Patients with narcolepsy in Slovenia

Bolniki z narkolepsijo v Sloveniji

Leja Dolenc Grošelj,[1] Marija Todosijević[2]

Clinical Institute of clinical neurophysiology, University medical center Ljubljana, Slovenia

Neurological department, Hospital Novo mesto

Korespondenca/ Correspondence:
Leja Dolenc Grošelj,
e: leja.dolenc@kclj.si

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Abstract

Background: To determine the number of patients with narcolepsy in Slovenia, describe their typical clinical features and the diagnostic criteria they met on polysomnography (PSG), the mean sleep latency test (MSLT) and HLA typing.

Methods: Retrospective study of all narcolepsy patients referred to the National Sleep Disorder Centre at the Institute of Clinical Neurophysiology, University Medical Centre Ljubljana in the period from May 1994 to September 2013.

Results: There are currently only 38 patients with the diagnosis of narcolepsy in Slovenia. The average time lapse from onset to diagnosis is 17 years. The time lapse is much longer in older patients. The prevalence of narcolepsy in Slovenia is 1.85 per 100,000 population. All patients had excessive daytime sleepiness (EDS), 89 % cataplexy, 66 % hallucinations and 37 % sleep paralysis at the time of diagnosis. Characteristic changes on PSG and MSLT were present in 97 % of all tested patients. HLA DQB1*0602 was present in 88 % of all tested patients. The most common differential diagnoses found were obstructive sleep apnoea syndrome (OSAS) and hypersomnia.

Conclusion: With a prevalence of 1.85/100,000, narcolepsy in Slovenia is seriously underdiagnosed. The reasons behind this are most likely that it is not recognized by general practitioners and probably not referred in adequate numbers by neurologists on the secondary level. General practitioners should be more aware of the disease and think about the possibility of it in patients with excessive daytime sleepiness and unexplained attacks, with additional symptoms such as hallucinations and paralysis during sleep. Both general practitioners and neurologists should refer such patients to the Sleep Disorder Centre, where the diagnosis can be confirmed and treatment started as soon as possible, thereby reducing the patients' pathological symptoms and improve their quality of life.

Izvleček

Izhodišča: Namen študije je bil določiti število bolnikov z narkolepsijo v Sloveniji, njihovo prevalenco, povprečno starost ob postavitvi diagnoze, trajanje od začetka simptomov do postavitve diagnoze ter opredeliti klinične simptome: prisotnost čezmerne dnevne zaspanosti, katapleksije, paraliz v spanju, hipnagognih in hipnopompnih halucinacij ter najpogostejše diferencialne diagnoze. Želeli smo opisati njihove značilne laboratorijske spremembe na polisomnografiji in objektivnih testih zaspanosti čez dan ter HLA tipizacijo.

Metode: Retrospektivna študija vseh bolnikov z diagnozo narkolepsije, ki so bili od maja leta 1994 do septembra leta 2013 obravnavani v terciarnem Centru za motnje spanja na Inštitutu za klinično nevrofiziologijo UKC Ljubljana. Vključili smo vse bolnike z napotno ali odpustno diagnozo narkolepsije, ki so bili v tem obdobju obravnavani v Centru za motnje spanja, ter statistično obdelali vse dostopne podatke o starosti in spolu bolnikov, simptomih in znakih bolezni ter njihovem trajanju, zastopanosti po regijah ter opravljenih preiskavah in predpisanem zdravljenju.

Rezultati: V Sloveniji je trenutno samo 38 bolnikov s potrjeno diagnozo narkolepsije (19 žensk in 19 moških). Prevalenca je 1,85/100.000 prebivalcev. Povprečna starost ob postavitvi diagnoze je bila 41 let, ženske so bile stare 37 let, moški pa 44 let. Vsi so čezmerno zaspani podnevi, 84 % žensk, 95 % moških in 89 % vseh bolnikov ima katapleksijo; 63 % žensk, 68 % moških in 66 % vseh bolnikov ima halucinacije; 32 % žensk, 42 % moških in 37 % vseh pa paralize. Značilne spremembe na polisomnografiji so imele vse testirane ženske, 94 % moških in 97 % vseh testiranih

