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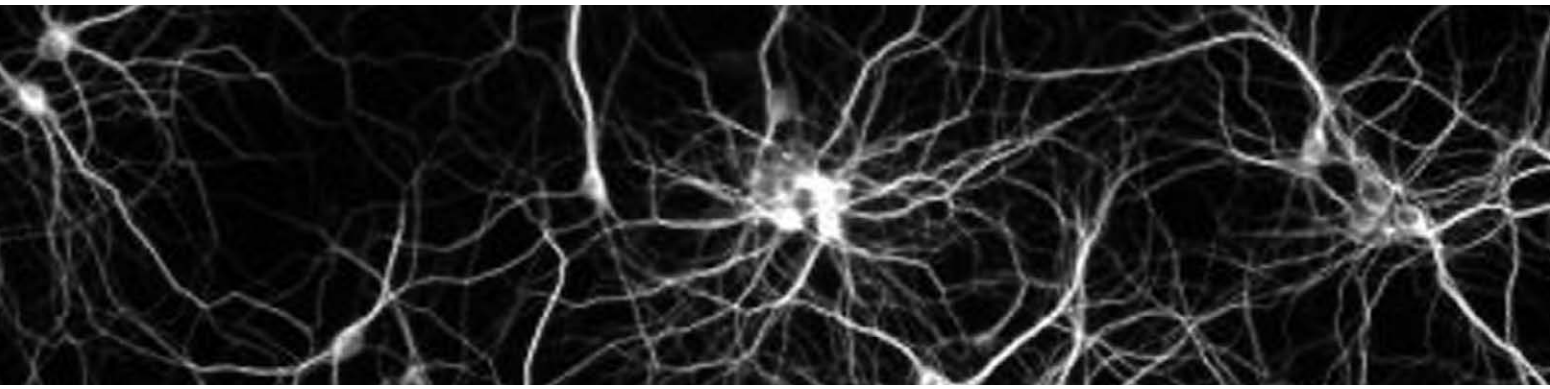

Evaluation of pharmacological treatment efficacy and short-term mortality in patients with status epilepticus at Požega General County Hospital, Požega, Croatia

Borislav Vuković[1], Ivana Vuković[2], Dobrinka Petković[3], Zdravko Kolundžić[4]

ABSTRACT – *Objective:* To determine efficacy of pharmacological treatment and short-term mortality in patients with status epilepticus (SE). *Methods:* This retrospective study included 109 episodes of SE recorded in 102 patients aged 18 years or older admitted to Požega General County Hospital during the period from January 1, 2006 until December 31, 2015. Patients were followed up on day 30 after SE onset to assess their living status. *Results:* Among 102 patients, 52 (51.0%) patients had a history of prior epilepsy. Initial antiepileptic drug was intravenous diazepam in 109 SE episodes. Of these, 97 (89.0%) SE episodes resolved with first- or second-line therapy (diazepam, phenobarbital, levetiracetam). For 12 (11.0%) SE episodes, third-line therapy (midazolam, propofol) was administered. Of these, eight (7.3%) SE were classified as refractory status epilepticus (RSE) and four (3.7%) as super-refractory status epilepticus (super-RSE). Out of 102 patients, nine (8.8%) patients died within 30 days after SE. All patients died during their hospital stay. Five (55.6%) patients died due to the underlying disease and four (44.4%) patients died from clinical complications. Age and negative history of epilepsy were not predictors of mortality (p=0.321 and p=0.191, respectively). *Conclusions:* The SE mortality rate was lower than reported in previous studies and was not related to age and negative history of epilepsy. SE resolved with first- or second-line therapy in nine of ten patients.

Key words: status epilepticus, therapy, mortality rate

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INTRODUCTION

Status epilepticus (SE) is one of the most common neurologic emergencies with significant associated morbidity and mortality, which needs fast diagnosis and therapy to avoid long-term consequences including neuronal injury and neuronal death. SE is defined as an epileptic seizure that shows no clinical signs of arresting after a duration encompassing the great majority of seizures or recurrent seizures without interictal resumption of baseline central nervous system function. Duration of seizures in SE varies from 5 to 30 minutes, depending on the definition (1-6). The Task Force of the International League Against Epilepsy (ILAE) recently defined SE as a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms that lead to abnormally prolonged seizure after five minutes for generalized convulsive SE and 10 minutes for focal SE with impaired consciousness (formerly complex-partial SE), which can have long-term consequences including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures (5-7). In the new classification, non-convulsive SE (NCSE) is divided into NCSE with or without coma (5,7,8).

The incidence of SE varies across studies from 6.2 to 61/100,000 people/year, and in most of the reports from 10 to 41/100,000 people/year. It has been found higher in the United States and lower in central Europe (9-17). The incidence is highest in the elderly and has a second peak in the neonatal period (9,16,18). Generalized convulsive status epilepticus (CSE) is the most common and most serious type of SE, representing 45% to 75% of cases (9,12). The incidence of CSE is 18-28/100,000 people/year (3). In developed countries, the incidence of CSE is 17-23/100,000 people/year (10).

The mortality of SE is around 20%, ranging from 3% to 40%. It may be as high as 40% in the elderly with acute symptomatic SE and comorbidities (13,18-22). Old age, acute symptomatic etiology of seizure, longer duration of SE, coma at presentation, higher rate of comorbidities, refractory SE and negative history of epilepsy were predictors of higher mortality in some studies (10,14,20,22-25). In patients with acute brain infarction and SE, mortality is three times higher than in patients with acute brain infarction without SE (26). Mortality rate was 18% in a meta-analysis of 12 studies in children and adults with SE (3). In a study of SE in French-speaking Switzerland, mortality rate was 7.6% (13). In the study by Classen *et al*. including 85 SE episodes in 74 patients, 21% of the episodes were fatal. Old age and acute symptomatic seizures were predictors of higher mortality (22). In the study by Sokic *et al*. including 920 SE episodes in 750 patients, short-term mortality was 13% (20). In the study by Stelzer *et al*. including 105 patients with epileptic seizures lasting for more than 30 minutes, short-term mortality was 36.2% (21). In the study by Kulkantrakorn *et al*., 13% of patients had refractory SE and 25% died. Advanced age, longer duration of seizure and coma were associated with higher mortality rate (23).

