnancy. Malformations are unrelated to second- and third-trimester exposures. The likelihood that exposure to an SSRI at any time during pregnancy affects outcomes at birth is biologically implausible and conflicts with the findings of Chambers et al. (4) and Cohen et al. (5), who found that only third-trimester SSRI exposure affected birth outcomes. Pastuszak et al. (6) also found no relationship between first-trimester exposure to fluoxetine or a tricyclic antidepressant and gestational age or birth weight, contrary to such a statement by Dr. Simon et al. (p. 2060).

References

Terlipressin and gelafundin: safe therapy of hepatorenal syndrome.

Saner F¹, Kauker L, Bilgiami S, Frühauf NR, Schäfers RF, Malagó M, Broelsch CE.

Abstract

BACKGROUND AND AIM: Hepatorenal syndrome (HRS) occurs in about 20% of patients with liver cirrhosis and ascites and is characterized by intensive renal vasoconstriction, low glomerular filtration rate but preserved tubular function and normal renal histology. The potential of terlipressin and albumin to reverse HRS after a time period of 14 days has already been shown. However, intravenous albumin is expensive (approximately 25 per 50 ml 20% albumin in Germany) and has limited availability in some settings. Therefore we used an artificial plasma substitute, Gelatinepolysuccinat, which is less expensive (approximately 12 per 500 ml). The aim of our present study was to examine the effects of terlipressin and Gelatinepolysuccinat on renal function and hemodynamics in a time period of six days.

METHODS AND PATIENTS: Seven consecutive patients with cirrhosis and hepatorenal syndrome were included in a pilot study of terlipressin (6 mg 24 h iv) therapy associated with i.v. Gelatinepolysuccinat (Gelafundin 4% Infusionslösung, Company Braun, Mr: 30 000 D).

RESULTS: In five of the seven patients treatment was associated with a marked reduction of serum creatinine after six days (3.85 +/- 0.44 mg/dl vs. 1.9 +/- 0.32 mg/dl; p < 0.018). Creatinine clearance improved (20 +/- 8.8 ml/min vs. 43 +/- 11.7 ml/min; p < 0.12). There was a remarkable improvement in circulatory function in all patients, with an increase in mean arterial pressure (58 +/- 4.4 mmHg vs. 75 +/- 4.5 mmHg, p < 0.001). No patient developed signs of intestinal, myocardial or distal ischemia.

CONCLUSIONS: Terlipressin and Gelatinepolysuccinat appear to be a safe and effective treatment of hepatorenal syndrome.
Wernicke's encephalopathy: unusual contrast enhancement revealed by magnetic resonance imaging.

Kanuk T, Amsellem VY, Goertler A, Kastrup O, Dehde A, Maschke M, Diener HC

Abstract

Wernicke's encephalopathy is a serious neurologic disorder caused by vitamin-B1 or thiamine deficiency. The classical triad of clinical symptoms described by Wernicke (gait ataxia, ophthalmoplegia, and confusion) are found in only a third of patients upon initial examination. Typical findings upon MR imaging in patients with Wernicke's encephalopathy are well documented, with signal intensities in the medial thalami and periaqueductal regions of the midbrain. We report a case of Wernicke's encephalopathy revealing an unusual contrast enhancement. It is therefore important to note that the acute stage of Wernicke's encephalopathy may be associated with an intense contrast enhancement upon MR-imaging reflecting the disruption of the blood-brain barrier and inflammatory processes caused by thiamine deficiency. As a consequence from the guideline for managing Wernicke's encephalopathy by the Royal College of Physicians early B-vitamin treatment in suspected is recommended cases.

PMID: 14644703

[Indexed for MEDLINE]
Komorbidität zwischen kardiovaskulären Erkrankungen und Depressionen

Interaktion zwischen depressiven und kardiovaskulären Erkrankungen


Nachdem auch die Ergebnisse neuerer epidemiologischer Studien weitgehend übereinstimmend Hinweise für eine signifikante Komorbidität zwischen depressiven und kardiovaskulären Erkrankungen lieferten, wurde in den letzten Jahren einem pathophysiologischen Zusammenhang zwischen diesen beiden Erkrankungen vermehrt Beachtung geschenkt (21). Zusammenfassend wurde festgestellt, dass etwa 16–23% aller Patienten mit kardiovaskulären Erkrankungen gleichzeitig an schweren, behandlungsbedürftigen Depressionen (in der internationalen Literatur sog. „Major Depression“ nach DSM-III-R bzw. DSM-IV) leiden, wobei sich die Punktprävalenz für depressive Syndrome auf über 40% erhöht, wenn leichtere Formen einer Depression (sog. „Minor Depression“) mit berücksichtigt werden [Obersicht in (35)]. Dabei besteht offenbar kein Zusammenhang zwischen dem Grad der körperlichen Behinderung durch die kardiovaskuläre Erkrankung und dem Ausprägungsgrad des depressiven Syndroms bzw. der Intensität der depressiven Symptome (8,15,16,40). Weiter konnte gezeigt werden, dass depressive Syndrome das relative Risiko für eine spätere Manifestation kardiovaskulärer Erkrankungen auch bei zunächst Gesunden erhöhen (4,11,12,13,14,36,37), wobei allerdings die Angaben über die relative Risikoerhöhung für kardiovaskuläre Erkrankungen mit dem 1,7- bis 4,5-fachen Risiko (13,37) in der Literatur noch erheblich streuen. Bei Patienten mit bereits zuvor bestehenden Herz-Kreislauf-Erkrankungen gelten depressive Syndrome als ein unabhängiger, prognostisch negativer Faktor, wobei das Vorhandensein einer Depression das kardiovaskuläre Mortalitätsrisiko signifikant erhöht (15,16,17,20,27).

