CREUTZFELDT—JAKOB DISEASE RISK IN SLOVAK RECIPIENTS OF HUMAN PITUITARY GROWTH HORMON

MITROVA E, BELAY G

RIZIKO CREUTZFELDTOVEJ—JAKOBOVEJ CHOROBY U PACIENTOV LIEČENÝCH RASTOVÝM HORMÓNOM PRIPRAVENÝM Z ĽUDSKÝCH HYPOFÝZ

Abstract

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Bratisl Lek Listy 1999; 100 (4): 187–191

Creutzfeldt—Jakob disease (CJD) is a transmissible, fatal degenerative disorder of the CNS. CJD is known in a sporadic, familial and iatrogenic form. Iatrogenic form has been accidentally induced through corneal and dura mater transplantation or surgical procedures. The largest number of iatrogenic CJD developed in patients who had received human growth hormone (hGH). The minimal incubation period appears to be 4—15 years, the maximal 21—30 years after receiving hGh treatment.
An increasing number of new CJD cases in hGH recipients in France, providing evidence of unusually long incubation period and an occurrence of genetically cotrolled (mutation E200K carrier) CJD-risk group in Slovak population induced this second investigation of hGh treated patients.
***The aim of this study* is to verify whether the absence of CJD in hGH recipients in Slovakia reflects the actual epidemiological situation or a lack of informations. The objective of the study was to investigate signs of clinical manifestation of CJD and to perform molecular genetic study on prion protein (PrP) gene in hGh recipients.**
***Patients and methods:* 32 hGH treated patients (23 men and 9 women) at the age of 17—38 years were investigated. The occurrence of codon 200 (E200K) mutation and polymorphism at codon 129 of PrP gene was studied.**
***Results:* Neurological, including cerebellar signs of CJD, intellectual or psychological changes were not observed in investigated patients. The shortest duration of hGH treatment was 2 years, the longest 9 years. The time interval since the beginning of hGH administration was 12—19 years. Restriction endonuclease analysis of the PrP gene revealed one patient with E200K mutation, 8 patients homozygous for methionin, 2 patients homozygous for valin and 16 heterozygous patients at codon 129.**
***Conclusion:* No evidence of CJD has been observed in investigated group of hGH recipients. Considering the long incubation**

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Abstrakt

Mitrová E., Belay G.:
Riziko Creutzfeldtovej—Jakobovej choroby u pacientov liečených rastovým hormónom pripraveným z ľudských hypofýz
Bratisl. lek. Listy, 100, 1999, č. 4, s. 187–191

Creutzfeldtova—Jakobova choroba (CJch) je prenosné, smrteľné degeneratívne ochorenie CNS, ktoré sa vyskytuje v sporadickej, rodinnej a iatrogénnej forme. Iatrogénna forma sa zistila po transplantácii rohovky, dura mater, a v súvislosti s niektorými chirurgickými výkonmi. Najviac iatrogénnych prípadov CJch vzniklo u pacientov liečených rastovým hormónom humánneho pôvodu (hRH). Minimálna inkubačná doba je 4—15 rokov, maximálna 21—30 rokov po podávaní RH. Narastajúci počet nových prípadov CJch u recipientov hRH vo Francúzsku, ktoré prinášajú dôkaz o neobyčajne dlhej inkubačnej dobe a výskyt geneticky kontrolovanej rizikovej skupiny CJch (nosiči mutácie E200K) v slovenskej populácii, viedli k opakovanému kontrolnému vyšetreniu pacientov liečených hRH.
Cieľ *štúdie*: Overiť, či absencia CJch u recipientov hRH na Slovensku odráža skutočnú epidemiologickú situáciu, alebo je výsledkom nedostatočných informácií. Zámerom bolo vyšetriť prípadný výskyt prejavov klinickej manifestácie CJch a vykonať molekulárne genetické vyšetrenie prionového (PrP) génu v skupine recipientov hRH.
Pacienti a metódy: Vyšetrených bolo 32 pacientov (23 mužov a 9 žien) liečených hRH, vo veku 17—38 rokov. Na PrP géne sa sledoval výskyt mutácie na kodóne 200 (E200K) a polymorfizmus na kodóne 129.
Výsledky: U vyšetrených pacientov sa nezistili neurologické (vrátane mozočkových) príznaky CJch, ani poruchy intelektu alebo psychické zmeny. Liečba hRH trvala najmenej 2 roky, najviac 9 rokov. Analýzou PrP génu pomocou reštrikčnej endonukleázy sa zistil 1 pacient s mutáciou E200K. Na kodóne 129 boli 8 pacienti homozygotní na metionín, 2 homozagotní na valín a 6 heterozygotní.
Záver: Vo vyšetrovanej skupine recipientov hGH sa nezískal žiaden dôkaz o výskyte CJch. Vzhľadom na poznatky o dlhej inkubačnej dobe CJch vyvolanej podávaním hRH a na získané časo-