The causes of SE can be divided into acute and chronic. Acute symptomatic causes are associated with higher mortality than chronic ones (10,15,19,27-29). The etiology of SE can be determined in 65%-70% of patients, whereas in the rest the cause remains unknown (9). The most common causes of SE include AED withdrawal and ischemic stroke (23). SE can occur as the first manifestation of epilepsy (14).

There are many types of SE as there are many types of epileptic seizures. The classification based on Gastaut is simplest for clinical practice (2).

Table 1. *Clinical course of convulsive status epilepticus (CSE) divided into four subsequent phases (11,30)*

Early SE: convulsive epileptic activity for more than 5 minutes
Established SE: continuous seizure activity with convulsions or intermittent seizures without regaining consciousness between the seizures for more than 10 and up to 30 minutes
Refractory SE (RES): SE continuous for more than 30 and up to 60 minutes
Superrefractory SE (super-RSE): seizures continue despite maximal treatment with intravenous (IV) anesthetics for more than 24 hours in an intensive care unit

Intravenous (IV) diazepam or lorazepam or intramuscular midazolam are used for initial treatment of early SE (11,31). In established SE, intravenous antiepileptic drugs (AEDs; phenytoin/fosphenytoin, phenobarbital, valproate, levetiracetam) are most commonly used. Refractory SE (RSE) and super-refractory SE (super-RSE) are treated with anesthetics (propofol, midazolam, thiopental) (11).

PATIENTS AND METHODS

This study was designed as a retrospective study and included patients of both genders aged 18

years and older who presented with SE during the period from January 1, 2006 until December 31, 2015 to Department of Neurology, Požega General County Hospital. Upon admission to the hospital, they were transferred to the Neurology Stroke Unit, which is equipped with facilities for vital function monitoring. Only patients with super-RSE and patients with respiratory depression (RD) were dislocated to the Intensive Care Unit (ICU).

Status epilepticus is defined as a condition in which epileptic activity persists for five minutes or longer for CSE (6) and 30 minutes or longer for other forms of SE (7). RSE is defined as absence of clinical and/or EEG control of the seizure for more than 30 minutes and up to 60 minutes (11,21). Super-RSE is defined as SE that continues or recurs 24 hours or more after the onset of anesthetic therapy (30).

According to clinical presentation and EEG features, SE is classified as generalized convulsive SE (CSE), focal motor SE, focal onset evolving into bilateral convulsive SE, epilepsia partialis continua (EPC), myoclonic SE (MSE) and non-convulsive SE (NCSE) (5).

All subjects underwent complete hematologic, metabolic and electrolyte workup, EEG, CT or MRI of the brain. Lumbar puncture was performed as needed. Serial 18-channel electroencephalogram (EEG) (Oxford Instruments, United Kingdom) was obtained following 10-20 International System of electrode placement. We performed first EEG examination within three days of SE occurrence.

The etiology of SE is classified as acute symptomatic (AS), progressive symptomatic (PS), remote symptomatic (RS), or idiopathic/cryptogenic (IC) according to the ILAE recommendations. AS is considered when SE occurs within a week of an acute central nervous system (CNS) or systemic insult (i.e. stroke, meningitis, encephalitis, hepatic encephalopathy, neurotrauma, or alcohol intoxication or withdrawal). PC is considered when SE is related to progressive CNS diseases (i.e. tumors, multiple sclerosis, or degenerative neurologic disease). RS is considered in the presence of a history of CNS insult presumed to result in static encephalopathy associated with an increased risk of epilepsy (i.e. cerebral palsy, stroke, head trauma, encephalitis or meningitis). I/C means that the cause of SE is unknown (32). Short-term mortality is defined as death in the first 30 days following the episode of SE (19).

Patients were treated according to the following protocol: first-line treatment of SE was diazepam 10 mg IV (diluted in 100 mL normal saline/5 minutes). In case of prolonged SE duration, diazepam 20 mg diluted in 500 mL normal saline was administered. If seizures did not resolve, we used second-line drugs, i.e. phenobarbital 10 mg/kg IV (infusion at a maximum dose of 100 mg/min) or levetiracetam 500 mg diluted in normal saline (infused at a maximum dose of 3000 mg/day). If clinical and EEG control was not achieved with first- or second-line therapy (diazepam, phenobarbital or levetiracetam), the patient was considered to have RSE. Patients with RSE and super-RSE were treated with anesthetics, midazolam 0.2 mg/kg as a loading dose, followed by infusion at 0.1-0.4 mg/kg/h or propofol IV 2 mg/kg/h. Patients with super-RSE were dislocated to the ICU. Patients were followed up on day 30 after SE onset.

Statistical analysis was performed using the SPSS for Windows, version 18.0. Differences in quantitative variables were analyzed using χ^2- test with the level of significance less than 5% ($p<0.05$). Descriptive statistics was used and data were presented as mean and standard deviation (SD).

RESULTS

During the study period, we observed 109 episodes of SE in 102 patients. There were 66 (64.7%) male and 36 (35.3%) female patients, yielding the male to female ratio of 1.8:1. The mean patient age was 56.75±18.88 (median 59.5, range 19-94) years. One patient had four SE episodes, four patients had two SE episodes, and 97 (95.1%) patients had a single SE episode. SE started before admission to the hospital in 100 (98.0%) patients and after admission in two (2.0%) patients. Fifty-two (51.0%) patients had a history of prior epilepsy, and they had a mortality rate of 3.8% compared with 14% in those with negative history of epilepsy (p=0.191). The mean duration of hospital stay in all patients with SE was 8.37±4.67 (median 7) days. The mean duration of hospital stay in patients who died was 6.88±7.38 (median 5) days, and in patients who survived 8.50±4.67 (median 8) days (p=0.028).