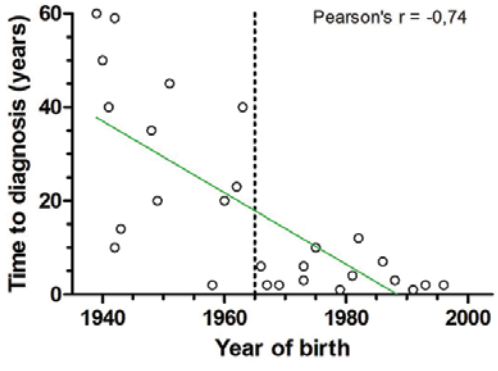
bolnikov. Na testih zaspanosti čez dan so prav tako imele vse testirane ženske, 93 % testiranih moških in 97 % vseh testiranih bolnikov. Značilno HLA tipizacijo ima 100 % testiranih moških, 76 % testiranih žensk oz. 88 % vseh testiranih bolnikov. Povprečno obdobje od pojava prvih simptomov in znakov bolezni do postavitve diagnoze je 17 let, mediana je 9 let. Ugotovili smo statistično pomembno korelacijo ($p < 0{,}0001$) med starostjo bolnikov in časovnim razkorakom v diagnozi, ki je naraščala s starostjo bolnikov.

Zaključek: Prevalenca bolnikov z narkolepsijo v Sloveniji je nizka glede na prevalenco v svetu, ki je okoli 25/100.000 prebivalcev in govori v prid velikega števila neprepoznanih bolnikov. Zamuda v diagnozi je povprečno 17 let, veliko več pri starejših bolnikih. Splošni zdravniki in nevrologi moramo biti bolj pozorni in posumiti na narkolepsijo pri bolnikih s čezmerno dnevno zaspanostjo in nepojasnjenimi napadi izgube mišičnega tonusa, posebej če so prisotni še drugi tipični simptomi, kot so paralize v spanju ter hipnagogne in hipnopompne halucinacije. Takšne bolnike je potrebno čim prej napotiti v ambulanto za motnje spanja, kjer diagnozo lahko potrdimo in zdravljenje začnemo čimprej ter na ta način bolnikom zmanjšamo patološke simptome in izboljšamo kakovost življenja.

Introduction

Narcolepsy is a chronic sleep disorder characterized by sudden, uncontrollable attacks of sleep during daytime. The prevalence of narcolepsy worldwide ranges from 20 to 180/100,000 and is estimated to be around 25/100,000 in Caucasian population. There are about 200,000 people suffering from narcolepsy in Europe.[1-3] Apart from excessive daytime sleepiness (EDS), other common features are cataplexy, sleep paralysis, hypnagogic and hypnopompic hallucinations and sleep fragmentation.[1,4] EDS usually takes the form of short sudden attacks of sleep, after which the patient feels refreshed. Cataplexy is a sudden complete or partial loss of muscle tone, triggered by intense emotions, usually positive ones, and can lead to falls. Hallucinations can be visual or auditory or both, and combined with paralysis may cause great discomfort and stress for the patient. The disease frequently starts in adolescence and sometimes in childhood. In most cases the first sign of the disease is EDS, which is later joined by other symptoms. EDS can cause accidents in the workplace or on the road, with sometimes devastating consequences. Before being diagnosed with narcolepsy, patients are often misdiagnosed with epilepsy or depression or simply mislabelled as lazy and passive at school or workplace.[5]

Polysomnography (PSG) is the gold standard used to diagnose narcolepsy, supplemented with objective testing of excessive sleepiness, called the multiple sleep latency test (MSLT). The most characteristic signs are sleep onset REM (SOREM) and short sleep latency (less than 15 minutes) both during night and daytime tests. At least two SOREMs are necessary during five sleep latency tests and a medium sleep latency of



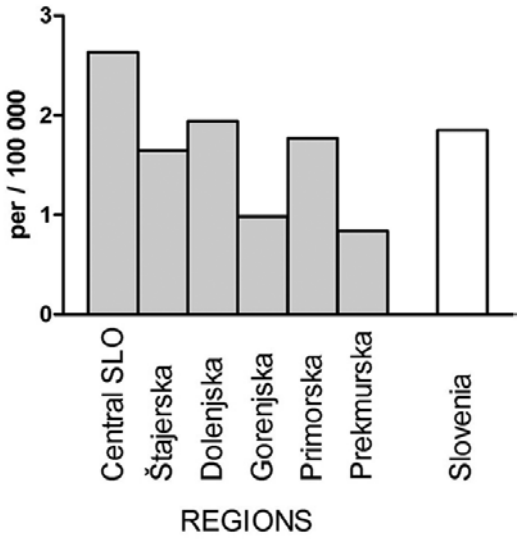


Figure 1 (left): Correlation between patients' age and time to diagnosis ($p < 0{.}0001$).
Figure 2 (right): Prevalence of narcolepsy in Slovenia by different regions.