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period of hGH-induced CJD and the obtained results, clinical and genetic investigation on the whole relatively small group of Slovak hGH recipients is recommended. ***(Tab. 2, Fig. 1, Ref. 22.)***
Key words: Creutzfeldt—Jakob disease, human growth hormon, genetic risk.

vé a molekulárnogenetické údaje sa odporúča klinické a genetické vyšetrenie celej, relatívne malej skupiny pacientov na Slovensku, liečenej hRh. *(Tab. 2, obr. 1, lit. 22.)*
Kľúčové slová: Creutzfeldtova-Jakobova choroba, rastový hormón humánneho pôvodu, genetické riziko.

Transmissible spongiform encephalopathies (TSE) are a group of fatal neurodegenerative disorders that affect humans and animals. TSE agents are characterized by unconventional properties as an increased resistance to procedures of chemical and physical inactivation, an unusually long incubation period (years) and the absence of detectable immune response. A pathognomic finding is an accumulation of the abnormal, protease resistant isoform (PrPres) of the normal, host-encoded cellular prion protein (PrPc) in the brain. In humans, this PrP gene is located on chromosome 20. PrPc is a cell surface glycoprotein, its biological function is still unclear.

A number of TSEs have been described in animals: scrapie in sheep and goats, transmissible mink encephalopathy, chronic wasting disease of captive mule deer and elk, bovine spongiform encephalopathy (BSE) and feline spongiform encephalopathy. Human TSEs include kuru, Creutzfeldt—Jakob disease (CJD), Gerstmann—Sträussler—Scheinker syndrom (GSS), fatal familial insomnia (FFI) and recently the allarming new variant of CJD (nvCJD).

CJD is the most important human TSE. Clinically it is characterized by a progressive dementia and motor disturbances (pyramidal, extrapyramidal and cerebellar). CJD occurs as a sporadic, familial and iatrogenic disease. Besides neurosurgical transmissions (corneal transplants, stereotactic electrodes, human dura mater grafts), the largest number of iatrogenic CJD developed in patients who had received human growth hormon (hGH).

In April 1985 the National Institutes of Health decided to suspend the distribution of hGH. In May 1985 pituitary hGH was withdrawn from patients with pituitary deficiency also in United Kingdom. The reason was that four patients who had received the hormone, derived from pooled cadaveric human pituitary glands, developed CJD (Koch et al., 1985, Gibbs et al., 1985). Additional CJD-affected hGH recipients have been identified in The United States (Brown et al., 1985, Marzewski et al., 1988; Fradkin et al., 1991), United Kingdom (Ellis et al., 1992), New Zaeland (Croxon et al., 1988) and in France (Dray et al., 1987; Goujard et al., 1988). The largest number of cases (51) occurred in France (Huillard et al., 1998), despite of a modified hormonal extraction which incorporated isoelectric precipitation and two chromatographic steps. Besides hGH, CJD was induced also by administration of gonadotrophin extracts (Cochius et al., 1990). Since 1995 all hypopituitary deficiencies were treated with the recombinant growth hormon.

Investigation of potential risk of CJD in hGH recipients in Slovakia started in 1987. No suspect case of CJD was found in that preliminary study (Mitrová, 1989).

Increasing number of new CJD cases in hGH recipients in France, providing evidence of unusually long incubation period and an occurrence of genetically controlled CJD-risk group in Slovak population induced the second investigation of hGH treated patients. The aim of this study was to verify whether the absence of CJD cases in Slovak hGH recipients is based on the actual epidemiological situation or it is a lack of relevant data. The objective of this study was to investigate signs of clinical manifestation of CJD and to perform molecular genetic study on PrP gene in selected group of hGH recipients.