Status epilepticus was classified as generalized convulsive (CSE) in 50 (45.9%), focal motor in five (4.6%), focal onset evolving to bilateral convulsive SE in 36 (33.0%), epilepsia partialis continua (EPC) in one (0.9%), myoclonic (MSE) in one (0.9%) and non-convulsive (NCSE) in 16 (14.7%) episodes. EEG was performed in seven (6.4%) episodes dur-

Table 2. *Etiology of status epilepticus*

	n	%
Acute symptomatic (AC)	**10**	**9.8**
Acute cerebrovascular accident	5	4.9
Meningitis/encephalitis	2	2
Alcohol withdrawal	3	2.9
Progressive symptomatic (PS)	**15**	**14.7**
Tumors	9	8.8
Multiple sclerosis	3	2.9
Dementia	3	2.9
Remote symptomatic (RS)	**60**	**58.8**
History of cerebrovascular accident	41	40.2
History of head trauma (contusio cerebri, traumatic subarachnoid hemorrhage, epidural/subdural hemorrhage)	11	10.8
History of meningitis/encephalitis	6	5.9
Hydrocephalus	1	1
Mesial temporal sclerosis	1	1
Idiopathic/cryptogenic (I/C)	**17**	**16.7**

Table 3. *Causes of death in patients with status epilepticus*

Diagnosis	n	%
Acute cerebral infarction	3	33.3
Acute meningoencephalitis	1	11.1
Meta cerebri	1	11.1
Pneumonia/respiratory failure	2	22.2
Pneumonia and cardiac decompensation	2	22.2

ing SE and in 92 (84.4%) episodes after termination of SE.

Initial AEDs were IV diazepam in 109 SE episodes. Diazepam IV stopped SE in 81 (74.3%), phenobarbital IV in 13 (11.9%) and levetiracetam IV in three (2.8%) episodes. Third-line therapy was used in 12 (11.0%) SE episodes, i.e. midazolam in 10 (9.2%) and propofol in two (1.8%) episodes. In this group, eight (7.3%) episodes were classified as RSE and four (3.7%) as super-RSE. Intravenous immunoglobulin was used in one (1%) patient who suffered from autoimmune encephalitis. In our study, complications of benzodiazepines (apnea) were recorded in one (1%) patient. Four (3.9%) patients needed artificial ventilation.

During the study period, nine patients died, including seven men and two women. The mortality rate was 8.8%. According to clinical assessment and the course of disease, there are two major causes of death in SE: underlying disease (acute cerebral infarction, acute meningoencephalitis, meta cerebri) and complications (pneumonia, respiratory failure, cardiac decompensation). Five (55.6%) patients died due to the underlying disease and four (44.4%) patients died from complications. Severe clinical complications were pneumonia, respiratory failure and pneumonia, and cardiac decompensation. The mean age of patients who died was 66.44±16.14 (median 72, range 40-84) years and the mean age of patients who survived was 55.81±18.93 (median 58, range 19-94) years. Mortality rate did not differ between genders (p=0.332). Age and negative history of epilepsy were not significant predictors of mortality in our patients (p=0.321, p=0.191).

Table 4. *Factors influencing mortality rate of status epilepticus*

Variable	p value
Sex (female/male)	0.332
Age	0.321
Duration of hospital stay	0.028
Epilepsy history (+/-)	0.191

The patients who died had CSE in three (33.3%) cases, focal onset evolving to bilateral convulsive SE in five (55.6%) cases and epilepsia partialis continua (EPC) in one (11.1%) case. Following clinical and EEG criteria, SE was not stopped until death in one (1%) patient.

DISCUSSION

In our study, SE mortality was similar as in some previous studies (13,33,34) and lower than reported in some other epidemiology studies (3,19-21,24,35). The probable reasons of lower mortality in our research were early treatment, improved treatment, nursing and prevention of complications.

In our investigation, 45.9% of SE episodes were initial and mortality rate was 8.8%. Mortality rate was similar as in an the study from Switzerland where mortality among patients with SE was 7.6%, although 57% of their patients had initial SE (13). In the study by Seltzer *et al*., 52.4% of patients had a history of prior epilepsy, which was similar as in our investigation (21). In other hospital samples, 30%-44% of patients with SE had a history of epilepsy (20,33).

One of the best prognostic factors of SE is etiology, and the highest mortality rates are observed in patients with AS or PS etiology. In earlier investigations, underlying disease was the primary determinant of SE outcome (19,20,28,29,36,37). In our sample, severe underlying disease was the main etiology of death in five (55.6%) patients. In the study of short-term mortality in 750 patients, severe underlying disease was the main etiology of death in 65.8% of patients (20), and in a meta-analysis of 12 studies death was due to severe underlying disease in 89% of cases (3). In our study, respiratory complications occurred in 44.4% of patients who died, which was almost the same as in the study by Sokic *et al*. (20). In our investigation, the presence of a history of CNS insult was the most common cause of SE. Previous studies have reported on advanced age in SE patients as a predictor of higher mortality (14,20), but age was not a significant predictor of mortality in our patients. The length of hospital stay was not a significant predictor of mortality in the study by Moghaddasi *et al*. (24). In our investigation, we found a negative correlation between the length of hospital stay and mortality. Negative history of epilepsy was associated with a significantly higher mortality rate in the study by Mogaddasi *et al*. (24), but not in our study. In the study by Seltzer *et al*., mortality associated with SE was not related to age, specific etiology or SE duration. Mortality was independently related to the occurrence of medical complications (21). A study conducted in an urban public hospital revealed little variation in the etiology of SE over two decades (36). In our study, the etiology of SE was known in 85 (83.3%) patients and the cause remained unknown in 17 (16.7%) patients, which was a greater number of known causes than in the study conducted in Rochester (9). AED withdrawal in previously epileptic patients is typically associated with low mortality (28,33). In our investigation, there was no death in patients with previous epilepsy with low AED levels or AED withdrawal.