Bezüglich dieser Datenlage wurde oftmals hinterfragt, ob depressive Erkrankte nicht ohnehin ein höheres kardiovaskuläres Risikoprofil haben würden, z.B. durch Zigarettenrauchen, Bewegungsmangel, eine ungenügende Ernährung und mangelhafte Mit- arbeit sowohl bei Rehabilitationsmaßnahmen als auch bei der Einnahme der verordneten Medikation (6,19). Aber auch wenn die genannten Faktoren statistisch adäquat berücksichtigt wurden, zeigten depressive Erkrankte im Vergleich zu psychisch Gesunden ein relativ höheres kardiovaskuläres Mortalitäts- und Mortalitätsrisiko (3,4,12,36,37), wenngleich auch wenige Studien keine derartige Risikoerhöhung ergaben (10,18,46).


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Bibliografie


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Electrically evoked nociceptive potentials for early detection of diabetic small-fiber neuropathy

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Keywords: diabetes mellitus, pain-related evoked potentials, small-fiber neuropathy

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Background and purpose: This study investigated the utility of pain-related evoked potentials (PREP's) elicited by a nociceptive electrical stimulation of the skin (= electrically evoked nociceptive potentials) in early detection of diabetic small-fiber neuropathy.

Methods: We studied 36 'young' (19–35 years) and 24 'older' (36–65 years) healthy subjects as well as 35 patients (35–64 years) with diabetes and neuropathic symptoms and 22 patients (34–64 years) with diabetes without neuropathic symptoms. Only patients with normal standard nerve conduction testing were included.

Results: In patients with neuropathic symptoms, we found a significant increase in PREP latencies and decrease of amplitudes elicited from both, upper and lower limbs. In non-symptomatic diabetic patients, we observed PREP abnormalities from lower limbs only.

Conclusions: These data suggest that the method of pain-related evoked potentials elicited by a nociceptive electrical stimulation of the skin may contribute to the early detection of diabetic sensory neuropathy.

Introduction
Small-fiber neuropathy (SFN) has recently been defined as 'a neuropathy characterized by autonomic abnormalities and/or positive (spontaneous or stimulus-induced) and negative sensory symptoms, caused by the selective dysfunction of Aδ- and C-fibers as assessed by specific neurophysiologic and neuropathologic tests. Asymptomatic impairment of small fibers may occur in certain conditions' [1]. SFN predominantly affects small Aδ- and C-fiber function resulting in tingling, burning or prickling sensations, shooting pain or aching. Although common, pain is not synonymous with small-fiber dysfunction and also occurs with large-fiber disorders [2]. The most common causes of SFN are diabetes mellitus, drugs and toxics, infections, autoimmune diseases, inherited sensory and autonomic neuropathies and idiopathic [1].

Diagnosis of SFN [3,4] is difficult because standard nerve conduction studies are generally normal. More specialized tests of small-fiber function include plantar sympathetic skin response (SSR) [1] or assessing sudomotor axon reflex (QSART) [5]. Laser-evoked potentials (LEP) were proposed as an alternative electrophysiological tool in detecting small-fiber dysfunction in diabetic SFN [6,7]. Contact heat-evoked potentials (CHEP's) are another valid means in studying nociceptive pathways [8]. Histological assessment of intra-epidermal nerve fiber (IENF) density appears to be reliable, but requires a slightly invasive skin biopsy procedure [3]. Quantitative sensory testing (QST) is another important tool for analyzing small-fiber dysfunction. Recently, in a profound analysis of 124 patients with sensory neuropathy, the authors proposed that a combination of QST, IENF examination and the presence of at least two abnormal clinical signs could be used as a new diagnostic 'gold standard' to confirm a clinical suspicion of SFN [4].

We developed a concentric surface electrode for non-invasive stimulation of cutaneous nociceptive fibers. By virtue of its concentric geometry and small anode–cathode distance a high current density can be achieved at relatively low current intensities, which limits depolarization to nociceptive fibers in the superficial layer of the dermis, without recruitment of deeper lying non-nociceptive fibers (Fig. 1) [9].
Neues zur Epidemiologie von Kopfschmerzen

Recent New Information on Epidemiology of Headache

Zusammenfassung


Abstract

We reviewed the epidemiology of headache disorders for the most frequent primary headache-syndromes: migraine, tension-type headache and trigemino-autonomic headache syndromes. In the last years scientific data about headache disorders have increased. New studies investigated not only the prevalence of headaches, but also economic costs of this disorder. Epidemiologic headache research also investigates the quality of life.

Einleitung


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Bibliografie

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Airway nitric oxide in infants with acute wheezy bronchitis


Concentrations of nitric oxide (NO) in exhaled air are increased in children and adults with asthma, and NO measurements are used as a non-invasive marker to monitor airway inflammation in these patients. To define the role of NO in infants with acute wheezy bronchitis, we measured nasal and end-tidal NO concentrations in 17 infants with acute virus-associated wheezy bronchitis, in 22 term infants without respiratory disease, and in nine premature infants. Nasal NO measurements were performed with an olive placed in the infant’s nose; end-tidal NO concentrations were assessed during tidal breathing through a snugly fitting face mask. Both end-tidal NO concentrations and nasal NO concentrations were reduced in infants with acute wheezy bronchitis. There were no differences in NO concentrations between term infants and premature infants. Measurements by both techniques were highly reproducible, as assessed by repeated measurements three times daily on three consecutive days in eight premature infants. Reduced airway NO concentrations in infants with virus-associated acute wheezy bronchitis are in contrast to findings in adults where both upper and lower airway NO levels are increased in patients with asthma. Whether this reflects a different inflammatory reaction to upper airway infections in acutely wheezy infants or pathophysiologic differences in airway response remains to be determined.