Patients and methods

A total of 32 hGH treated patients (23 men and 9 women) from Bratislava region were investigated.

Anamnestic data were obtained directly from patients. They were asked for following informations: dates of birth, the use of hGH, dates when a therapy was started and finished, duration of the treatment, pathological events and highest achieved education level.

Clinical investigation was focused on neurological, mainly cerebellar signs, on behavioural and intellectual changes.

DNA studies: In 16 patients DNA was isolated from peripheral blood leukocytes. The open reading frame of the PrP gene was amplified by PCR using Taq polymerase and oligonucleotide primers. The restriction endonuclease BsmA-I was used for the detection of the lysine for glutamate point mutation at codon 200 (E200K mutation) and MaeII was used for characterizing the methionine/valine polymorphism at codon 129.

Results

The investigated 32 hGH recipients were at the age of 17—38 years (years of birth 1959—1980). The ratio of men to women was 2.5:1.

All patients were treated with i.m. injection of CRESCORMON (Kabi).

Duration of the treatment: mean 5.5 years, range 2—9 years. Of the 32 patients: 53.1 % was treated 2—3 years, 40.6 % for 4—6 years and 2.3 % for 7—9 years.

The time interval since the beginning of hGH administration was: 12—13 years in 46.9 %, 14—16 years in 15.6 % and 17—19 years in 37.5 % (Tab. 1).

Tab. 1. Duration of the hGH treatment (in years) and time interval since the beginning of hGH treatment in investigated patients.
Tab. 1. Dĺžka podávania hRH (v rokoch) a časový interval od začiatku podávania preparátu u vyšetrovaných pacientov.

Duration of hGH treatment			Interval since the beginning of hGH treatment		
Years	No. of patients		Years	No.of patients	
2-3	17	53.1 %	12-13	15	46.9 %
4-6	13	40.6 %	14-16	5	15.6 %
7-9	2	2.3 %	17-19	12	37.5 %

Tab. 2. PrP gene: Codon 200 CJD-specific mutation and codon 129 polymorphism in human growth hormone treated hipopituitary patients.
Tab. 2. Výskyt CJch-špecifickej mutácie na kodóne 200 a polymorfizmus na kodóne 129 ľudského PrP génu u pacientov liečených ľudským rastovým hormónom.

No	Patients	Codon 200 mutation		Codon 129 polymorphism		
	+	–		met/met	met/val	val/val
16		115862				
	6.3%	93.7%		50%	37.5%	12.5%

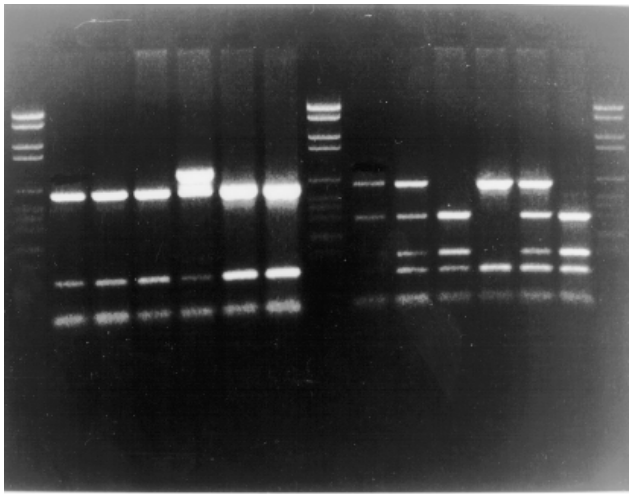

Fig. 1. DNA analysis in hGH treated patients. PCR amplification of PrP coding region. Left: PrP mutation at 200 (E200K) PrP coding region after digestion with BsmAI: — without mutation shows 2 bands (621 and 182 bp), — with mutation shows 3 bands (803,625 and 182 bp). Right: Polymorphism at codon 129: PrP coding region after digestion with MaeII.: Met/Met (lines 2 and 5), Met/Val (line 4), Val/Val (lines 3 and 6). Obr. 1. DNA pacientov liečených preparátom hRH. Amplifikácia PrP kódujúceho fragmentu DNA pomocou PCR. Vľavo: Vyšetrenie mutácie PrP génu na kodóne 200 (E200K), štiepenie reštrikčným enzýmom Bs,A1: — bez mutácie vznikajú 2 pruhy (621 a 182 bp), — s mutáciou (4. stĺpec vľavo) vznikajú 3 pruhy (803, 625 a 182 bp). Vpravo: Vyšetrenie polymorfizmu PrP génu na kodóne 129: štiepenie reštrikčným enzýmom MaeII.: Met/Met (2. a 5. stĺpec vpravo), Met/Val (4. stĺpec vpravo), Val/Val (3. a 6. stĺpec vpravo).