In our investigation, IV diazepam effectively controlled SE in 74.3% of episodes, similar to the study performed by Chamberlain *et al*. in a group of pediatric SE patients (38). Phenobarbital and levetiracetam controlled SE in 14.7% of episodes. Ninety-seven (89.0%) patients responded to treatment with first- or second-line therapy, which was similar as in the study by Moghaddasi *et al*., where 84.6% of patients responded to the treatment of tonic-clonic SE (24). In another study, RSE developed in 24% to 43% patients with SE (25), whereas in our study it developed in 11% of patients. In the study by Giovannini *et al*. on 83 SE episodes, third-line therapy was needed in 31% of cases; in this group, 14% were classified as RSE and 17% as super-RSE (25). In our investigation, third-line therapy was needed in 11% of patients, which was similar to the study by Mogaddasi *et al*. (24). In our study, 7.3% of SE were classified as RSE and 3.7% as super-RSE. Propofol and midazolam were used for the treatment of RSE and super-RSE in 11.0%, which was similar to the study by Moghaddasi *et al*. (24). There are no class I data to support recommendations for most AEDs in the treatment of established RSE and super-RSE (11).

In our study, complications of diazepam (apnea) appeared in one (1%) patient. Benzodiazepines may provoke apnea and RD in 3.7%-24% of patients (33). A meta-analysis of the literature indicates that, compared with placebo, after diazepam administration there is a lower risk of requirement for ventilation support and continuation of SE requiring a different drug or general anesthesia with diazepam (39).

In our study, following clinical or EEG criteria, SE was not stopped until death in one (1%) patient, which was similar to the study by Sokic *et al*. (20), and multiply lower than in the study by Seltzer *et al*. (21).

In the London-Innsbruck Status Epilepticus Collegium, major therapeutic advances include the use of benzodiazepines in out-of-hospital situations, especially buccal midazolam and the use of valproate, levetiracetam and lacosamide in the stage of established SE (40). If it is not possible to apply IV therapy in SE patient, intramuscular midazolam is at least as safe and effective as IV lorazepam for pre-hospital seizure cessation (41). Until now, we have no experience with the use of buccal midazolam, IV valproate and IV lacosamide in SE.

CONCLUSION

In our study, mortality rate associated with SE was lower than reported in previous studies. The probable reasons of lower mortality were early treatment, improved treatment and better health care system. Underlying disease and clinical complications influenced the outcome of SE. Age and negative history of epilepsy were not significant predictors of mortality. SE was resolved with first- or second-line therapy in nine of ten patients. For patients with SE, IV diazepam is safe and effective for hospital seizure cessation.

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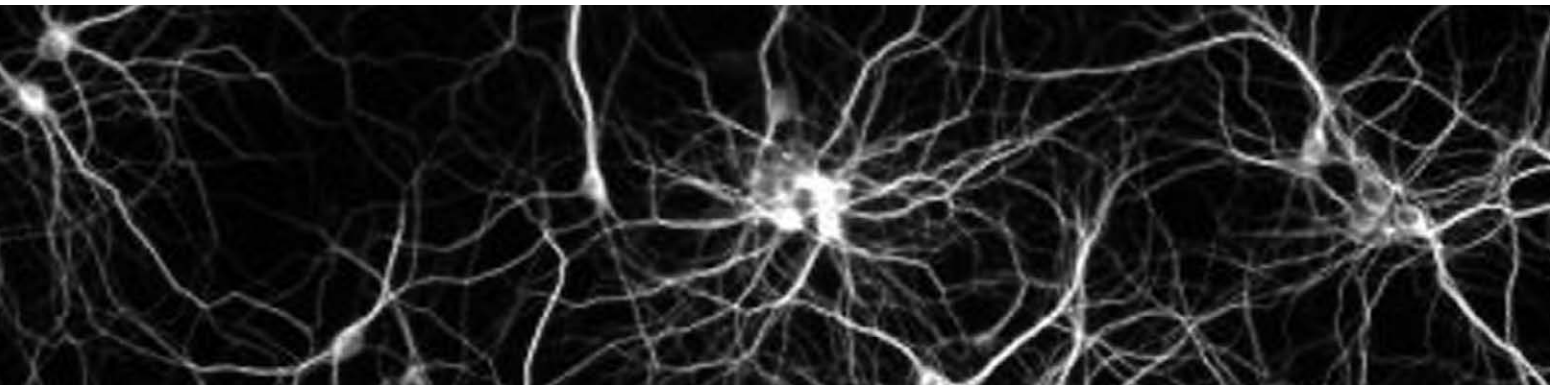
Praćenje učinkovitosti liječenja i procjena smrtnosti bolesnika s epileptičnim statusom u Općoj županijskoj bolnici Požega

SAŽETAK – *Cilj:* Odrediti uspješnost liječenja i smrtnost kod bolesnika s epileptičnim statusom. *Metode:* Retrospektivna studija obuhvatila je 109 epileptičnih statusa registriranih kod 102 bolesnika u dobi od 18 i više godina koji su liječeni u Općoj županijskoj bolnici Požega od 1. siječnja 2006. do 31. prosinca 2015. godine. Stanje bolesnika procijenjeno je tridesetog dana od početka epileptičnog statusa. *Rezultati:* Od ukupno 102 bolesnika, 52 (51,0 %) su od ranije bolovala od epilepsije. Početna terapija je bio intravenski diazepam kod 109 epileptičnih statusa. Od 109 epileptičnih statusa, u 97 (89 %) slučajeva status je prestao na prvu ili drugu liniju terapije (diazepam, fenobarbital, levetiracetam). Kod 12 (11,0 %) epileptičnih statusa od kojih je osam (7,3 %) bio refraktorni epileptični status, a četiri (3,7 %) superrefraktorni epileptični status, primijenjena je treća linija terapije (midazolam, propofol). Unutar 30 dana od pojave epileptičnog statusa umrlo je devet (8,8 %) bolesnika. Svi bolesnici su umrli tijekom bolničkog liječenja. Uzrok smrti je bila osnovna bolest kod pet (55,6 %), a kliničke komplikacije kod četiri (44,4 %) bolesnika. Dob i negativna osobna anamneza epilepsije nisu bili prediktori smrtnosti (p=0,321, p=0,191). *Zaključak:* Smrtnost uzrokovana epileptičnim statusom bila je niža nego u većini ranijih istraživanja i nije bila povezana s dobi i negativnom osobnom anamnezom epilepsije. Epileptični status je prestao nakon primjene prve ili druge linije terapije kod devet od 10 bolesnika.