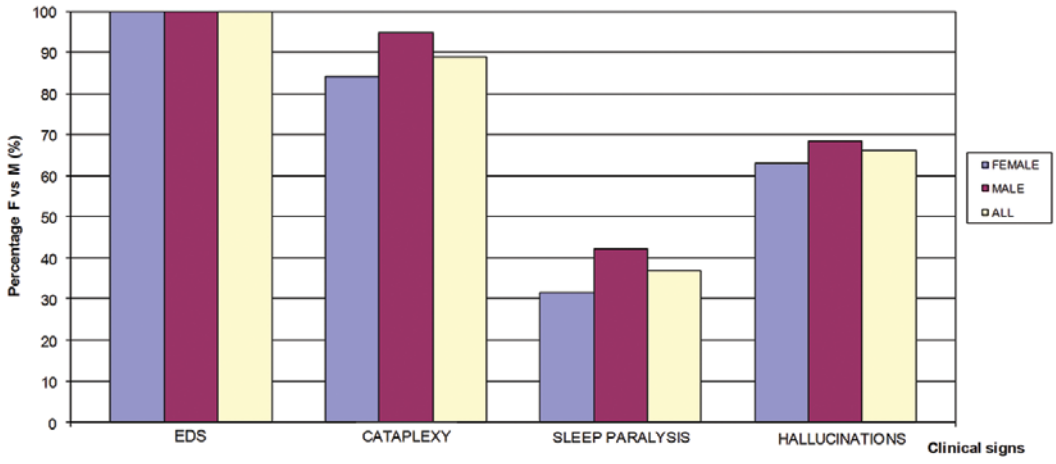


Figure 3: Presence of clinical signs of narcolepsy.

less than 8 minutes. Sleep fragmentation during night sleep is also present.[1,6]

Additional diagnostic tools are used to determine the levels of hypocretin in the cerebrospinal fluid (CSF) and typical human leukocyte antigen (HLA). Levels of hypocretin in CSF lower than 110 pg/ml are usually found. HLA DQB1*0602 is found in 85 % of patients with narcolepsy with cataplexy, but in only about 40 % of patients with narcolepsy without cataplexy.[7,8]

Treatment is both non-pharmacological and pharmacological. The only drug that is currently used for the treatment of EDS and cataplexy is sodium oxybat, while antidepressants, mostly selective serotonin reuptake inhibitors (SSRI) are used for cataplexy, and modafinil and methylphenidate to treat EDS.[9-11]

Objective

The aim of our study was to determine the number of patients with narcolepsy in Slovenia, their prevalence, gender, age at time of diagnosis, time lapse from the first symptoms to the confirmation of diagnosis; the presence of clinical features such as EDS, cataplexy, sleep paralysis, hypnagogic and hypnopompic hallucinations, diagnostic criteria they met on PSG and MSLT, presence of HLA DQB1*0602.

Methods

We searched for patients who were referred to the Sleep Disorder Centre at the Institute of Clinical Neurophysiology, University Medical Centre Ljubljana, with suspicion of having narcolepsy, and those who were discharged with the same diagnosis in the period from May 1994 to September 2013. From our data, the number of male and female patients with narcolepsy, their age at the time of diagnosis and the period between the time of onset and the time of diagnosis were calculated. Patients who were diagnosed in less than a year were treated as being diagnosed one year after the onset of symptoms. By using statistical data from the Statistical Office of the Republic of Slovenia, the prevalence of patients with narcolepsy was calculated on the national level and for different regions of the country. The percentage of male and female patients with cataplexy, sleep paralysis, hallucinations, typical features on PSG and MSLT, HLA-DQB1*0602 was also calculated. We tried to prove the correlation between the patient's age and the time lapse from disease onset to the time of diagnosis.