Nitric oxide (NO), which is formed by enzymes in a variety of tissues, is involved in many physiologic processes within the respiratory tract, including regulation of bronchomotor tone, inflammation, and host defence (1). Airway NO concentrations are increased in diseases associated with airway inflammation, such as asthma and upper respiratory tract infections (2,3). Recent studies suggest that the elevated levels of NO in exhaled air may reflect the degree of airway inflammation in both paediatric and adult patients with asthma and, in some centres, NO is currently used to monitor response to treatment (4–7).

Wheezing associated with viral upper airway infection is very common in infants. Epidemiological studies suggest that ~30% of all children under 3 years of age will have at least one episode of wheezing (8). Only a fraction of these children will have continuous symptoms compatible with the diagnosis of childhood asthma. Currently there is no simple and non-invasive technique available to monitor the evolution of airway inflammation in wheezy infants. Techniques to measure airway NO in infants differ from those used in older children and adults as infants breathe mainly through the nose. Airway NO is therefore invariably contaminated by upper airway NO, the concentration of which is known to be much higher than that of the lower airway (9,10). In the present study we used two different techniques to measure airway NO in infants, and report our findings on airway NO concentrations in normal infants and in infants with acute virus-associated wheezy bronchitis.

Materials and methods
The study population consisted of three groups of infants:
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Susanne Koeppen
Markus Agelink
Arnd Dörfler
Volker Limmroth
Hans-Christoph Diener

Transient MRI abnormalities associated with partial status epilepticus

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Sirs: Neurological disorders of different etiology may cause identical clinical symptoms requiring additional diagnostic procedures for a precise diagnosis. Focal epileptic seizures have been shown to cause increased signal intensities in T2 and diffusion-weighted magnetic resonance images (MRI), mimicking other neurological disorders or diseases such as viral encephalitis [1]. In some cases even the combination of neuroimaging and cerebrospinal fluid (CSF) analysis is not sufficient to obtain the final diagnosis, since epileptic seizures may cause pleocytosis as well. We present three cases of focal status epilepticus with severe but reversible MRI changes.

Three patients with focal status epilepticus who underwent cranial MRI during or within two days of a status epilepticus were studied. Clinical evidence of epileptogenic causes, such as metabolic imbalance, systemic hypertension, encephalitis or hypoxic encephalopathy, was excluded. All patients had suffered a status of a complex partial seizure [2]. They had all recurrent complex partial seizures without full recovery of consciousness between seizures.

The seizures in the first case began with impairment of consciousness without other features. We were able to perform MRI during the status, after 7 hours. The status lasted nearly 15 hours and the patient had no motor symptoms. Treatment was with clonazepam intravenously (IV). After a non-response to clonazepam we gave valproate IV which was successful.

In the second case complex partial seizure began with cognitive and affective symptoms and the duration was nearly 20 hours. MRI was performed during the phase of returned consciousness (after 9 hours). We began a treatment with valproate IV.

The last case began as a simple partial seizure with initial weakness of the right hand and progressed to impairment of consciousness. This patient underwent cranial MRI within 28 hours. At first we gave lorazepam IV, which improved the motor symptoms, but not the impairment of consciousness. It was while consciousness was impaired (and without motor symptoms) that the patient underwent cranial MRI. Also in this case we began treatment with valproate IV. For establishing the diagnosis of epilepsy, all patients underwent clinical examination, electroencephalography (EEG), analysis of CSP (see Table 1). MRI was performed using a 1.5 Tesla clinical scanner (Sonata, Siemens, Erlangen, Germany).

MRI of the head showed focal hyperintensity in the temporo-medial or temporo-polar lobe after a status of complex partial seizure in all patients. The abnormalities were reversible.

Many conditions can imitate focal epilepsy of prolonged duration. EEG remains the most sensitive investigation. Also EEG has a prominent position in the diagnostic criteria of the International Classification of Seizures and is

Table 1 Summary of Clinical Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pat. 1</th>
<th>Pat. 2</th>
<th>Pat. 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset (years)</td>
<td>72</td>
<td>56</td>
<td>50</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>First MRI within (h)</td>
<td>7</td>
<td>9</td>
<td>28</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CT</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CSF</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cell count/μl</td>
<td>4</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Protein analysis (mg/l)</td>
<td>400</td>
<td>190</td>
<td>284</td>
</tr>
<tr>
<td>PCR</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>ECG</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Epileptiform Potentials/Focus</td>
<td>Delta-focus in the left temporomedial lobe with spikes and spike-wave complexes</td>
<td>Delta-focus in the left frontotemporal lobe</td>
<td>Delta-focus in the right frontotemporal lobe</td>
</tr>
</tbody>
</table>
Allein die enge Verbindung beider Fachdisziplinen im klinischen Alltag begründet die Existenz eines Buches zu dem Thema. Zudem sind es der Essener Prof. Berlit und dem inzwischen zum IQWIG gewechselten Prof. Sawicki zwei klinisch und wissenschaftlich renommierte Herausgeber geworden.


I. Kavuk, Bottrop
PSYCHOLOGICAL FACTORS IN THE IRritable BOWEL SYNDROME

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Abstract

Objective: The role of psychological factors in the irritable bowel syndrome (IBS) is a matter of debate. The prevalence of psychiatric disorders is high in IBS patients. Positive response to antidepressant therapy and presence of family history of depression in IBS patients have led speculations whether this syndrome might be regarded as an affective spectrum disorder. In this study we tried to examine the possible association of IBS with affective spectrum disorders.

Method: Forty IBS patients from gastroenterology outpatient clinics of a university hospital and state hospital, 32 controls with inflammatory bowel disease and 34 healthy hospital workers were included in the study. Psychiatric interviews were done using SCID-NP (Structured Clinical Interview for DSM-Non-patients) and psychological factors were assessed by the SCL-90-R (Symptom Checklist-90-Revised), the Beck Depression Inventory, the Beck Anxiety Scale and the Hamilton Rating Scale for Depression. Family histories were obtained by FH-RDC (Family History Research Diagnostic Criteria). All groups were matched for sociodemographic variables.

