

## In Search for Symptoms of Impaired Function of Glymphatic System in Older People

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### Abstract

The authors emphasize significance for people caring for the elderly of the knowledge on the glymphatic system, discovered a few years ago. They present the basic data about the contemporary possibilities of objective estimation of the function of this system. The authors postulate that it would be reasonable to search for clinical symptoms indicative for the impairment of function of glymphatic system in older people. They believe that it is possible to propose some candidatures of such symptoms on the basis of analysis of the content of interviews with elderly people suffering from ineffective sleep. They postulate also to review the known psychometric tests designed for sleep quality assessment. As results of these considerations they propose some possible indicative symptoms, however they emphasize that these propositions should be verified by neuroscientist, which can apply the contrast-enhanced MRI.

**Keywords:** Glymphatic system; Sleep; Ineffective sleep; Neurodegenerative diseases; Dementia; Alzheimer disease

### Introduction

Nadia Aalling Jessen in her frequently cited review paper wrote: "The glymphatic system is a recently discovered macroscopic waste clearance system that utilizes a unique system of perivascular tunnels, formed by astroglial cells, to promote efficient elimination of soluble proteins and metabolites from the central nervous system" [1].

The action of the glymphatic system is fascinating, because it occurred that it can function only when we are sleeping. It clarifies the physiological role of sleep. So only a few years ago, it occurred that not only in humans but also in most animal species simultaneous cognitive performance and the clearing of brain tissue from waste metabolites is not possible.

It can be summarized in intuitive way that during sleep the neuronal cells must be shrunk to increase significantly the volume of the space containing the waste metabolites. Information processing and clearing must take place in alternating periods of time.

The glymphatic system is contemporary one of the most studied functional systems of the human body [1,2]. Much work has also already been devoted to the significance of impaired function of the glymphatic system for the development of dementia and other neurodegenerative diseases [3,4]. Some researchers emphasized that the function of the glymphatic system is impaired in the elderly [5].

It is known that the quality of sleep is often decreased in the elderly. The reasons of poor quality of sleep in the elderly can be different [6]. Many syndromes of chronic diseases like pain, difficulties with urination etc. disturb the effective, invigorating, reviving sleep. Probably the effectiveness of function of the glymphatic system is various in different elderly people. The probability of premature

dementia and neurodegenerative diseases depends from the efficiency of the glymphatic system, which is also responsible for the elimination of misfolded beta-amyloid [5].

It would be helpful for physicians, nurses and caregivers of older people to be able to detect and distinguish these manifestations of sleep disorders, which are indicative for a significant impairment of the functioning of the glymphatic system.

We try in this text of our commentary to consider this problem and to formulate some suggestions and hypotheses relevant to the search for symptoms indicative for the impairment of the function of glymphatic system in older people.

### Some remarks on contemporary possibilities of objective estimation of the function of the glymphatic system

Despite such significant physiological importance of the glymphatic system its operation was discovered only a few years ago after implementation of very sophisticated research techniques.

The action of the system was demonstrated using so called two-photon microscopy, what allowed to assess periarterial cerebrospinal fluid influx of tracers injected in the cisterna magna [1]. It was found that: "in vivo 2-photon imaging of glymphatic function showed that the cerebrospinal fluid influx in the awake state was reduced by 90% compared to anesthetized mice [1]. It was demonstrated then that during sleep the volume fraction of interstitial space expand about 80% [1].

The delivering of contrast agent into cistern magna allowed the track of the movement of cerebrospinal fluid in real time across the entire brain. The studies using contrast-enhanced MRI provided the first data for evaluation of glymphatic pathways [7,8].

Nadia Aalling Jessen quote Yang et al. and remarks that "intrathecal lumbar injections, which are routinely used in clinical myelographic

studies, provide a viable route to assess the basic parameters of glymphatic function” [1,9].

But it seems, that contemporary the clinical neuroscientists try to develop a safe and minimally invasive technique based on MRI imaging [10].

### **Analysis of the content of interviews with elderly people suffering from ineffective sleep**

We are convinced that among the many symptoms reported by people who feel their sleep is not likely to be effective there are signs indicative for the impaired function of glymphatic system.

This conviction is based on results of our multiple interviews with older people aimed at detecting risk factors for impairment of cognitive performance. We published formerly the data on the results of such structured interviews [11].

Another source of insights related to the task of searching for symptoms indicative for the impairment of the function of the glymphatic system can be the recognized, effective psychometrical tests designed for sleep quality assessment. One of such know test it is the Pittsburgh Sleep Quality Index [12].

Of course, we are not currently able to prove that the suggestions formulated below of indicative symptoms are really related to impaired function of glymphatic system. We treat only these propositions as working hypotheses, which aim to incline neuroscientists to their experimental verification. The clinician's discussion on this issue would be also valuable.

### **The proposition of the approximate structured interview for symptoms indicative for impaired function of the glymphatic system**

We suggest that the function of the glymphatic system is probably impaired when an older patient reports the statements:

- It happens often, some days during a week, that my sleep was not deep enough
- and I woke up feeling bad
- For a long time, in most days of the week I try to improve my feeling by having an
- afternoon slumber (nap, snooze)
- It happens often, some days during a week, that after waking, already since morning
- I have a problem to keep up enthusiasm to get things done?
- Taking diazepam, as a means of improving the fall to sleep, causes me to feel bad in the morning.

### **Discussion**

It seems to us that finding out which manifestations of sleep disorders result from impairment of function of glymphatic system is very important for clinicians and all people who care for the elderly. The knowledge of the real activity of the glymphatic system will lead probably also to the elaboration of specific therapeutic methods [13]. Detection of such symptoms will be possible probably soon by investigations performed in those centers, which can apply the contrast-enhanced MRI techniques [10].

### **Conclusions**

- It is important to disseminate the knowledge about the role of the glymphatic system
- among people who care for the elderly.
- The further discussion of neurologists and geriatricians related to clinical symptoms
- indicating impairment of glymphatic function is desirable.
- It is necessary to encourage researchers using modern brain imaging techniques to verify
- which symptoms really result from impairment of glymphatic system.

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