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Olfactory Dysfunctions in Alzheimer's Disease

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1. Introduction

Alzheimer's disease is not only the most frequent cause of dementia that takes its toll on the elder population, but it is also the disorder for which, despite the complex research performed, a certain diagnosis may only be performed through anatomic-pathologic examination.

Alzheimer's disease is a neurodegenerative disease whose defining anatomic-pathologic trait is the deposit of amyloid plaques at the level of certain areas of the brain, the presence of fibrillary degeneration in the neurons and vascular changes with an amyloid deposit, all of which result in the impressive reduction of the cerebral mass noticed in the final stages of the condition.

Studies of over 30 years have established that olfaction is impaired in AD, however not invariably.

As early as 1987, Rezek described olfactory deficit as a neurological sign in Alzheimer dementia. Recent research has started to clear up potential mechanisms of olfactory loss in Alzheimer's disease.

Alzheimer disease has a selective vulnerability of the cerebral structures to the pathologic process, inducing a distinctive lesion pattern with a slow evolution in time and that is constantly invariable in the study cases. It begins in the transtentorial region and it then expands to the cortical and subcortical components of the limbic system and it may include the association areas of the neocortex. The pathologic process may be progressive, containing 6 stages. In stages 1-2, the pathologic process takes place at the level of the anteromedial temporal lobe mesocortex, the entorhinal allocortex and the horn of Ammon. Such structures are not only related to memory and learning, but also to the olfactory system. Therefore, stage 1-2, considered "clinically silent", includes a series of non-cognitive clinical changes that are essential for the timely diagnosis of the disease, including olfactory changes.

The deficit of the olfactory system in Alzheimer's disease, as early as its incipient stages, is currently a generally recognized fact. The correlation between olfaction and Alzheimer's disease is particularly exciting, with important diagnosis practical implications.

The olfactory system is a unique system of the human brain; it belongs to archaic structures, its anatomic route is distinguished by the fact that it is the only means of sense that approaches the brain directly, it is the only sensory system with direct cortical projections, without a thalamic relay, it is the only part of the brain where neurogenesis persists, it has a special reaction to the aging process, it plays an essential role in behavior (food behavior, orientation and sexual behavior) and it influences memory, as there is also a smell memory.

2. Olfaction and memory - investigating the olfactory system

The olfactory primary cortex is the place processing the olfactory information at the highest level and it is directly related to the amygdale and the hippocampus. The amygdale plays an important role in the formation and modulation of emotions, as well as in emotional memory. The hippocampus is involved in memory processes, especially in working memory and in short term memory. Olfaction is the sensory manner that is closest to the limbic system, including both the amygdale and the hippocampus, and that is responsible for emotions and memory. Olfaction and memory are so infused that they allow us to make connections with certain experiences we have been subject to (the capacity of a smell to evoke memories).

This is probably why memories evoked by smells are particularly strong at an emotional level. An individual olfactory stimulus may trigger different perceptions that depend on previous experiences and olfactory learning. Recent studies of cerebral imagery have indicated changes based on experience of the piriform cortex. (Li et al 2008) The anatomic bases of olfactory learning in such cerebral regions may involve a complex system of association fibers connecting neurons from the same areas or different cortical areas and whose synapse power may be changed by olfactory experience. (Wilson et al 2004) Olfactory learning may amplify the discrimination of smells and it may be important in survival. In humans, changes in the neuronal cortical activity determined by olfactory learning are correlated with the improvement in the discrimination of similar smells. (Li et al 2008)

Olfaction has often been involved in learning processes.

Since the olfaction system is connected to the limbic system, which explained earlier is responsible for the storing and creation of memories, this leads us to the conclusion that each receptor will recognize a specific scent if it had previously been exposed to it, basically creating memories.

It can also be significant that demyelinated olfactory fibers make olfaction the sense with the slowest driving. Not only does it require a longer time for the brain to perform the olfactory perception, but the sensation of a smell also persists more than, for example, visual or auditory sensation. Moreover, the fact that olfactory receptors are the only sensory receptors that are directly exposed to the environment may explain the relation between olfaction and memory.

Despite the fact that initial studies have not recognized it, there is also a short term olfactory memory.

White and Treisman have suggested that olfactory memory occurs due to the fact that humans assign verbal meanings to olfactory stimuli. The memory of smells is improved by familiarity and the capacity of identification.

Episodic information is an essential constituent of olfactory memory, comparative with the form and structure of the visual and auditory memory systems. All smells are encoded as "items" in the piriform cortex. The perception of smells is totally dependant on the integrity of this memory system and the loss thereof leads to the dysfunction of perception.