Clinical findings: Neurological, including cerebellar signs, intellectual changes or psychological events were not present. Visual impairment, observed in two patients, were unlikely related to the administration of hGH. Of the 32 patients, 4 complained for tiredness, vertebral and arthritic pain, temporary depression and nervousenness has occurred in 1 patient, headache in 1 patient. Minor events notified amongst patients are not consistent with clinical manifestation of CJD. The achieved education was as follows: primary school 10 %, educational establishments 60 %, secondary school 15 % and University 15 %.

Genetics: Restriction endonuclease analysis of the opening reading frame of the PrP gene, using the enzymes BsmA-I (for codon 200) and MaeII (for codon 129), revealed one patient with E200K mutation, 8 patients homozygous for methionine, 2 patients homozygous for valin and 6 patients heterozygous at codon 129 (Tab. 2, Fig. 1).

Discussion

In Slovakia a great attention has been paid to CJD since 1975. To important findings belong two focal accumulations of CJD with occurrence of CJD-specific E200K mutation (Mitrová, 1991). Despite of that E200K is the worldwide most frequent CJD-specific mutation, when and from where it came and how it does influence the manifestation of CJD, is more hypothetically suggested than clearly proved.

The highest number of E200K carriers (CJD affected patients and 33 % of their asymptomatic relatives) was notified in Slovak Orava region, mainly in villages founded by Ruthenian immingrants in 15th and 17th centuries (Mitrová, 1991). Concerning the occurrence of E200K mutation in Orava, some informations provide a family, divided into two branches at the end of the 19th century. In both branches, the one left in Orava as well as in that emmigrated to USA, E200K carriers developed CJD. There is even an earlier trace of E200K mutation in Slovakia: the genealogical study, which revealed common ancestors of 3 CJD-affected branches with E200K mutation in 1690 (Mitrová et al., 1991). These data demonstrate that in the 17th century the CJD-specific E200K mutation has already occurred in the country.

The role of E200K mutation in a clinical manifestation of CJD is not yet satisfactorily clarified. The original interpretation that mutation indicates a genetically increased susceptibility to CJD (Goldfarb et al., 1990), was replaced by classification of CJD cases with E200K among the familial TSEs, as an autosomal dominant disorder. In comparison to typical familial TSEs (GSS and FFI) with high penetrance and rather uniform clinical course, CJD with E200K characterize a broad scale of clinical manifestations, an easy transmissibility to experimental animals, just as in typical sporadic CJD (Brown, 1988) and — an incomplete penetrance. Therefore, search for an occurrence of E200K carriers among hGH recipients (a possible double CJD-risk) might be not without interest.

Analysis of Slovak CJD group (109 definitive cases) provide an evidence that patients with E200K mutation and homozygous for methionin at codon 129 survive significantly less after the clinical onset of CJD than other CJD cases. Also the percentage of patients with duration of the disease longer than 12 months is conspicuosly smaller. This evidently demonstrate an unfavourable acceleration of the clinical course induced by both, codon 200 mutation and methionin homozygosity at codon 129.

No one of 109 verified Slovak CJD patients was a recipient of hGH. In countries where hGH-induced CJD have occurred, large numbers of children with primary or secondary pituitary deficiencies were treated with growth hormon (approximately 10 000 in USA, 2500 in France, 2000 in England). Comparing to this, only a small group of children was treated with hGH in Slovakia. It is an interesting contrast to the fact that Slovakia was one of the most active exporters of human cadaveric pituitary glands. It is worthwhile to mention that due to the recommendation of the National Reference Laboratory of Slow Virus Neuronfections, contraindications and criteria for collection of pituitary glands became strictly modified according to the contemporary knowledge on CJD prevention.