Results

There are currently 38 patients with narcolepsy in Slovenia, 19 females and 19 males. The average age at the time of diagnosis is 37 years for females, 44 years for males and 41 years for all patients. The average time lapse from onset to diagnosis is 17 years, median value is 9 years and it varies from less than a year to 60 years. The time from the first symptoms to diagnosis is significantly longer ($p < 0.0001$) for older patients (Figure 1). The prevalence of narcolepsy in Slovenia is 1.85 per 100,000 inhabitants; we also

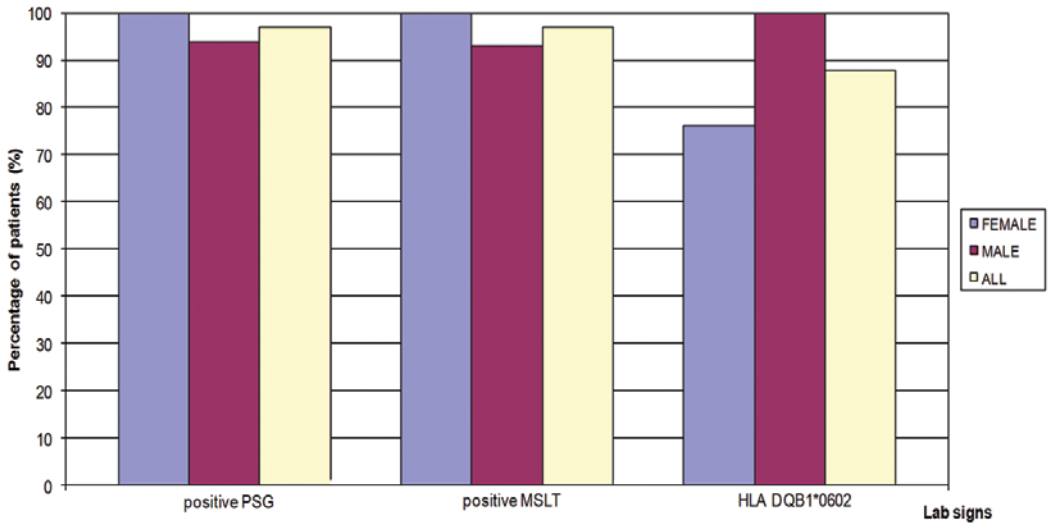


Figure 4: Presence of typical signs on polysomnography (PSG), mean sleep latency test (MSLT) and typical HLA.

calculated prevalence for different regions (Figure 2). All patients had EDS. 84 % of females, 95 % of males and 89 % of all patients had cataplexy, 63 % of females, 68 % of males and 66 % of all patients had hallucinations and 32 % of females, 42 % of males and 37 % of all patients had sleep paralysis at the time of diagnosis (Figure 3). Characteristic changes on PSG were present in all tested females, 94 % of tested males and 97 % of all tested patients; one female and two males were not tested. Characteristic changes on MLST were found in all tested females, 93 % of tested males and 97 % of all tested patients. One female and three males were not tested. HLA DQB1*0602 was present in all tested males, 76 % of tested females and 88 % of all tested patients. Two females and two males were not tested (Figure 4). There is one patient on our records with symptomatic narcolepsy due to astrocytoma. We also diagnosed symptomatic narcolepsy in a patient with anti-LGI1 limbic encephalitis; symptoms (EDS and cataplexy) subsided after appropriate immunosuppressant treatment. This patient was only referred to the Sleep Disorder Centre for diagnostic purposes. With respect to treatment, four of our patients are without therapy owing to very mild symptoms or refusal of medications. Three of our patients, all of them females, discontinued treatment with sodium oxybat due to side effects, mostly weight loss. 29 patients are or were on sodium oxybat. Other medications used are antidepressants (tricyclic antidepressants (5 patients), selective serotonin reuptake inhibitors (SSRI) (4 patients) and norepinephrine/ serotonin reuptake inhibitors (NSRI) (2 patients)), modafinil and methylphenidate (Figure 5). During the observation period, 68 patients were referred to the Sleep Disorder Centre with a diagnosis of narcolepsy, and out of those, 30 were confirmed to have narcolepsy. Other diagnoses on discharge were obstructive sleep apnoea syndrome (OSAS) (11 patients), hypersomnia (8 patients), circadian rhythm disorder (2 patients), depression (2 patients), insomnia, asthma, transitional ischemic attack, restless legs syndrome, and disorder of autonomic nervous system (1 patient had pruritus). 8 of our patients with confirmed narcolepsy were referred to the Sleep Disorder Centre with a different diagnosis.