Ključne riječi: epileptični status, terapija, smrtnost



Wilson's disease: importance of early recognition and genetic testing of family members

Srđana Telarović[1,2], Irma Telarović[3], Kristina Starešina Ivičak[4]

ABSTRACT – *Objectives:* Wilson's disease (WD) is a rare autosomal recessive hereditary disorder of copper metabolism with an effective treatment available if diagnosed in the early stages, preferably before symptoms show. However, due to sometimes unspecific signs and symptoms, diagnosis is only possible with a high index of clinical suspicion. Therefore, for early recognition of asymptomatic patients, genetic testing of family members is extremely important. In addition, the aim of this article is to emphasize the role and importance of multidisciplinary approach in the diagnosis and treatment of WD. *Case description and results:* We present a patient with WD that was accidentally detected after routine ophthalmologic examination following head injury. Owing to efforts invested by different members of our multidisciplinary team for WD, a genetic mutation was determined, pathologic parameters of copper metabolism were examined and appropriate therapy was introduced. Genetic testing was also carried out in the patient's daughter, his sister and her son. The patient's 5-year-old nephew was found to be a homozygote for the mutation. He was referred to pediatric hepatologist. *Conclusion:* The nephew was the youngest asymptomatic person diagnosed with WD from establishment of our multidisciplinary team. This dramatically improved the outcome of this boy and is certainly going to increase his overall quality of life.

Key words: Wilson's disease, copper, genetic testing

INTRODUCTION

Wilson's disease (WD) or hepatolenticular degeneration is a rare autosomal recessive disorder of copper metabolism (1,2). It was first described by Samuel Alexander Kinnier Wilson in 1912 (3).

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Mutation of the ATP7B gene on chromosome 13 (13q14.3) results in disturbance of copper metabolism with consequent accumulation of copper in the liver and extrahepatic tissues such as brain and corneal Kayser-Fleischer (KF) ring. WD may be presented with hepatologic, neurologic and psychiatric symptoms or their combination. However, many other symptoms may be present, for example hematologic, such as hemolytic anemia, leukopenia, thrombocytopenia, etc. (4,5).

Diagnostic algorithm for WD includes complete blood count, kidney tests (proteinuria, creatinine clearance), ceruloplasmin, copper in serum, copper in 24-hour urine and copper in 24-hour urine after d-penicillamine challenge, biomicroscopy (KF ring), brain magnetic resonance imaging (MRI), and in doubtful cases liver biopsy with copper concentration *per* gram of dry liver tissue and histopathologic analysis of liver tissue. However, genetic testing is needed in some cases to confirm the diagnosis (3,4).

In therapy of WD we use copper chelators (d-penicillamine, trientine, tetrathiomolybdate) and zinc salts (2). Zinc salts are first-line therapy in asymptomatic and pregnant patients (6).

About 400 mutations are known, including missense and nonsense mutations, deletions and insertions. The most common mutation in Caucasians is H1069Q located on exon 14 of WD gene. Therefore, routine genetic testing applies to this one as the most frequent mutation. If the patient with clinical suspicion of WD is not homozygous for this mutation, then complete sequencing of the gene is indicated (7,8).

Ceruloplasmin is a serum copper transporting protein the concentration of which is decreased in most WD patients. However, the clinical value of this test could be limited because a decreased ceruloplasmin level may be present in 1% of controls, 10% of individuals heterozygous for WD mutation, as well as in malabsorption and chronic liver failure (8). Therefore, diagnosing WD may be difficult and complete diagnostic algorithm is needed in some patients. In this scenario, genetic testing may be very important not just for the patient but also for his/her family members.

CASE REPORT

A 37-year-old male was admitted to emergency unit following a head trauma after an accident while playing football. He was examined by a surgeon and then by an ophthalmologist, who detected KF rings in the patient. The patient's records were looked into and no KF rings were detectable during previous ophthalmolgic exams, one year before diagnosing WD. Following this finding, the patient was referred to gastroenterologist and neurologist in the subspecialist outpatient unit for movement disorders as there was a high suspicion of WD. Available tests were performed and the following significant results were obtained: serum copper 11.8 mmol/L (12.2-25.1), ceruloplasmin 0.06 g/L (0.20-0.60), copper in 24-hour urine 4.58 mmol/dU (<1.7). In addition, fine bilateral postural hand tremor was recorded during neurologic exam. Following initial examination, he was hospitalized in the specialized Unit for Heredodegenerative Disorders.

Medical history revealed that the patient had been hospitalized in a psychiatric department at the age of 25 due to a psychotic episode. He was successfully treated with fluphenazine and biperiden. He also suffered from chronic bronchitis. He was a worker in metal industry, in regular contact with copper. His family history showed that his mother suffered from liver cirrhosis.

Next, more detailed tests were performed. MRI showed slightly enlarged cerebellomedullary cistern, bilateral microvascular ischemic lesions predominantly in the subcortical parietal regions, and no metal deposition in basal ganglia or other loci. HLA typing established HLA B27 positivity. Neurological examination was abnormal with mild postural tremor of both hands, predominantly on the left, with activated rigidity also positive on the left side. Fast alternating movements were normal. Important laboratory findings during his hospital stay were as follows: platelets 129-141x10^9/L (158-424), glucose 7.3-7.7 mmol/L (4.4-6.4), creatinine 160 mmol/L (79-125), serum copper 9.3 mmol/L (12.2-25.1), ceruloplasmin 0.06 g/L (0.20-0.60), proteins in 24-hour urine 0.26 g/dU (<0.15), 24-hour urine copper 6.12 mmol/dU (<1.7), and copper in 24-hour urine after the penicillamine test 26.4 mmol/dU. Genetic testing revealed a homozygous mutation, H1069Q, in ATP7B gene. Abdominal ultrasound and liver enzymes were normal.

After discussion with a gastroenterologist of the multidisciplinary team for WD, d-penicillamine in a dose of 300 mg and vitamin B6 substitute were introduced. At two-month follow up examination, a decrease in tremor was observed. The patient felt good and laboratory tests showed the following results: copper in serum 8.3 mmol/L (12.2-25.1), copper in 24-hour urine 6.62 mmol/dU (<1.7),

AST 40 U/L (11-38), ALT 17 U/L (12-48), GGT 20 U/L (11-55), and platelets 146x10^9/ L (158-424).