Neuro-transmitters in the olfactory system are responsible for the neuronal plasticity and behavioral changes. Noradrenaline and acecoline influence both implicit and explicit memory.

Implicit memory

It does not imply the conscious memory of the initial exposure to smell. The proof of the implicit memory formation of smells is given by habit, sensitization, perceptual learning and classic conditioning tests. Olfaction includes a strong tendency of habit.

Habit

It involves the decrease of the level of attention and response to a stimulus that is no longer perceived as new. It refers to decreasing the levels of response to a smell due to extended exposure. It involves the adaptation of cells in the olfactory system. It concerns both receptors, mitral cells of the BO, and cells in the piriform cortex with a rapid adaptation rate. Noradrenaline is deemed to have an effect in the operation of mitral cells and in increasing the response level thereof.

Explicit memory

Is a phenomenon encountered exclusively in humans. It concerns the assigning of associative meanings to different smells. The testing thereof uses the identification and recognition of smells.

In humans it was noticed that the Korsakoff syndrome, with an important memory dysfunction, the memory of smells is less impaired than other types of memory, thus suggesting a separate mechanism than other types of memory.

The testing of the olfactory sense is relatively complex and difficult at the same time. An attempt is made to assess the capacity to detect, identify, recognize and differentiate smells.

- The odor detection threshold is the lowest concentration of a certain odor compound that is perceivable by the human sense of smell. The threshold of a chemical compound is determined in part by its shape, polarity, partial charges and molecular mass
- The identification of smells is a semantic task, referring to general individual knowledge or to experience with a specific smell. (Schab 1999, Tulving 1993) The identification of smells is related to semantic memory, as there is a relation between smells and the name thereof. No significant relation was ascertained with intelligence, short term memory and episodic memory.

The episodic memory of smells is mediated by semantic factors (familiarity and identification of smells); the difficulty in the identification of common smells is based on deficits of the smell memory.

It is worth noting that it is the strong influence of the perception of intensity on the identification of smells. Individual variations in the perception of intensity are a major element for successful identification and it must be considered in the study assessing identification.

Odor identification ability is sensitive to prefrontal lobe dysfunction.

The objectification of smells by the identification of the name makes the subtle connection between memory and the environment.

Olsson (1999) suggested that the identification of smells interferes with memory. The identification of smells has a positive effect on the recognition of smells and it deems the name of smells to be a high level of cognition.

There is also a peri-semantic implicit episodic memory of smells and this spontaneous smell memory remembers especially connections with experienced situations.

Identification provides the individual with a secondary memory channel, however, the question remains if this is for smell itself.

Once identified, the name is remembered and the memory of this name is reactivated when the smell is identified again.

In order to test whether smell can be identified without verbal mediation, Moller carried out an experiment of incidental versus intentional learning recognition with unusual smells,

using young and old subjects. In incidental learning, the elderly proved more successful; in intentional learning, the young proved better, as they had fewer false alarms and because they did not use verbal mediation and not because of the deterioration of their working memory.

If smell memory operates independently from its name, it is mainly tuned at detecting changes.

- Smell recognition is a simple method of checking olfactory memory that does not involve language. It only requires that the subject establish, after a period of latency, if the substance it smells is the same as that which was provided for it to smell before.

3. Examination of olfaction

Ideal examination is carried out for each nostril separately. Starting with the asymmetry of neuropathologic changes, there is a functional asymmetry in olfactory performances. Apparently, in order to diagnose the difference of the olfactory identification capacity and of olfactory memory between subjects with MCI and AD, it is useful to test unilateral smell. The testing of performances is carried out by considering the affected nostril; a difference may be noticed between patients with MCI and AD. If the assessment is made by considering the healthy nostril (the olfaction of the two nostrils), the differences between MCI and Alzheimer's disease are no longer present. (Bacher-Fuchs, Moss, 2010).

Olfactory tests:

It is necessary for the battery of tested smells to reduce errors and to be adapted at a multicultural and ethnic level. It should consider all causes that may lead to the dysfunction of the olfactory sense, paying great care to pathological history, associated disorders, the therapy the patient is subject to, the pollution it was exposed to (job), etc.

They must be supplemented and correlated with other factors involved in AD, as well as with other situations that may prevent the cognitive function.

The used tests are:

1. UPSIT - The University of Pennsylvania Smell Identification Test, "a scratch and sniff odor identification test", including:
 - tests for odor threshold (n butanol testing by means of a single staircase)
 - odor discrimination (16 pairs of odorants, triple forced choice)
 - odor identification (16 common odorants, multiple forced choice from four verbal items per test)
2. "Sniffin' sticks" - pen like odor dispersing devices which include tests for odor identification, discrimination and thresholds
3. CCCRC (Connecticut Chemosensory Clinical Research Center Test) - a combined odor identification and odor threshold test.