Results: The prevalence of psychiatric disorders and mood disorders was higher in the IBS group than the control groups. Also IBS group rated higher on anxiety and depression scales than the other groups, where the differences were statistically significant. Presence of positive family history for mood disorders was higher in the IBS group.

Conclusion: These results support the hypothesis that IBS might be linked to affective spectrum disorder. Psychiatric assessment and therapy might be useful in the course of irritable bowel syndrome.

Key words: Irritable bowel syndrome, mood disorders, depression, anxiety

INTRODUCTION

Irritable bowel syndrome (IBS) is a common condition seen in gastroenterology clinics and affects 8-26% of general population (Drossman et al. 1988, Kettel et al. 1992, Lydiard et al. 1993). At 1978, Manning identified four signs most widely seen in IBS patients. These are abdominal distention, pain relieving by bowel movements, increasing frequency of bowel movements with the beginning of pain. These symptoms are called Manning Criteria. These criteria make the clinical IBS diagnosis possible without hindering of a severe underlying organic disorder (Jones 1989, Talley et al. 1990, Maxton et al. 1991). Investigators studying the relationship between irritable bowel syndrome and psychiatric disorders found that the prevalence of psychiatric disorders were high in IBS patients (Wender and Kalm 1983, Langeludeke 1985, Bergeron and Montol 1985, Ford et al. 1987, Whitehead et al. 1988, Kumar et al. 1990, Walker et al. 1990a, Walker et al. 1990b, Lydiard et al. 1993, Garakani et al. 2003, Hudson et al. 2003). Drossmann (1988) reported that there was physical or sexual trauma history in childhood or afterwards in 44% of patients with functional gastrointestinal complaints. Svedlund et al (1985) compared 101 patients with IBS to 677 healthy women and reported that women with IBS showed more anxiety. It was emphasised that the most frequent symptoms were fatigue, anger, sadness, sleep disorders, mild depressive symptoms, obsessive compulsive symptoms, ritual behaviours, decreased libido and decreased appetite, and only few patients had not signs of affective disorder. It has usually been accepted that an anxious or depressed mood may increase the severity of IBS symptoms either because individuals who are more anxious and depressed experience a given level of physical symptoms as more severe, distressing, and disabling or because the physiological changes that accompany mood disorders have a direct influence on gastrointestinal function, increasing the objective experience of IBS symptoms, though there may also be reports finding no association between the severity of depression and reported IBS symptoms (Crane at al. 2003).

Whitehead et al. (2002) note that comorbidity of IBS with other functional gastrointestinal disorders is high and may be caused by shared pathophysiological mechanisms such as visceral hypersensitivity. Psychiatric disorders, especially major depression, anxiety, and somatoform disorders, occur in up to 94%. The nongastrointestinal non-psychiatric disorders with the best-documented association are fibromyalgia (median of 49% have IBS), chronic fatigue syndrome (51%), tempo-
Vertebral artery dissections after chiropractic neck manipulation in Germany over three years

Abstract Vertebral artery dissection (VAD) has been observed in association with chiropractic of the neck. However, most publications describe only single case reports or a small number of cases. We analyzed data from neurological departments at university hospitals in Germany over a three-year period of time of subjects with vertebral artery dissections associated with chiropractic neck manipulation. We conducted a countrywide survey at neurological departments of all medical schools to identify patients with VAD after chiropractic therapy followed by a standardized questionnaire for each patient. 36 patients (mean age 40 ± 11 years) with VAD were identified in 13 neurological departments. Clinical symptoms consistent with VAD started in 55% of patients within 12 hours after neck manipulation. Diagnosis of VAD was established in most cases using digital subtraction angiography (DSA), magnetic resonance angiography (MRA), or duplex sonography. 90% of patients admitted to hospital showed focal neurological deficits and among these 11% had a reduced level of consciousness. 50% of subjects were discharged after 20 ± 14 days of hospitalization with focal neurological deficits. 1 patient died and 1 was in a persistent vegetative state. Risk factors associated with artery dissections (e.g. fibromuscular dysplasia) were present in only 25% of subjects.

In summary, we describe the clinical pattern of 36 patients with vertebral artery dissections and prior chiropractic neck manipulation.

Keywords chiropractic · neck manipulation · artery dissection · disability

Introduction

Spinal manipulation has become increasingly popular since the introduction of this technique in the 18th century. In the last decade about 10 million patients accounted for 125 million chiropractic visits annually in the western world for a variety of reasons. Among these headaches and musculoskeletal disorders such as neck and back pain are most frequent. The risk for severe vascular or neurological complications due to chiropractic is not clear and has been estimated between 1/5,850,000 and 1/100,000 manipulations and therefore considered relatively low [1, 30]. However, some authors consider these numbers underestimated due to underreporting. In addition, most recent prospective surveys among chiropractors investigating the side effects of spinal chiropractic indicate mild and moderate transient adverse events (e.g. local discomfort, headache) in up to 50% of all cases [28, 29].

Several fatal neurological complications such as vertebral artery dissection and combined vertebral and carotid artery dissection have been documented after cervical manipulation in case reports and question the
MRI CHANGES ASSOCIATED WITH PARTIAL STATUS EPILEPTICUS

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Abstract: Neurological disorders of different etiology may cause identical clinical symptoms requiring additional diagnostic procedures for a precise differential diagnosis. Focal epileptic seizures have been shown to cause increased signal intensities in T2 and diffusion-weighted magnetic resonance images (MRI), mimicking other neurological disorders or diseases such as viral encephalitis. In some cases even the combination of neuroimaging and cerebrospinal fluid (CSF) analysis is not sufficient to obtain the final diagnosis, since epilepsy seizures may cause pleocytosis as well. Some epilepsy centers presented cases of focal status epilepticus with severe but reversible MRI changes.