We recommended genetic testing for the patient's daughter, his sister and nephew. The sister was found to be heterozygote, while her 5-year-old son was homozygote positive for H1069Q mutation, without any clinical symptoms. The patient's 6-year-old daughter was heterozygote, and testing was highly recommended for his younger, 2-year-old daughter. There were no data on the marriage of relatives in the involved families.

DISCUSSION

The incidence of WD is estimated to 1 *per* 30000 to 50000, with no discernible geographical pattern (6-8). The most common mutation in Europe is the H1069Q mutation (7), also present in the described patient. WD gene is located on chromosome 13 (13q14.3) (8).

Wilson's disease is an autosomal recessive disorder with disturbance of copper metabolism that results in the accumulation of copper in the liver, brain, cornea and other tissues. Symptoms rarely occur before the age of 5 and after the age of 50 (6,8).

Gastrointestinal disturbances in WD range from asymptomatic state to increase of liver enzymes, chronic hepatitis, or even fulminant liver failure. Neurological signs and symptoms appear due to the accumulation of copper predominantly in basal ganglia. Large deposits can be visible on MRI. The most common neurological signs are speech problems, tremor, dystonia and other extrapyramidal signs. Very large amplitude tremor ('flapping tremor') is considered pathognomonic.

Our patient experienced only mild bilateral tremor, later found to be predominantly on the left side with discrete activated ipsilateral rigidity. Tremor decreased after therapy with chelator had been introduced. This confirms the importance of keeping WD in mind as a potential cause of tremor in young people. In addition to neurological disturbances, WD can also begin with psychiatric symptoms such as depression, psychosis, etc. (1,9). Initial clinical presentation of WD in our patient was indeed psychiatric at the age of 25. Therefore, in atypical psychosis and unusual psychopathological presentations in general in a young person (up to around 55 years), we must consider WD.

Diagnostic algorithm for WD includes complete blood count, liver enzymes, kidney tests (proteinuria, creatinine clearance), ceruloplasmin, copper in serum, copper in 24-hour urine and copper in 24-hour urine after d-penicillamine challenge, biomicroscopy (KF rings), brain MRI, and in doubtful cases liver biopsy with copper concentration *per* gram of dry liver tissue and histopathologic analysis of liver tissue (1,3,6,8).

According to our patient's history data, KF rings were not recorded during ophthalmologic examinations (for other reasons) but were found on detailed examination after head trauma. This was a crucial step for our patient as it made him referred to a gastroenterologist and neurologist, and subsequently to WD experts. This obviously indicates the need and importance of education of ophthalmologists and other specialists with the aim of early recognition of WD. If WD is diagnosed and consequently appropriately treated on time, the outcome is generally good, and duration and quality of life are comparable to the general population.

In the treatment of WD we use chelators to bind and remove excess copper from affected tissues (10), or zinc salts to decrease intestinal absorption of copper. D-penicillamine is the most commonly used chelator in Europe. As it can cause vitamin B6 deficiency, all patients are required to take supplemental B6. This combination proved effective in our patient as well, and is to be taken for the rest of his life. Zinc therapy is usually the treatment of choice in asymptomatic patients and pregnant women (2,8,11). Liver transplantation is an option in patients with irreversible liver damage. In addition to medication, patients with WD must carry out a diet low in copper, which was therefore also recommended to our patient and his nephew who was found to be a homozygote for WD.

The nephew has since been under permanent supervision of pediatric hepatologist. At the moment, he is without symptoms, but depending on future findings, his doctor plans to introduce zinc salts. This demonstrates the role of genetic testing of family members of patients with WD, which is obviously of vital importance in order to ensure adequate quality of life of all family members (12). The course of events in diagnosing our patient with WD, efficacy of therapy when introduced at a proper time and the role of early genetic testing of family members speak for the importance of coordinated activities and collaboration of our polyvalent multidisciplinary team for WD. The team combines experts from various fields including a neurologist, gastroenterologist-hepatologist, pediatric hepatologist, pediatric neurologist, molecular geneticist, psychiatrist, ophthalmologist, genetic advisor, neuroradiologist, abdominal surgeon, nu-

tritionist, social worker, and other experts depending on specific needs of patients.

CONCLUSION

Wilson's disease is often unrecognized, and therefore left untreated with fatal outcome being unfortunately not rare. Considering that therapy is available and very effective if introduced in early stages (preferably before symptoms occur), the importance of early detection is obvious. Appropriate timing of therapy induction results in the quality of life and survival of patient comparable to the general population. Thus, diagnosing as early as possible, as well as routinely testing family members for mutations is of great value in dealing with WD.

In addition, as proven in the case presented, continuing education in targeted groups of medical experts and establishment of polyvalent multidisciplinary teams in national reference centers (13) is the key in combating WD today.

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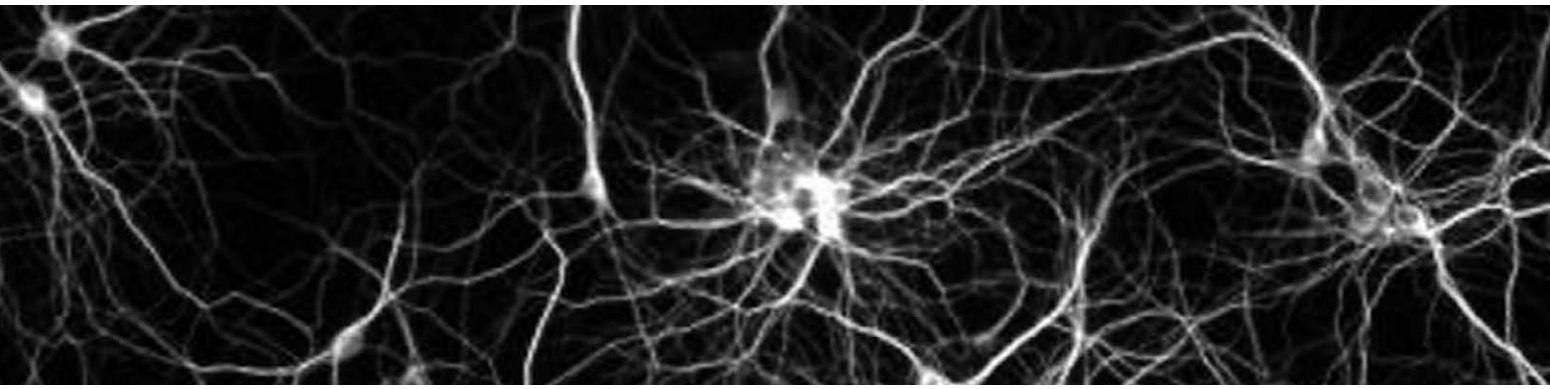
Wilsonova bolest: važnost ranog prepoznavanja i genetskog ispitivanja članova obitelji