Specialized testing may include EEG derived measures such as the recording of olfactory event-related potentials.

4. Olfaction and aging

Aging also leads to the decrease of all senses: sight, hearing, tactile, including taste and smell. There is a reverse proportionality between age and olfactory sensibility.

Olfactory senescence begins at 36 for both genders, and it accelerates with aging, impairing pleasant smells. Despite the fact that it is of lower interest for the patient compared to, for example, the loss of sight or of hearing, the loss of smell is frequent and often unacknowledged. Patients with congenital anosmia are diagnosed with it at about 10 years old.

It was reported that over 75% of the population over 80 years old has a tendency towards major olfactory dysfunction, as olfaction decreases considerably after the 7th decade. A more recent study has indicated that 62.5% of people between the ages of 80 and 97 are subject to olfactory dysfunction.

Aging is also accompanied by the decrease in the capacity to identify smells and of discrimination.

The loss of olfactory acuteness in elders may be caused by changes in the anatomy of the involved structures, the action of environmental factors, medication. Apparently, the main causes are: chronic illness, medication, dental and sinus problems.

Medical causes affecting smell:

- i. Neurological: - Bell's paralysis
 - chorda tympani dysfunction
 - epilepsy
 - cranial trauma
 - Korsakoff's syndrome
 - multiple sclerosis
 - Parkinson's disease
 - tumors
- ii. Nutritional:
 - cancer
 - renal chronic illness
 - liver disease
 - vitamin PP deficit
 - vitamin B12 deficit
- iii. Endocrinous:
 - corticoadrenal insufficiency
 - congenital adrenal hypoplasia
 - panhypopituitarism (Simon's disease)
 - diabetes mellitus
 - hypothyroidism
 - Kallman's syndrome
 - McCune-Albright syndrome
 - Turner syndrome
- iv. Local:
 - sinusitis, rhinitis, polyposis
 - asthma
 - xerostomic conditions, including the Sjogren's syndrome
- v. Viral:
 - acute viral hepatitis
 - flu-like infections

However, the studies have indicated that a series of disorders in elders do not impair olfaction, such as arterial hypertension and heart diseases.

The decrease of the olfactory sense in elders may occur by the alternation in the distribution, density, functionality of specific receptor proteins, of ionic channels or of signaling molecules affecting the ability of the neurons in the olfactory path to signal and process the odoriferous information.

The mechanisms leading to the decrease of the olfactory sense in high age are: the decrease of neurogenesis, the decrease in the number of synapses, a decrease of the total synaptic density in the glomerular layer, (STABLE TUBULE ONLY POLYPEPTIDE could be responsible for this phenomenon), the change of growth factors (TGF – alpha, FGF2, BMPs, TGF-beta, EGF, BDNF), the decrease in the number of nerve terminations at the level of the nasal mucous, the decrease in the quantity of mucus at the level of the nasal mucous, respectively of the olfactory epithelium, the decrease of neurotransmitters.

Anatomic changes consist of decreasing the number of olfactory receptors and fibers in the olfactory bulb. Losses in the olfactory bulb may be secondary to the reduction of neurons in the nasal mucous. Olfactory receptors die through an apoptosis process. The decrease in regeneration with age leads to reducing the surface of the olfactory epithelium. This is also accompanied by an increase in the death rate of receptors.

In some cases, olfactory loss occurs due to bone growth and the consequent reduction of the cribriform lamella orifices of the ethmoid bone with microlesions of the nerve fillets when crossing this structure.

Functional imagery studies have proved that the activity of the piriform/amygdalial region and of the orbitofrontal cortex is reduced in elder patients exposed to olfactory stimuli.

Moreover, it was noticed that areas of the cerebellum are activated by olfactory stimuli: the upper and inferior semilunar lobe, the posterior quadrangular lobe. In elders, olfactory stimulation leads to a higher activation of the cerebellum, suggesting a high response to attention requests or a compensating mechanism.

Age-related deficits concern both the recognition of smells and the identification of smells, which may be attributed to cognitive limitation.

The reduction of the olfactory sense has major consequences of the state of health and on the security of the respective patient: hyposmia is inseparably related to the altering of taste, leading to inappetence, the decrease of food intake, weight loss, malnourishment, reduction of immunity, the deterioration of the state of health. The altering of taste leads to the loss of the pleasure of eating, as the patient is deprived of the ability to savor a meal, which may lead to depression. As taste is altered, the patient has the tendency to have a high intake of salt and sugar which may lead to the aggravation of cardio-vascular diseases or, respectively, to diabetes.