These cases indicate that MRI changes following focal seizures are reversible over a different time window compared to MRI changes associated with other etiologies, such as viral infection. This data further suggest that in cases where focal seizures can not be ruled out, a follow-up MRI scan within a few days following the onset of symptoms significantly improves the precision of the differential diagnosis. Recently new scientific data were reported in this review.

Key words: Partial status epilepticus – Magnetic resonance imaging – Signal abnormalities

INTRODUCTION

A complex partial status epilepticus is a common neurologic emergency. Diagnosis and treatment of this disorder, in the past exclusively performed by a neurologist, has in recent years become a team effort in intermediate care units. Modern management of epilepsy now benefits from developments accomplished in neuroimaging. In epilepsy, magnetic resonance imaging (MRI) has two major clinical indications: first of all, identification or exclusion of a symptomatic cerebral abnormality in patients after an epileptic seizure, and secondly, characterization of epileptogenic foci for presurgical evaluation in patients with drug-resistant epilepsy. Over the last decade, new MRI methods have been developed including perfusion- and diffusion-weighted imaging that are now available for improving the non-invasive localization of an epileptogenic focus.

Up until the end of the eighties reports appeared on transient focal abnormalities observed upon computer tomography (CT) of the brain in patients with partial epilepsy [1]. Since MRI has been in use, Kramer et al. were the first to describe neuroimaging abnormalities related to focal status epilepticus [2]. Only a few studies have appeared describing MRI findings in patients after partial status epilepticus. All of these reports were based on small numbers of patients, of whom some were children [3-6]. Penfield already reported in 1933 a local hyperperfusion during an epileptic seizure while operating on a neurosurgical disorder, an abnormality that was confirmed decades later using functional MRI (fMRI), angiography and radioisotopic measurement (SPECT) [7-9].

Some study groups showed with MRI studies of the head focal hyperintensity in the tempo-medial or temporo-polar lobe after a status of complex partial seizures [29, 30]. In all of these patients the abnormalities were reversible. Optimal timing of neuroimaging with MRI can help to identify patients with a status of complex partial seizures and should also reduce the rate of misdiagnosis of other disorders.

Many conditions can imitate focal epilepsy of prolonged duration. Imaging techniques may be able to help identify such patients. EEG remains the most sensitive technique, but unfortunately it sometimes represents an insufficient marker of focal epileptic status, since EEG changes lack specificity.

MRI AND STATUS EPILEPTICUS

Neuroradiological methods, particularly MRI, are frequently used during a status epilepticus to exclude other neurological disorders. For this reason it has become more important to know the MRI changes which can be caused by a status epilepticus. The important question is whether MRI changes detected represent the consequence or the cause of the status epilepticus. It is also important to know whether the radiological signs (CT scan and MRI) of a status of complex partial seizures are similar to those related to an ischemic stroke, neoplastic processes or inflammatory diseases such as herpes-simplex-encephalitis. Most findings regarding the MRI studies were re-

LITERATUR:


CLINICAL FEATURES AND THERAPY OF MEDICATION OVERUSE HEADACHE

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Abstract: Inappropriate use of headache medication (>15 times/month) for the treatment of headache episodes may contribute to the development of chronic headache which is refractory to most treatments. Physicians experienced in the treatment of migraine and other headaches are well aware that the daily intake of antipyretic or antiinflammatory analgesics, opioids, ergot alkaloids and "tripants" may result in chronic daily headache. Conversely, if a patient complains of chronic headache and takes pain medication every day, this headache is most likely to be caused and sustained by the medication and will vanish or improve with abstinence. Treatment includes drug withdrawal followed by structured acute therapy and initiation of migraine prophylactic treatment.

Key words: Medication overuse headache; Epidemiology; Clinical features; Therapy

INTRODUCTION

The frequent use (>15 times/month) of medication for the treatment of acute migraine attacks may cause medication overuse headache [1]. This kind of headache can be caused by the intake of combination analgesics, opioids, ergot alkaloids and triptans [2]. The time between first intake and daily headache is shortest for triptans (1-2 years), longer for ergots (3-5 years) and longest for analgesics (5-10 years). Treatment includes drug withdrawal followed by structured acute therapy and initiation of migraine prophylactic treatment.

Since 2003 the classification of the International Headache Society (IHS) from 1988 was used [47], but it had lacked precision about triptan induced headaches. Some authors studied the clinical features of triptan misuse and described typical signs of this syndrome [28, 43, 48-50]. Based on this information the IHS created new classification criteria for drug induced headache in 2003 [51].

Up to now no experimental work has been done in this field, and the following review is based mainly on clinical series describing patients presenting at headache clinics with this problem, with subsequent treatment and follow-up.

PREVALENCE

Prevalence rates of chronic medication overuse headache are rare [3]. Our own data revealed that approx. 3.6% suffer from chronic daily headache [4]. To produce these figures, 523 employees of a large textile manufacturer were asked about headaches within the preceding 12 months according to criteria of the International Headache Society. Probands with headaches were studied by a neurologist. As a comparator group, Turkish migrants also employed there were also consulted. Amongst such individuals, the proportion of chronic daily headache patients was significantly higher at 10.7%. In a Spanish population based study, about 1% of the population suffered from daily headache combined with medication overuse headache [5]. Most headache centers report that between 5% and 10% of the patients they see fulfill the criteria of medication overuse headache [6]. Micieli et al. observed an incidence of 4.3% in 3,000 consecutive headache patients [7]. Patients with cluster headache almost never develop medication overuse headache. A survey in family doctors showed, that medication overuse headache was the third most common cause of headache [8]. Taken together, these studies indicate that medication overuse headache is a major health problem. This is also true if one considers the side effects of chronic intake of analgesics, ergotamine and triptans.