Discussion

Narcolepsy is a disabling neurological syndrome, with estimated prevalence around 25 per 100,000 in Caucasian population. Our results show that the prevalence of narcolepsy in Slovenia, with the diagnosis confirmed in the tertiary Sleep Disorder Centre is much lower than expected, 1.85/100,000. The essential diagnostic criteria for narcolepsy with cataplexy are clinical (complaint of excessive daytime sleepiness for at least 3 months and defined history of cataplexy), which could explain that patients are diagnosed but not referred to the Sleep Disorder Centre, however, whenever pos-

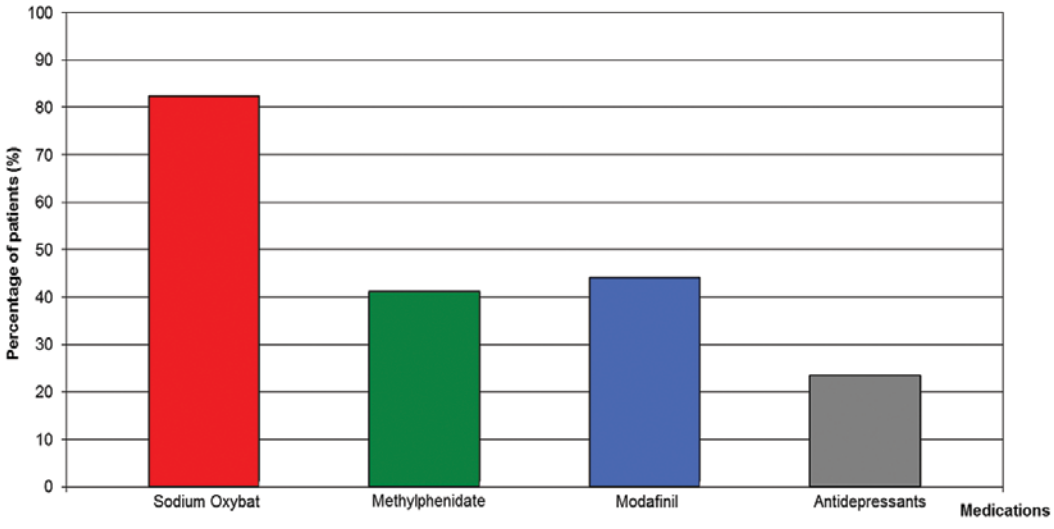


Figure 5: Pharmacological therapy in patients with narcolepsy.

sible, the diagnosis should be confirmed by PSG followed by MSLT, while the diagnosis of narcolepsy without cataplexy must be confirmed by nocturnal PSG followed by an MSLT. Furthermore, we found differences in the prevalence for different regions, which could be explained by the number of neurologists available, with the regions of Prekmurje and Gorenjska having only one neurologist each, while the region of central Slovenia has the highest number of neurologists. There are probably many more patients that are still undiagnosed. Therefore, it is important to raise awareness of narcolepsy among general population and general practitioners, for better understanding of symptoms, and earlier referral of patients to the Sleep Disorder Centre and introduction of effective therapy, which is nowadays only available to patients with polysomnography confirmed diagnosis. There is a positive trend, with the disease being more quickly recognized in recent years in younger patients presenting with typical symptoms. The reason behind more timely diagnosis could be attributed to better awareness of narcolepsy in general practitioners and secondary neurologists present in recent years. It is perhaps a result of the efforts of specialists in the field to inform colleagues and share the knowledge and different publications about the disease (different modules for narcolepsy, web page: "zaspan.si"). There were previous attempts to highlight the issue, with published case reports of patients with narcolepsy in Slovenia and an article about the importance of HLA typing in these patients.[12,13] In our study, the number of female and male patients is equal. EDS is present in all patients and is a leading sign, closely followed by cataplexy, with sleep paralysis being the least common. The vast majority of patients have typical signs on PSG and MSLT. 88 % of all tested patients have typical HLA DQB1*0602, which is in general consistent with data from other studies. Most patients are on one or more medications, with sodium oxybat being prescribed most frequently in recent years, which is in accordance with EFNS guidelines on the management of narcolepsy.[1] As with any other pharmacological therapy, side effects are present and can be a reason for discontinuation of treatment. If we look at discharge diagnoses of patients referred to as having narcolepsy, there are many with OSAS, which should always be taken into consideration when having a patient with EDS, specially, if there is a history of snoring, breathing pauses during sleep and recent weight gain.

Conclusion

Narcolepsy is a disabling neurological disorder, which is still under-diagnosed in Slovenia. We should all be more aware of the disease and consider the possibility of narcolepsy in patients with excessive daytime sleepiness and unexplained attacks or falls, with additional symptoms, such as hallucinations and paralysis during sleep, thus helping to establish diagnosis of narcolepsy

and refer the patients to the Sleep Disorder Centre. It is important to refer patients to a sleep disorder centre, where definite diagnosis can be made with certainty and not just based on clinical sings. By making or confirming the diagnosis, we can start treatment and help our patients take control of the disease and enjoy a better quality of life.

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