The reduction of the olfactory sense may lead to anxiety, the tendency of isolation. The altering of the perception of smell related to one's own body may lead to the decrease in the degree of personal hygiene, with consequent social implications.

The security of the life of patients with hyposmia is affected by the possibility of ingesting altered food, gas intoxication, etc.

Physical health, financial security, profession, partnership, friendship, emotional stability, free time are severely affected by the loss of olfaction.

The treatment of hyposmia generally has relatively modest results. Treatment may include the intake of zinc, vasodilatation substances such as pentoxifylline, as well as of vitamin A,

alpha-lipoic acid and NMDA receptor antagonists such as caroverine. Aside from such substances, the use of flavoring agents improves taste changes. Studies have indicated that the use of food supplements such as flavors leads to the increase of salivary Ig A, the increase in the number of T and B cells.

5. MCI and olfaction

The assessment of the olfactory function may be a method that is worth trying in order to identify patients with memory deficits. Identification performances were studied by using MCI. Comparing normal elder subjects with an MCI group, where the identification and the remembering of smells were studied, noticed that MCI subjects had significantly lower results in their tests, however, the performance in the assessment of smells was less affected than the cognitive assessment.

Moreover, after monitoring elder patients in time (5 years), who did not initially have cognitive dysfunctions, where the capacity of olfactory identification was also determined, it was ascertained that for those who have developed MCI, the olfactory identification score had a predictive value. Respectively, an olfactory score increased the risk of MCI by 50%. The results were not changed by the cognitive level in the presence of smoking. The reduction of olfaction was associated with a lower basic cognitive level and with a faster decline of episodic, semantic memory and of the perceptual speed. Therefore, in elders with no manifest cognitive disorder, the difficulty in identifying smells plays the role of prediction in the MCI development.

An important study has monitored 471 elder patients that were not subject to dementia or to cognitive disorder, for 5 years (Wilson-Olfactory impairment in presymptomatic Alzheimer's disease), for whom the capacity to identify familiar smells was initially assessed, by using the Brief Smell Identification Test, and they were clinically assessed annually and they were subject to cerebral anatomo-pathologic examination after their death. Moreover, the presence of the APOE epsilon 4 allele was determined. Low BSIT scores were associated with a faster decline of episodic memory, with a high risk of developing MCI. People who have deceased without a cognitive deficit and with lower BSIT scores were associated with a high level of the Alzheimer disease pathology, particularly with fibrillary degenerations in the central olfactory regions, especially in the entorhinal cortex and the horn of Ammon.

Such analyses suggest that in an elder population without clinical manifestations of Alzheimer's disease or MCI, the olfactory dysfunction is correlated both with the level of the Alzheimer's disease pathology in the brain and with the risk of the subsequent development of prodromal signs of the Alzheimer's disease symptoms as MCI and of the episodic memory decline. Therefore, olfactory manifestations may precede cognitive disorders in Alzheimer's disease with a substantial amount of time.

Furthermore, decline also occurs with age in other sensory systems in association with cognitive decline. As the entorhinal cortex processes multiple sensory impulses, it is possible that olfaction may also be accompanied by subtle changes in other sensory functions.

Therefore, the olfactory deficit occurs both in patients with symptoms of Alzheimer's disease, which was long proven, and in MCI patients or in carriers of the epsilon 4 allele, a well established risk factor for Alzheimer's disease. The respective analysis indicates that

the association between the olfactory dysfunction and the pathological changes specific to Alzheimer's disease may also occur in asymptomatic elders.

Another study has proven that in elders, the presence of APOE is associated with a high risk of MCI and a fast cognitive decline. It was also indicated that hyposmia associated with APOE has a 5 times higher risk of developing Alzheimer dementia than the general population.

The preliminary data of a study indicates the fact that MCI patients not only have an olfactory dysfunction compared to healthy persons, that progresses in time, but that those who are not aware of the decline of their olfactory sensibility, suffering from amnesic MCI, will develop the criteria for the diagnosis of Alzheimer's disease in the near future.

6. Alzheimer's disease and olfaction

Despite all the research carried out so far, it is still not known why the loss of olfaction occurs in victims of Alzheimer's disease. What is known is that the loss of olfaction is current. Anosmia and Alzheimer's disease go hand in hand. Anosmia was currently studied as a potential diagnosis instrument for Alzheimer's disease.

In 1994, Solomon examined the first cranial nerve in patients with Alzheimer's disease. He noticed that 90% of the patients had different degrees of anosmia.