Most headache experts agree that patients with migraine and tension-type headache have a higher potential for medication overuse headache [9]. Relapses of migraine occur in migraineurs who have been placed on analgesics for other ailments. The association between analgesic overuse and headache has been studied in conditions other than primary headache disorders. Chronic overuse of analgesics does not cause increased headache in nonmigraineurs [9]. For example, a group of arthritis patients who were consuming fairly large amounts of analgesics regularly for arthritis did not show increased incidence of headache [10]. The conclusion drawn from various clinical observations and studies is that medication overuse headache may be restricted to those who are already headache sufferers. The basis for this could either be genetic or the fact that migraine pain is more severe than joint pain. Different mechanisms probably contribute to the transition from the original headache to medication overuse headache. Psychological factors include the reinforcing properties of pain relief by drug consumption, a very powerful component of positive conditioning. Many patients report taking migraine drugs prophylactically because they are worrying about missing work (or, inevitably, the job) or missing an impor-
INTENSIVE CARE MANAGEMENT OF ACUTE LIVER FAILURE

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Abstract: Acute liver failure represents one of the most challenging conditions in intensive care treatment. In most cases there is no causal medical therapy available for survive making the intensive care treatment as the most important management tool, as bridge to transplant or still the recovery of the liver! These patients frequently develop multi-organ failure, placing them at risk of hemodynamic disorder, cerebral edema, coagulopathy and various renal and metabolic complications.

Key words: liver failure; intensive care; coagulopathy; multi-organ failure; renal failure

Acute loss of liver function is a devastating disease with a high mortality rate. The clinical course of patients with acute liver failure (ALF) depends on potential and time course of the regeneration of the liver. If the liver does not recover, a progressing multi-organ failure with circulatory instability, renal failure and a systemic inflammatory response syndrome are common clinical features [5].

Furthermore, hepatic encephalopathy (HE) in ALF is often associated with the development of intracranial hypertension. A rise in intracranial pressure is a distinctive feature of ALF, which is not seen in multiorgan failure caused by sepsis, pancreatitis or severe burn. The pathophysiology of circulatory instability is due to an increased nitric oxide production in the splanchic bed with blood pooling in this area, decrease of systemic vascular resistance and a high cardiac output [36]. The neurochemical mechanism responsible for HE is still controversial, but increased ICP is closely related to cerebral edema [8] and alterations in cerebral blood flow (CBF) [24].

ALF is rare and detailed experience of its management usually limited to specialist centres. In the following paper we will discuss recent developments in the treatment of this condition, and outline our current intensive care management (ICM) of patients with acute liver failure.

DEFINITION

Acute liver failure is a broad term used to describe the development of severe hepatic dysfunction resulting in hypotension, encephalopathy, coagulopathy, jaundice and renal failure. Since its first recognition in 1940s, a number of attempts have been made to more precisely define this condition. The most recent refinement of these conditions was made by O'Grady et al. [30]. This classification also recognizes the markedly different clinical course and outcome that each category may follow. O'Grady distinguishes three divisions reflecting the marked different clinical course and outcome:

"Hyper-acute liver failure", in which encephalopathy occurs within 7 days of the onset of jaundice: this includes a significant proportion of patients likely to survive with ICU treatment.

"Acute liver failure" with an interval of between 8 days and 28 days from encephalopathy; also with cerebral edema like hyperacute liver failure, but with much worse prognosis without transplantation.

"Sub-acute liver failure" occurring within 5-12 weeks of the onset of jaundice. These patients are characterized by a low incidence of cerebral edema but with very poor prognosis.

The majority of patients with ALF resulting from acetaminophen intoxication develop the picture of hyper-acute liver failure as well as patients with an acute hepatitis A or B [30]. Drug reactions tend to follow an acute or sub-acute clinical course.

ETIOLOGY

It's estimated that there are about 2000 cases of ALF in the USA per year. In Germany 56 patients with ALF were transplanted in the year 2002 (personal communication with Eurotransplant, Leiden), in Denmark the rate of ALF is about 8/1,000,000. Acetaminophen intoxication accounts for approximately 50% of ALF in the United Kingdom [32]. Acetaminophen overdose is also the most common cause for ALF in the USA accounting about 20% of patients with ALF [37]. Acute hepatitis A or B is the predominant cause of ALF in central and southern Europe. Acute viral hepatitis E has been reported to be a frequent cause [1]. The role of hepatitis C in ALF is somewhat controversial; Japanese studies have found evidence of HCV RNA in tissue from ALF patients [46]. This fact is not reproduced in Europe studies [13]. Other causes of ALF may be mushroom intoxication, drug-induced hepatotoxicity ( ecstasy, halothane, and valproate), autoimmune hepatitis, cardiac failure, Budd-Chiari syndrome and inherited metabolic disorders [45].
QUESTIONNING AGGRAVATION OF THE HEADACHE DURING MIGRAINE ATTACKS

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Abstract: While questioning patients about “aggravation of the headache by routine physical activity”, sensitivity of “walking stairs” and “lifting a heavy object” versus “head movements” and “bending down” in terms of aggravating the headache was aimed to be determined. Eighty-one migraine patients were questioned about the aggravation of their headaches with two sets of question groups. (The first set: “walking stairs” and “lifting a heavy object”; The second set: “rotating the head side to side” and “bending down”). 38 and 72 patients gave clear answers to the first and second set of questions respectively. Clear information was obtained from the first and second group of questions by 38 and 72 patients respectively. Some patients with severe migraine headaches may prevent themselves from rigorous daily activities while they could bend or make sudden head movements inadvertently during the attack. We think that aggravation of the headache due to head movements or bending down during migraine attacks seems more sensitive than walking stairs or lifting a heavy object to migraine patients.