SAŽETAK – *Cilj prikaza:* Wilsonova bolest (WB) je rijetka autosomno recesivno nasljedna bolest s poremećajem metabolizma bakra, s učinkovitom terapijom ako se bolest na vrijeme dijagnosticira, osobito prije pojave kliničkih simptoma. S obzirom na to da se bolest može prezentirati nespecifičnim simptomima i znakovima iznimno je važno postaviti kliničku sumnju na nju. Stoga je za rano prepoznavanje asimptomatskih bolesnika jako važno gensko testiranje članova obitelji. Uz to, cilj ovoga prikaza je ukazati na važnost multidisciplinarnog pristupa u dijagnostici i liječenju WB. *Prikaz bolesnika i rezultati:* Prikazujemo bolesnika s WB koji je dijagnosticiran slučajno, nakon rutinskog okulističkog pregleda zbog traume glave. Cjelokupnim angažmanom svih članova Multidisciplinarnog tima za WB naše ustanove otkrivena je patološka mutacija, poremećeni parametri metabolizma bakra te je uvedena odgovarajuća terapija. Gensko testiranje također je provedeno kod bolesnikove kćeri, sestre i sestrinog sina. Bolesnikovom 5-godišnjem nećaku utvrđena je homozigotna mutacija na WB te je upućen pedijatrijskom hepatologu. *Zaključak:* Pregledani nećak je dosad najmlađi asimptomatski bolesnik našeg Tima, kojemu je dijagnosticirana WB. Postavljanje dijagnoze, planiranje kontinuiranog praćenja i uvođenje pravodobne terapije dramatično poboljšavaju ishod i kvalitetu života ovakvih bolesnika.

Ključne riječi: Wilsonova bolest, bakar, gensko testiranje



Jadranka Sertić *et al.*

Clinical Chemistry and Molecular Diagnostics in Clinical Practice, 2nd Edition

Medicinska naklada, 2015
Zagreb, Croatia
Hard cover, 21x27, 713 Pages
ISBN 978-953-176-655-5

'Clinical Chemistry and Molecular Diagnostics in Clinical Practice is the second edition of the university textbook for medical students, which brings information on exact analysis in clinical practice, as well as in-depth approach to the processes, diagnostic methods and therapeutic effects at biochemical and molecular level. It clearly demonstrates how clinical chemistry and molecular diagnostics are applied in clinical practice.

Experts from various fields of clinical and laboratory practice have organized the book in 12 chapters, as follows: 1) Clinical Chemistry, Molecular Diagnostics and Laboratory Medicine; 2) Laboratory Diagnostics of Most Common Metabolic Diseases, Cardiac and Neurological Disorders; 3) Selected Topics from Molecular Diagnostics of Neurological Diseases; 4) Laboratory Diagnostics of Immunological and Lung Diseases; 5) Laboratory Diagnostics of Kidney Diseases; 6) Laboratory Diagnostics of Liver and Pancreas Diseases; 7) Selected Topics from Laboratory Endocrinology; 8) Selected Topics from Oncology of Solid Tumors and Laboratory Diagnostics; 9) Laboratory Diagnostics of Hematologic Diseases and Disorders of Hemostasis; 10) Laboratory Diagnostics of Psychiatric Disorders; 11) Laboratory Toxicology, Pharmacology and Nutrition; and 12) Laboratory Medicine – Selected Examples of Laboratory Results.

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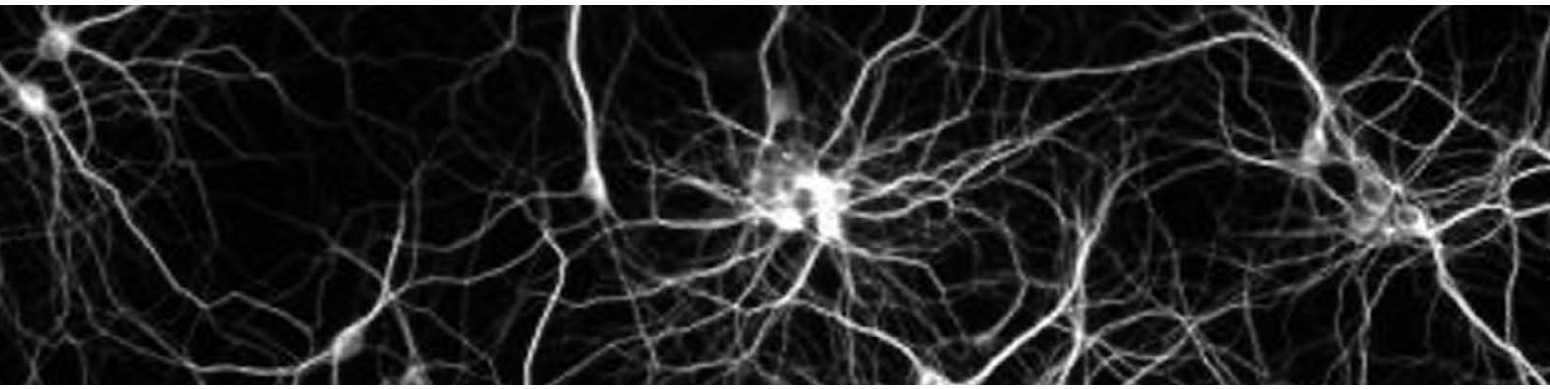
The book is comprehensive, systematic and well organized. It is based on the multidisciplinary approach and therefore offers not only an important source of knowledge for university students, but also a useful tool for experts from numerous specialties and subspecialties to improve their clinical practice.