Another experiment compared the olfactory capacity of 80 normal elders with that of 80 elders suffering from Alzheimer's disease, and the latter had a significantly lower olfactory capacity.

An attempt was even made to quantify the difference of olfactory capacity. Respectively, the study performed by Nordin in 1995 proved that 74% patients with Alzheimer's disease had a satisfactory olfaction only after smelling a sample with a concentration that was 9 times higher than the initial one, which 77% of the normal elders managed to identify. The same study also indicated that patients with Alzheimer's disease were not aware of the debut of their anosmia, nor of the severity of their impairment which is why they did not acknowledge the loss of their olfactory sense.

The amyloid deposit-olfactory impairment relation was proved by Zucco in 1994 in his study on patients suffering from Down's syndrome. It is known that due to the trisomy of the chromosome 21 they carry, they have an overexpression of the genes of this chromosome, including that of the amyloid precursor protein. Starting with the age of 40, they indicate deposits of amyloid plaques at a cerebral level, without however necessarily developing it. The risk of developing dementia in a patient suffering from Down syndrome is higher in persons with a family history of Alzheimer's disease, while others have the same risk as the general population. With age, patients with Down syndrome are also subject to an increase in the rate of Alzheimer's disease, so that, at 60 years old, 50-70% have Alzheimer's disease. Moreover, Alzheimer's disease has an earlier debut in patients with Down syndrome.

The decrease of the olfactory capacity was also noticed in adults with Down syndrome, many of which have a cerebral pathology that is analogue with Alzheimer's disease.

The question that was raised next was if adolescents suffering from Down syndrome and that were not subject to clear neuropathologic changes similar to Alzheimer's disease will develop an olfactory dysfunction.

The olfactory sense (the capacity of identification and discrimination) was tested for 20 teenagers suffering from Down syndrome (13.8 years average age), and the results were

compared with 20 patients with Down syndrome who were mentally retarded and 20 patients with Down syndrome who were not retarded. There were no differences between the three groups.

Another study tested the olfactory sense for 14 young people (20 - 31 years) and 14 adults (32 - 54 years) with Down syndrome. The scores were definitely lower in the older group. (Amyloid plaques were emphasized together with neurofibrillary degeneration in the olfactory mucous).

Such corroborated studies suggest that the olfactory impairments correlated with Down syndrome only occur in elders, when the pathology similar to Alzheimer's disease is present.

In MCI, the decrease in olfactory identification may be a marker for early Alzheimer's disease, and the Apo E genotype may be a part of the olfactory decline base.

In his study, Devanand proved that in patients with MCI, low base olfactory identification scores predict the diagnosis of Alzheimer's disease during monitoring. However, the MMSE should be considered, together with whether the patient is aware of the olfactory deficit or not. Devanand has indicated an association of olfactory and neuropsychological tests with an MRI examination for the cerebral volume (entorhinal cortex and horn of Ammon), the sensibility of predicting the MCI conversion to AD increases. Such studies have suggested that olfactory dysfunction may be a potential useful biomarker in estimating the debut and the progression of the disease.

The power of prediction increases if it is associated with the lack of awareness of the olfactory deficit. Low olfactory scores associated with the subjective reporting of the lack of olfactory problems are a stronger prediction factor. The correlation between being non-critical towards olfactory issues and the development of Alzheimer's disease is important as the awareness of the loss of olfactory sense may also be located in the medial temporal lobe structures, known to be impaired in the preclinical stages of the disease and associated with attention deficits.

Olfaction was studied (detection, quality of dissemination and identification) together with cognition (attention, rationale, memory, name, fluency) in patients with Alzheimer's disease, MCI and normal elders.

Patients with MCI had their olfactory sensibility and identification diminished, while discrimination was considered to be under normal limits.

Alzheimer's disease impairs all three areas, more than in MCI. It was noticed that the performances in the identification and discrimination of smells is correlated better than the detection with neuropsychological tests. Therefore, the deficits in detection and identification occur early in Alzheimer's disease, prior to the development of the clinical symptoms, and it progresses with the evolution of the disease. High detection thresholds together with the impairment of identification may be an early indicator of Alzheimer's disease.

Electrophysiological - olfactory evoked potential studies have confirmed the olfactory dysfunction both in patients suffering from Alzheimer's disease and in the preclinical MCI stage.

In Alzheimer's disease, the olfactory dysfunction progresses together with the disease and it is correlated with its severity. More advanced stages also register the impairment of olfactory discrimination.