Key words: migraine; aggravation; central sensitization; physical activity; head movements; bending down

INTRODUCTION

Migraine headache is often made worse by activities requiring physical effort such as ascending stairs, moving around rapidly or lifting [1] and some conditions other than requiring physical effort such as coughing, holding one’s breath, bending over or rotating the head side to side [2]. “Aggravation of headache by physical activity” was included in International Headache Society’s (IHS) “migraine without aura” criteria [3], as one of the four sub-criterion of “C” (Table 1). IHS questions this criterion by “walking stairs” or a similar routine physical activity [3].

Our observation is that when questioning aggravation of headache by “walking stairs” or similar routine activities such as lifting which depends on physical effort such as “lifting” generally do not transmit information about whether or not this sub-criterion is met. We noticed that although some patients gave unclear or negative answers to aggravation of the headache during “walking stairs” or “lifting”, they spontaneously reported that their headaches were aggravated by effortless simple movements such as “rotating the head side to side” or “bending down”.

Our aim was to determine the sensitivity of “activities requiring physical effort” such as “walking stairs” and “lifting” in contrast to simple head and body movements such as “rotating the head” and “bending down” in questioning headache aggravation.

MATERIAL AND METHOD

Consequent 103 patients who consulted our outpatient headache clinic and were diagnosed as migraine according to IHS criteria [3] were candidates for the study. The only inclusion criterion was “pulsating quality” of pain for the patients “migraine with aura”. As we wanted to study on “aggravation with physical activity” sub-criterion in migraine patients; we considered “migraine without aura” diagnosis independent of this criterion. So, in addition to “pulsating quality”, we required that “migraine without aura” patients meet one more “C” sub-criterion such as “unilateral location” or “moderate/severe intensity” to ensure that patients met “C” of “migraine without aura” criteria (Table 1). After these exclusion criteria were met, 77 patients with “migraine without aura” and 4 patients with “migraine with aura” were included in the study.

In order to evaluate the sensitivity of “activities requiring physical effort” in contrast to effortless “simple head/body movements” in questioning aggravation of the headache; two different sets of questions were composed. The first set questioned aggravation of the headache with “activities requiring physical effort” such as “walking stairs” and “lifting a heavy object”. The second set questioned aggravation of the headache with effortless “simple head/body movements” such as “rotating the head side to side” and “bending down” (please see appendix). Aggravation of the headache with one of these conditions in each question set was accepted as the question set’s being “sensitive”.

In statistical analyses, while age was accepted as numerical variable; gender, replies to the two sets of questions was accepted as categorical variables. Categorical variables were expressed as frequencies and percentages. Answers given by the patients to the first and the second set of questions were compared with McNemar chi-square test. Significance level was
ORGAN PROTECTIVE MANAGEMENT OF THE BRAIN-DEAD DONOR

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Abstract: The adequate management of brain dead donors on an Intensive Care Unit (ICU) is one of the major key points for a successful transplantation of harvested organs. In addition to an invasive monitoring like in any other ICU patient these patients needs a meticulous attention to their hemodynamic. The early administration of desmopressin to treat diabetes insipidus, a differentiated use of fluid resuscitation and a distinct catecholamine support are special features of an appropriate basic treatment. The administration of corticoids has to be considered if a sufficient circulation can not be regained.

Key words: Brain death, intensive care of organ donors, vasopressin, hemodynamic

INTRODUCTION

The maintenance of an appropriate intensive care treatment, after a proofed brain death, has a significant impact on graft function after transplantation. By an optimal management of the potential donor both, the number and quality of harvested organs can be improved. It could be shown that these organs have a better primary function after transplantation resulting in a faster recovery of the recipients [3, 8].

Fortunately traumatic brain injuries due to accidents are continuously declining. Thus, the number of healthy organ donors, without any comorbidities is decreasing. In spite of that the total number of harvested organs has remained nearly the same, due to the acceptance of organs of older donors [17, 52].

At the same time the number of harvested organs per donor has also increased. A careful monitoring and aggressive intensive care treatment is necessary due to the acceptance of older donors with also probable more comorbidities. A couple of possible complications during the stay on an intensive care unit (ICU) are listed in Table 1 (modified to [1]). The goal of the ICU therapy is to provide the possibility of organ donation. ICU treatment directed towards organ protection has to recognize the pathophysiologic sequel of the brain death.

The main target of this treatment is the maintenance of an optimal organ perfusion and oxygenation.

PATHOPHYSIOLOGIC DISORDER AFTER BRAIN DEAD

The initial phase after brain death is characterized by a central neurohumoral disorder. Proinflammatory mediators are released very early. The activation of PMN granulocytes is accompanied by a release of proteases and an oxygen burst with a local cell injury [34].

Additionally a couple of cardiopulmonary changes are observed: The lungs are at risk for alveolar haemorrhage and capillary leakage with consecutive lung edema [38]. In animal trials an extended rise of endogenous catecholamines could be demonstrated [4].