Srđana Telarović

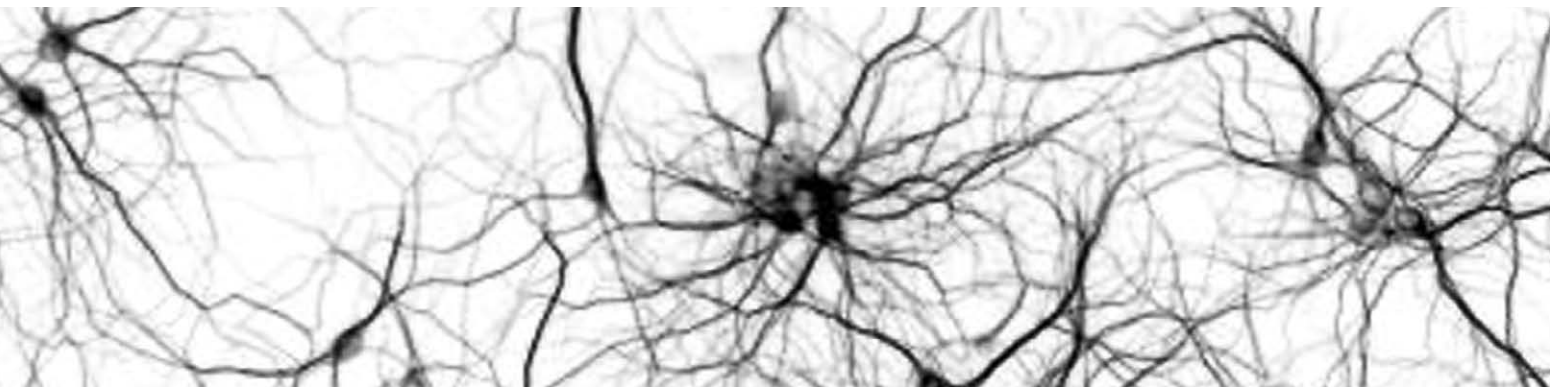


16th Brain Awareness Week

Karlo Toljan

Brain Awareness Week has been initiated by The Dana Alliance for Brain Initiatives as a global campaign to increase public awareness of the progress and benefits of brain research. The Croatian Society for Neuroscience encourages its members and the rest of Croatian neuro-community to actively participate in the campaign. The Student Society for Neuroscience at the School of Medicine, University of Zagreb has a traditional role in organizing workshops and lectures for elementary school and high-school students, as well as for other University students and general public. During the third week of March (March 13-17), at the Croatian Institute for Brain Research, student volunteers hosted more than fifty activities for more than a thousand young visitors ranging from preschool to high-school population. After concise presentation on the basics of neuroanatomy with emphasis on neural development in the first three years of life and how the brain processes spatial information (official topics for this year), a unique opportunity was given to the visitors by exhibiting real brain macro-specimens together with microscopic brain slices. The youngest were also provided with plaster casted brain hemispheres which were much appreciated souvenirs after the visit. Furthermore, volunteering students reached out to schools and held lectures in various high schools and elementary schools in Zagreb. Also, a public lecture for students at the Faculty of Food Technology and Biotechnology was organized as a joint event by the Student Society for Neuroscience and Probion student group. During the Week, an academic symposium dedicated to brain pathology research organized by the Department of Medical Sciences of the Croatian Academy of Sciences and Arts took place on March 16, with lectures given by neuroscientists and clinical practitioners from the domain of neurology, psychiatry, neurosurgery, neuropediatrics and neuroradiology. Additionally, Brain Awareness Week activities were organized in cities throughout Croatia, i.e. in Osijek, Split, Rijeka, Zadar, Vukovar, Dubrovnik and Slavonski Brod.

Student Society for Neuroscience, University of Zagreb, School of Medicine, Zagreb, Croatia



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Tables should be typed on separate sheets, not to be submitted as photographs. Illustrations should be provided unmounted, in the form and condition suitable for reproduction. Freehand drawings, raw laboratory material, e.g. strip charts, roentgenograms, etc., should be photographed in B/W. Photographs should not be larger than 20x25 cm. If the attachements are in colour (tables, photographs, etc.), the author should pay for the expenses of printing that page in agreement with the Denona Printing-House. For every photograph of a recognizable patient written permission is required. On the back of each photograph indicate its number and top of the photograph. Beside that, the set of illustrations accompanying master copy should have the name of the first author written on the back. The author(s) should be aware that the size of illustrative material may be reduced if needed. Tables and figures should be numbered in Arabic numerals in the order they are mentioned in the text. Legends for each of them should be typed separately, each legend on a separate sheet. The number of figures should not exceed 6.

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All authors to be listed in case there are six or less:

Mubrin Z, Kos M. Assessment of dementia. Flow chart approach to clinical diagnosis. Neurol Croat 1992; 41: 141-156.

If the article is written by seven or more authors, only names of the first three authors should be listed, followed by *"et al"*.:

Baršić B, Lisić M, Himbele J *et al*. Pneumoccocal meningitis in the elderly. Neurol Croat 1992; 41: 131 - 140.

Books

Critchley M. The ventricle of memory. New York: Raven Press, 1990.

Chapter in a book

Geschwind N. The borderland of neurology and psychiatry: some common misconceptions. In: Bensom DF, Blumer D, eds. Psychiatric aspects of neurologic disease. New York: Grune and Stratton, 1975; 1 - 9.

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Upute autorima

NEUROLOGIA CROATICA, službeno glasilo Hrvatskoga neurološkog društva i Hrvatskoga neurokirurškog društva, izdaje Klinika za neurologiju, Klinički bolnički centar Zagreb, dva puta na godinu. Neurologia Croatica objavljuje radove iz područja kliničke neurologije, temeljnih neuroznanosti i drugih pridruženih područja.

Neurologia Croatica objavljuje slijedeće tipove članaka:

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Knjige

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Poglavlje u knjizi

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