1996 meta-analyses were performed on 43 olfactory perception and AD studies, and significant deficits were noticed in the olfactory detection threshold, the olfactory identification and olfactory recognition in confirmed or potential AD cases compared to the case-controls of the same age. Such deficits were correlated with genetic factors associated with a high risk for AD.

Gilbert and Murphy have proved that even one or two copies of the APOE allele e4 have a significant deficit in smell recognition compared to patients who do not have this allele. The authors have indicated that the deficit only applies to olfaction and not to visual stimuli.

7. The theories of olfactory impairment in Alzheimer's disease

In terms of olfactory impairment in Alzheimer's disease, two theories were raised: the olfactory vector theory and the degenerative theory.

The olfactory vector theory

In 1985, Pearson et al suggested that in terms of the impairment of the olfactory system in striking contrast to the minimal changes of other cerebral areas, it is possible that the olfactory system is the gateway for the agents triggering the disease. Therefore, the loss of smell may be a consequence of virus access or the access of toxins from the nose to the brain via the olfactory path.

This theory is supported by the following:

1. In the intranasal instillation of virus or toxins, they can enter the brain by the active transport of olfactory cells and it induces the alteration of olfactory structures (Stroop, 1995)
2. Studies suggesting histopathologic changes occur in the olfactory epithelium in patients with Alzheimer's disease (Jafek et al, 1992)

Amyloid plaques and degeneracy are preferentially located in the limbic system receiving fibers directly from the olfactory bulb, including the anterior olfactory nucleus, uncus and the medial amygdaline nucleus. (Pearson et al, 1985)

Secondary degeneration theory

It postulates that the loss of olfaction is determined by retrograde secondary degeneration. A version postulates that limbic structures are particularly susceptible to alteration in the processes of Alzheimer's disease.

Potential arguments are:

1. Patients with Alzheimer's disease have a reverse correlation between the UPSIT scores and the metabolic activity in the anterior portion of the medial temporal cortex measured by PET (Buchsbaum et al, 1989)
2. The association between low olfactory scores and the number of hippocampal lesions in patients with Alzheimer's disease (Serby et al, 1992)
3. Mice which have recently become anosmic do not have a learning deficit, unlike those in which anosmia was induced earlier (Kurtz et al, 1989)

8. The structural bases of the olfactory impairment in Alzheimer disease

Multiple areas of the brain that are crucial for the normal olfactory function are severely impacted by the pathology of Alzheimer's disease. The olfactory dysfunction of Alzheimer's disease is associated with anatomical-pathological changes specific to the disease both at the

level of the olfactory mucous and at the level of the olfactory bulb, of the olfactory tracts and of the central region for the projection of olfactory tracts, including regions involved in the recognition of smells and memory (entorhinal cortex and the horn of Ammon).

Deposits of amyloid and neurofibrillary tangles, the two pathological hallmarks of AD, are located differentially by crossing these regions. Few studies have approached the connection between the prevalence of these pathologies with the olfactory function.

A study has suggested that for elders (87 ± 6 years), olfactory loss is determined by the loading of neurofibrillary tangles in the central areas processing olfactory information; another study has indicated that the severity of the pathology in the olfactory system is correlated with the neuropathologic progression of the disease starting from the MCI stage.

Olfactory identification is impaired early on in Alzheimer's disease and it may be influenced by the cognitive status more than the olfactory acuity or detection that is not alerted until late stages. The hyposmia pattern in Alzheimer's disease suggests that the disease does not begin "in the nose", as was theorized so far.

Talamo examined the changes in the olfactory neurons in Alzheimer's disease and he indicated that there are histopathologic changes at the level of the olfactory epithelium.

In 1991, Hyman used neuroanatomic and neurochemical studies to describe the changes at the level of the olfactory bulb with deposit of amyloid plaques and neurofibrillary tangles with degenerations of other areas: the anterior olfactory nucleus, the olfactory tubercle, uncus and subiculum.

A 1993 study indicated a less severe impairment in Alzheimer's disease of the olfactory tract and bulb in Alzheimer's disease than in the central part of the olfactory system.

Immunohistochemical determinations in the olfactory epithelium for the polyclonal protein, for amyloid plaques and for ubiquitin have proved the presence thereof in Alzheimer's disease, so that nasal mucous biopsy may be useful.

It was also noticed that neuroblasts from donors with Alzheimer's disease have high levels of precursor amyloid.

Imagistic and immunohistochemical studies have proven the correlation between the deposit of amyloid plaques and neurofibrillary tangles at the level of the olfactory bulb with those at the level of the cortex.