The serum concentration of epinephrine and norepi-

Table 1. Complication in brain dead (modified to [1])

<table>
<thead>
<tr>
<th>Complication</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>72 %</td>
</tr>
<tr>
<td>Diabetes insipidus centralis</td>
<td>79 %</td>
</tr>
<tr>
<td>Electrolyte disorder</td>
<td>75 %</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>65 %</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>50 %</td>
</tr>
<tr>
<td>Pulmonary complication</td>
<td>39 %</td>
</tr>
<tr>
<td>Coagulation disorder</td>
<td>5 %</td>
</tr>
</tbody>
</table>

Table 2. Target values of the donor. (modified due to [52])

1. MAP: 70 - 90 mmHg
2. CVP 10 - 12 mmHg
3. urine output 1 - 2 ml/kg/h
4. paO₂ > 80 mmHg or SaO₂ > 95 %
5. regular Electrolyte – and acid/base balance
6. Hämatocrit 20 – 30 %
7. Blood sugar 100 - 150 mg/dl

Abbreviation:
MAP: mean arterial pressure
CVP: central venous pressure
paO₂: oxygen partial pressure
SaO₂: arterial oxygen saturation
Letter to the Editor

CHRONIC HEADACHE: A FOCUS ON MEDICATION OVERUSE

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Sirs,
in 2003 we published a review about the epidemiology of chronic headache (CH) [1]. With this letter to the editor we want to focus a special interest of headache research in the last years. Medication overuse by headache-prone patients frequently produces CH accompanied by dependence on symptomatic medication [2-4]. Patients with frequent headache often overuse analgesics, narcotics, ergots and triptans. In addition, medication overuse can make headaches refractory to prophylactic medication. Stopping the symptomatic medication may result in the development of withdrawal symptoms and a period of increased headache.

Since 2003 the classification of the International Headache Society (IHS) from 1988 was used [5], but it had lacked precision about drug-, especially triptan-, induced headaches. Some authors studied the clinical features of triptan misuse and described typical signs of this syndrome [6-10]. Based on this information the IHS created new classification criteria for drug induced headache in 2003 [11]. Drug induced headache (DIH) is defined as frequent (more than 15 days per month) primary headache with medication overuse in more than 15 days per month in the last 3 months, which improves after a withdrawal therapy. The drugs leading to DIH vary considerably in the different series depending probably on both selection of patients and cultural factors [12]. It is, however, difficult to identify a single substance as 90% of patients take more than one compound at a time [13]. The management of DIH includes restricting the dose of ergots per attack (4 mg ergotamine), per week (no more than twice per week) and per month (no more than 20 mg ergotamine) is also helpful in avoiding dependency. In a similar way, the number of doses of triptans should be limited per attack and per month. Migraine drugs that contain barbiturates, codeine, or tranquilizers as well as mixed analgesics should be avoided. Probably an early start of migraine prophylaxis, either by medical or behavioural treatment, can be a preventive measure to avoid DIH [14].

REFERENCES


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A FUNCTIONAL-STRUCTURAL MODEL TO UNDERSTAND CARDIAC AUTONOMIC NERVOUS SYSTEM (ANS) DYSREGULATION IN AFFECTIVE ILLNESS AND TO ELUCIDATE THE ANS EFFECTS OF ANTIDEPRESSIVE TREATMENT

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Abstract: Numerous studies provide evidence that major depression (MD) is associated with certain disorders of cardiac autonomic nervous system (ANS) function, in particular, with an autonomic neurocardiac imbalance characterized by a low cardiovagal modulation, a raised sympathetic nerve activity and a high resting heart rate. We assume that such MD-associated cardiac ANS disorders are mainly caused by functional-structural abnormalities within the central autonomic network (CAN), in particular, by well-defined abnormalities of hypothalamic structures in MD. In view of the well-known association between an autonomic neurocardiac imbalance and the risk for cardiac arrhythmias, we assume that MD-associated cardiac ANS disorders are at least partly responsible for the high cardiovascular mortality risk in MD. It is, however, still unclear whether antidepressive treatment will lower the risk for cardiovascular complications in MD. There is convincing evidence that a successful antidepressive treatment with electroconvulsive therapy, cognitive behavioral therapy, or pharmacotherapy with primarily non-antimuscarinergic antidepressants can improve an initially disturbed cardiac ANS function in MD. These studies correspond well to our findings that treatment with both, nefazodone or reboxetine, can induce a reduction of central sympathetic nerve activity and an increase of the initially lowered cardiovagal modulation depending on the improvement of depressive symptoms after treatment. Since both effects occurred obviously independent from the primarily serotonergic or noradrenergic action of the antidepressants, our findings suggest the existence of a generally supracardinal and uniform mechanism underlying the ANS effects of antidepressive treatment with drugs inhibiting serotonin- or noradrenaline reuptake.

Key words: cardiac autonomic nervous system; antidepressive treatment

INTRODUCTION

Numerous epidemiological studies revealed a significant comorbidity between depressive and cardiovascular diseases. Depressive illnesses are also considered as predictors for a higher cardiovascular morbidity and mortality (summary in [29]). Various mechanisms have been discussed to explain the probably multicausal interaction between depressive and cardiovascular diseases [53]; one of these hypotheses focuses on disorders of the cardiac autonomic nervous system (ANS) in depressive patients [1].

CARDIAC AUTONOMIC NERVOUS SYSTEM (ANS) REGULATION WITHIN THE CENTRAL AUTONOMIC NETWORK (CAN)

The ventromedial, prefrontal cortex including the anterior cingulum forms the primary supramedullary exchange for controlling and integrating emotions, cognition and ANS regulation within the central autonomic network (CAN). Numerous neural connections originate there that extend to the orbitofrontal cortex, the insular region, the limbic system with the central nucleus of the amygdala (CENA) and also to the nucleus tractus solitarii (Fig. 1). The CENA provides all subcortical projections to autonomic hypothalamic and brainstem regions. It also projects to the bed nucleus of the stria terminalis, which is thought to relay amygdalar influences on cardiovascular autonomic responses. The hypothalamus contains several regions that innervate autonomic nuclei of the brainstem and the spinal cord; these include the paraventricular nucleus (PVN), the dorsomedial nucleus and the lateral hypothalamic area. The PVN is a major site for integrating autonomic and neuroendocrine responses to stress and has been called the "master controller" of the ANS because it innervates all autonomic centers [13]. The connection between the subfornical organ (SFO)