According to R.T. Johnson and J. Gibbs (1998), more than 100 cases of CJD have been related worldwide to hGH and gonadotropic

hormones. Iatrogenic CJD in all hGh recipients are characterized by distinct clinical features: atypical, young age of patients, early cerebellar ataxia and movement disorders with late development of dementia and an absence of typical EEG. The minimal incubation period after receiving hGH tretament appears to be 4—15 years, the maximal 21—30 years. There are some data suggestive of the relationship between the dose of the agent and the incubation time. A striking similarity of clinical findings with other human horizontally transmitted TSEs as kuru and vCJD could not be overlooked.

Molecular genetic studies on PrP gene performed in hGH recipient CJD patients revealed no pathogenic mutation. The noteworthy finding in this group of iatrogenic CJD was an overrepresented homozygous valine genotype at codon 129 (Owen et al., 1990; Collinge et al., 1991). Data obtained by investigation of 23 French patients (Deslys et al., 1994) and other combined studies (Brown et al., 1994; Jaegly et al., 1995) provide an evidence that homozygosity itself rather than homozygosity for valin at codon 129 is associated with an increased susceptibility to iatrogenic CJD.

Analysis of the genotype at codon 129 in our patients (Met/Met 37.5 %, Met/Val 50 %, Val/Val 12.5 %) reveals some differences (Met/Met 50 %, Met/Val 50 %, Val/Val 0 %) when compared with uninfected hypopituitary control patients (Brown et al., 1994) and is comparable (Met/Met 37 %, Met/Val 51 %, Val/Val 12 %) to data found in healthy normal population (da Silva and Esmonde, 1994).

Observed polymorphism, if compared to the Slovak healthy E200K carriers with an increased percentage of homozygosity for methionin, shows different pattern and does not indicate an increased proportion of homozygous patients, more susceptible to CJD.

In this study, performed in a small group of hGH recipients a carrier of CJD-specific E200K mutation has been found. The question is how many E200K carriers are among all hGH treated patients in the country? It would be worthwhile to follow their health condition together with the group of E200K carrier relatives of CJD patients.

Obtained data show that to a half of our investigated patients was hGH administered more than 4 years, and the shortest treatment lasted not less than 2 years. Observed duration of hGH treatment is consistent with data obtained in hGh recipients, peripherally infected by CJD i. e., the investigation of hGH treated patients was justified.

Time intervals from the beginning of hGH administration lasted from 12 to 19 years. Comparing to other relevant studies, they did not reach the longest known incubation period of hGH induced CJD.

In conclusion, no evidence of CJD have been observed in investigated group of patients treated with hGH. Nevertheless, the very long incubation time in hGH induced CJD does not allow to exclude completely the risk of CJD, even if it appears as minimal.

Considering a predisposing factor for iatrogenic CJD in our patients — the observed 50 % homozygosity at codon 129 — and a patient with E200K mutation, it appears as reasonable to continue the clinical and genetic investigation with all hGH treated patients in the country.

Presented report contribute to the analysis of hGH receivers and raise the number of countries, where epodemiological informations on this topic are available.*

* This study was supported by EU project BIOMED1 on Surveillance of CJD. The authors are grateful to Leopolda Scheidova, MD, PhD, for her help in collecting material for DNA study.

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Received August 15, 1998.

SPOMIENKA

NEDOŽITÉ ŽIVOTNÉ JUBILEUM

Dňa 14. novembra 1998 zomrel v Trnave po zdĺhavej ťažkej chorobe emeritný primár oddelenia patológie nemocnice v Trnave MUDr. František Tomík — výrazná osobnosť slovenskej patológie. Len tri týždne mu chýbali k dovŕšeniu 75 rokov.