The study of Wilson and his collaborators, performed in 2007, indicated that the difficulty in identifying familiar smells at a high age is partially due to the neurofibrillary pathological accumulation in the central olfactory regions, respectively in the entorhinal cortex and the CA1/subiculum area in the horn of Ammon, as the density of degeneracy is inversely proportional with the olfactory identification.

In 2009, Thomann carried out MRI studies to indicate the reduction in the sizes of the olfactory bulb and tract in the early stage of Alzheimer's disease.

An MRI study also described the decrease in the volume of the left horn of Ammon in Alzheimer's disease, reflected in the reduction of olfactory identification performances.

Experiments carried out on rodents with AD have provided evidence that both the neurofibrillary tangles and the beta-amyloid lead to olfactory loss. For example, a recent study carried out on a transgenic mouse with the overexpression of the human amyloid beta protein precursor indicated that such mice have an age-dependent olfactory dysfunction compared to the control group of the same age. Such olfactory deficits include the abnormal investigation of smells, olfactory habit (short term memory) and olfactory discrimination. Furthermore, such behaviors are correlated with the spatial-temporal deposit of the fibrillary and/or non-

fibrillary beta-amyloid. It is worth mentioning that the amyloid deposit first occurs in the olfactory bulb, followed by the deposit in the olfactory cortex and horn of Ammon. Such data suggest that the beta-amyloid deposit in the olfactory bulb and in the olfactory cortical areas may contribute to olfactory loss in early and, respectively, late stages.

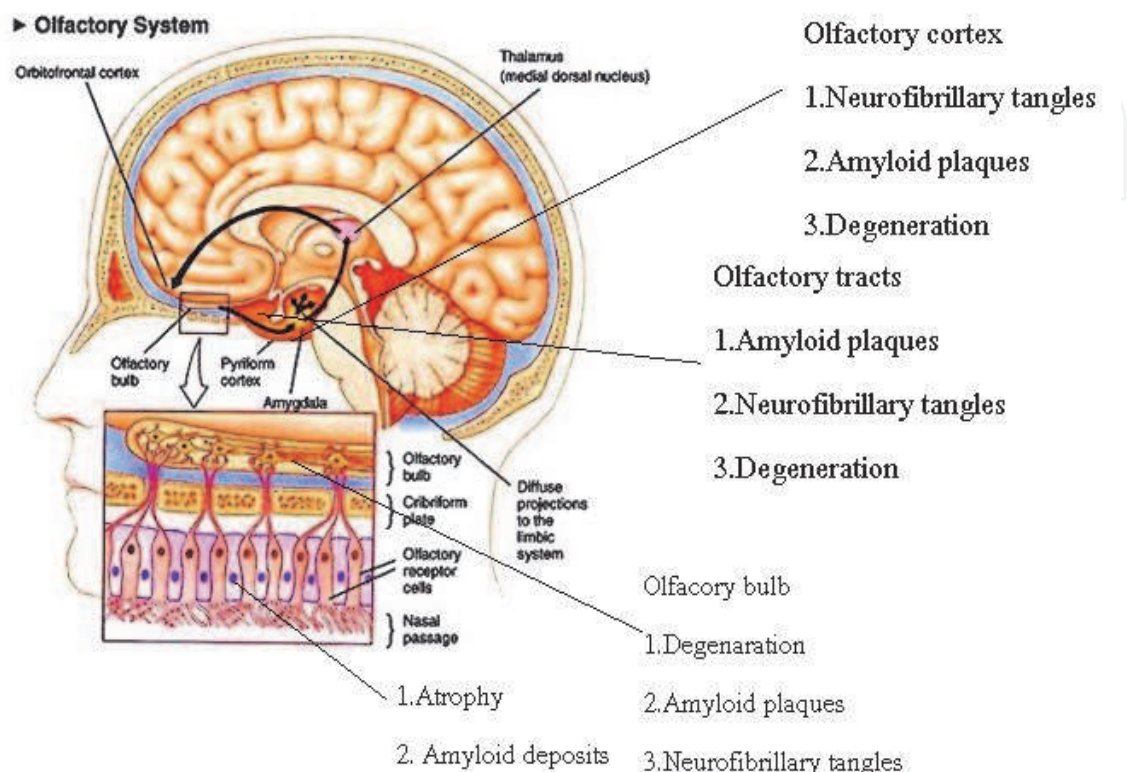


Fig. 1. Anatomical changes of the olfactory pathways in AD

9. Olfactory sense and other neurodegenerative disease

The decrease of the olfactory sense is also associated with other neurodegenerative diseases: Parkinson's disease and Lewy corpuscles dementia, Olfactory impairments in Alzheimer's disease and Parkinson's disease are initially similar, and they are later on set apart in terms of quality. In Parkinson's disease, cerebral lesions are rarer and the olfactory impairment is more stable. However, it is worth noting that in initial studies, the extent of the olfactory changes in Parkinson's disease is the same as that in Alzheimer's disease.

During the post-mortem examination, patients suffering from anosmia dementia seem more likely to have Lewy body dementia.

Progressive supranuclear palsy -In this disease, the olfactory function is relatively intact, with no significant differences between the olfactory scores of such patients compared to the case-controls.

Multiple system atrophy- They have lower olfactory scores than the case-controls, however they are better than patients with Parkinson's disease (Wenning et al, 1993). The olfactory impairment has no correlation with the disability scores, and the pathological changes are more expanded than in Alzheimer's disease.

In Huntington's chorea there is impairment in the discrimination and identification of smells, however not in the detection thereof.

10. Olfaction-marker of Alzheimer disease

A major effort in AD research is directed towards the identification of the markers of the disease. Such biomarkers should ideally predict the AD prognosis before the significant development of the neuropathology and the consequent loss of the cognitive function. Early indicators of the disease are especially important for the implementation of interventions as long as the brain is still operating normally. Therefore, the finding of a robust and accurate biomarker may be a pivot in the reduction of the AD global impact.

An overview of the biomarkers' progression has indicated that the first elements that are detected are beta-amyloid, followed by the neurodegeneration and the cognitive markers.

Despite the fact that they are not normally used, perception impairments may serve as AD biomarkers. Perception impairments are common in AD, including the loss of olfaction, of visual and hearing abilities.

The answer to the question on whether olfaction can be used as an AD marker is not simple. There are numerous causes of hyposmia. The high prevalence of anosmia in other neurodegenerative diseases - PD, DLB, D fronto-temporal indicates that olfaction alone is not specific enough as an AD biomarker. Together with other biomarkers, the olfactory perception screening may be useful in consolidating the sensitivity and specificity of an AD diagnosis, especially due to the fact that it is non-invasive, easy to repeat, it reflects the operation of the neuronal circuits impaired in the initial stages of AD, it is not costly and it does not require technological equipment.

Considering the fact that the olfactory deficit is developed with a high frequency in intact cognitive subjects, carriers of the e4 allele, olfaction can be a particularly useful and non-invasive measure in the intervention or prevention of risk trials.

The testing of the olfactory sense may be useful in differentiating Alzheimer's disease from major depression.

Anosmia may be a respectable method of diagnosis in Alzheimer's disease. The careful monitoring of the decline of the olfactory sense may indicate the debut of Alzheimer's disease.

Anosmia may be used as a probable indicator in the diagnosis of Alzheimer's disease, however it cannot be a decisive factor by itself.

Longitudinal studies during the progression of the disease, correlated with independent measurements of the structural and functional deficits in relevant areas of the brain will establish the usefulness of olfactory tests.

The smell identification function may be useful as a clinical measure for the assessment of the clinical response to donepezil, as the entorhinal cortex, the olfactory bulb, critical areas for smell, are high in acetylcholine, a neurotransmitter involved in the pathology of Alzheimer's disease and treatment.

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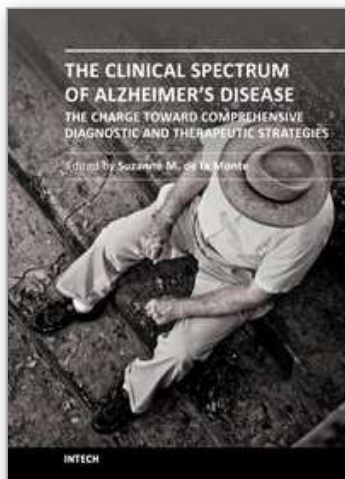
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The Clinical Spectrum of Alzheimer's Disease: The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies is highly informative and current. Acknowledged experts in the field critically review both standard and under-appreciated clinical, behavioral, epidemiological, genetic, and neuroimaging attributes of Alzheimer's disease. The collection covers diverse topics of interest to clinicians and researchers alike. Experienced professionals and newcomers to the field will benefit from the read. The strengths and weaknesses of current clinical, non-invasive, neuro-imaging, and biomarker diagnostic approaches are explained. The perspectives give fresh insights into the process of neurodegeneration. Readers will be enlightened by the evidence that the neural circuits damaged by neurodegeneration are much broader than conventionally taught, suggesting that Alzheimer's could be detected at earlier stages of disease by utilizing multi-pronged diagnostic approaches. This book inspires renewed hope that more effective treatments could be developed based upon the expanding list of potential therapeutic targets.

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