Narodil sa 3. decembra 1923 v Skalici, kde vychodil základnú školu aj gymnázium. Po absolvovaní Lekárskej fakulty UK v Bratislave svoju lásku k patológii, ktorú v ňom vzbudil počas štúdií prof. MUDr. F. Klein, prednosta Ústavu patológie LFUK v Bratislave, realizoval v Trnave roku 1949 na oddelení patológie, kde bol primárom prof. MUDr. F. Šubík a po jeho odchode do exilu sa stal roku 1952 primárom. Špecializáciu z patológie získal u prof. MUDr. F. Kleina roku 1953. Vojenskú prezenčnú službu v rokoch 1954—1956 absolvoval ako odborný lekár v Ústave patológie VLA v Hradci Králové u prof. MUDr. Fingerlanda, DrSc., žiaka zakladateľa modernej českej patológie prof. MUDr. H. Šikla. Obohatený Šiklovou školou vrátil sa roku 1956 do Trnavy a v krátkom čase prebudoval celé oddelenie patológie na veľmi dobrú úroveň. Prísne dbal o perfektnú nekroptickú aj bioptickú dokumentáciu. Jeho snahou bolo prispieť k vylepšeniu diagnostiky v nemocnici čo najrýchlejším vybavením biopsie, ako aj zavedením klinickopatologických konferencií. Zároveň začal intenzívne prednášať na vedeckých fórach a publikovať v odborných časopisoch. Témou boli smrteľné ochorenia, ktoré sa v tých časoch vyskytovali. Týkali sa detskej patológie, ako napríklad kongenitálna fibróza pečene, cystická fibróza pankreasu, cytomegalická choroba u detí, komplikácie antibiotickej a cytostatickej liečby, ktoré sa prejavovali ako generalizovaná stafylokoková sepsa alebo generalizovaná mykóza. Po medzinárodnom hepatologickom sympóziu v Havane požiadal prof. Niederland, prednosta II. internej kliniky LFUK, primára Tomíka o spoluprácu pri histologickom vyšetrení pečeňových punkčných biopsií. Takto začal primár Tomík po dôkladnej teoretickej príprave ako prvý na Slovensku vyšetrovať pečeňové punktáty a vypracoval sa na najlepšieho odborníka v tejto oblasti na Slovensku, o čom svedčí množstvo publikácií a prednášok na túto tému. Po študijnom pobyte u prof. MUDr. Weplera v Kasseli (SRN) zhrnul svoje poznatky do reprezentačnej anglicko-slovenskej monografie *Farebný atlas biopsie pečene*, ktorý vyšiel vo vydavateľstve Osveta v Martine roku 1978.

Primár MUDr. Tomík bol 10 rokov hlavným odborníkom pre patológiu na Slovensku a súčasne členom kolégia ministra zdravotníctva ČSSR a 8 rokov bol vedeckým sekretárom Spolku lekárov v Trnave.

V 70. rokoch zaviedli prof. MUDr. J. Dušek, DrSc., a doc. MUDr. Č. Dvořáček, CSc., veľmi cenné bioptické "slide" seminára, ktoré boli raz za mesiac striedavo v Olomouci a v Ostrave. Spolu s kolegami patológmi sa na týchto seminárov aktívne zúčastňoval, debatoval o každom prípade a čoskoro sa vypracoval na vrcholového účastníka, takže jeho názor pri spornej diagnóze bol často rozhodujúci. Tieto vedomosti a skúsenosti zúžitkoval potom v ďalšej monografii *Farebný atlas nádorov mäkkých tkanív*, ktorý vyšiel roku 1982 vo vydavateľstve Osveta v Martine a dodnes slúži ako učebnica pre adeptov atestácie z patológie.

Zdĺhavá choroba ho žiaľ prinútila vzdať sa vedenia patológie, ale napriek tomu ešte stále pracoval ako sekundárny lekár, kým ho choroba trvale nepripútala na lôžko. Svoj ťažký údel trpezlivo znášal do konca svojho života pri stále vysokej mentálnej úrovni.

Primár MUDr. Tomík publikoval približne 200 vedeckých prác doma aj v zahraničí a odprednášal vyše 300 odborných prednášok, ktoré sa vyznačovali vysokou vedeckou úrovňou a hlbokou znalosťou danej problematiky. Ku každému problému pristupoval vždy po dôkladnom teoretickom štúdiu odbornej literatúry. Jeho diskusné príspevky na vedeckých fórach boli vecné, jasné a vyvierali z bohatých vlastných aj literárnych poznatkov, často podfarbené zdravým sarkazmom.

Aj keď primár MUDr. Tomík nedosiahol nijakú vedecko-pedagogickú hodnosť, ktorú si za svoju prácu nesporne zaslúžil, vychoval 2 docentov a 6 primárov, čo sa často nestalo ani na univerzitných ústavoch. Svojou vedeckou prácou pozdvihol nielen úroveň trnavskej nemocnice, ale aj slovenskej patológie. Bez zveličovania môžeme konštatovať, že sa natrvalo zapísal ako veľká osobnosť do dejín slovenskej patológie.

Česť jeho pamiatke.

Š. Kopecký