

ORIGINAL ARTICLE


The Concept of Alzheimer's Disease in Unani System of Medicine: A Historical Perspective

Abstract

Alzheimer's disease is an irreversible progressive brain disorder which slowly affects memory and thinking skills and also the ability to carry out the simple tasks. Unani system of medicine has a history of clinical experience and rich traditional knowledge in the management of neuro-degenerative disorders. Unani Physicians, like *Ali Ibn-e-Abbas Majusi* (930-994 AD), in his book *Kamilus sana*; *Abu Bakr Muhammad bin Zakariya Razi* (850-925 AD), in *Al Hawi*; *Sheikh-ur-Rais Ibn-e-Sina* (980-1037), in his book *Al-Qanoon fit tib*; *Ibn-e-Hobal Baghdadi* (1122-1213), in *Kitab-al-Mukhtarat fit tib*; *Abul Hasan Ahmed bin Muhammad Tabri* (11th century), in *Al Moalijat-e-Buqratiya*; *Azam Khan* (19th century), in his book *Rumooz-e-Azam* have described conditions called *Fasad-e-Zikr* and *Nisyan* which are characterized by the loss of memory, resembling Alzheimer's disease. They have not only mentioned its etiology and pathogenesis but also designed a specific line of treatment. These references can be traced up till *Buqrat* (Hippocrates) 377-460 B.C. and *Jaalinoos* (Galen) 130-200 AD.

Key words: Alzheimer Disease, Dementia, Unani Medicine, Memory Disorders, *Fasad-e-Zikr*, *Nisyan*

Received: 26 Jun 2020; Accepted: 28 Oct 2020; Online published: 29 Nov 2020
Research on History of Medicine/ 2020 Nov; 9(4): 281-290.

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Citation:

Javed Gh, Ahmed F. The Concept of Alzheimer's Disease in Unani System of Medicine: A Historical Perspective. *Res Hist Med.* 2020; 9(4): 281-290.



Introduction

It has been reported that the most common cause of dementia, in the population over 45 years, is Alzheimer's disease. The first description of this disease was reported in a 55-year-old woman by Professor *Alois Alzheimer* in Germany in 1907. Studies suggest that almost 6% of persons above the age of 65 suffer from severe dementia, and 10% to 15% have mild to moderate dementia. After the age of 65 years, the syndrome of dementia doubles after the span of 5 years. It has been estimated that the global prevalence of dementia is as high as 24 million and it is anticipated that the number will double every 20 years until 2040. (Mayeux and Stern, 2012, a006239)

In early stages of the disease, memory loss may not be recognized or may be attributed to benign forgetfulness. It has been observed that these cognitive problems slowly interfere with daily activities, for example, tracking finances, difficulty in driving, doing shopping and household work as well as following job instructions. Both short term and long term memory are affected but defects in the former are usually more evident. This disease also puts high emotional burden on family members and the associated care givers. (Christopher and Edin 1999, p. 987; Braunwald et al. 2001, p. 2391; Qureshi et al. 1998, pp. 2-5)

In Unani Classics, this disease has not been mentioned by the name Alzheimer. A lot of similarities, however, can be found with the signs and symptoms described in *Fasad-e-Zikr* and *Nisyan*. Both *Fasad-e-zikr* and *Nisyan* are conditions characterized by impairment/loss of memory. The signs and symptoms of *Nisyān* described in Unani classics are *Butlān-i-Takallum* (speech impairment), *Butlān-i-Tahrīr* (writing impairment), and *Fasād-i-Fikr* (Impaired thoughts) which gradually worsen over time. The other symptoms may include inability to describe dreams, headache, giddiness, discharge of fluids from the mouth and nose, excessive sleepiness, and difficulty in speech. (Standard Unani Medical Terminology, 2012, p.184, Kabīr al-Dīn, 2009, pp. 80-83)

An attempt is made in the current paper to present the causes, pathophysiology and management of Alzheimer's disease, as described in the classical Unani literature. Relevant quotations from Unani classical books have been reproduced followed by their English translation.

Etiology and pathogenesis of Alzheimer's Disease

The etiopathogenesis of Alzheimer's disease can be formulated by tracing the different textual descriptions of *Nisyan* and *Fasad e Zikr* given by ancient Unani physicians. *Ali Ibn Abbas Majusi* (930-994 AD) in his book '*Kamilussana*' (Vol. II, page 255), has written:

”ان حدوثه يكون عن سوء مزاج بارد مفرداً و عن سوء مزاج بارد مع مادة بلغمية تغلب على جزئي الدماغ المقدم و المؤخر“

'Loss/derangement in memory results from *Su-e-Mizaj Barid Sada* (an abnormal cold temperament which is not associated with the substance or matter) or *Sue-e-Mizaj Barid Maddi* (an abnormal cold temperament which is associated with the substance or matter) of anterior or posterior part of brain.' (Majoosi, 2005, pp. 255 -256)



Abu-Bakr Muhammad Bin Zakriya Razi (850-925 AD), in his book *Al-Hawi* (Vol. I, page 87) states:

”قد تحدث علل في الدماغ من اجل نقصان كميته و لذلك تنقص عقول الهر ماء لان الدماغ و المخ ناقصين“

‘Sometimes the volume of brain is reduced in older people which affects the cognitive function of the brain.’

Razi has also quoted *Ibn-e-Rabn Tabri* (770-850 AD) and stated:

”قال قد يكون ضروب من ذهاب الحفظ عن اليبوسة الا ان اكثره يكون عن الرطوبة“

‘Types of loss of memory are many which result from the excess of *Yabusat* (dryness) but usually loss of memory results from the excess of *Ratubat* (wetness)’. (Razi, 1955, pp. 86-94)

Zakariya Razi further states, in his book *Kitab-al Fakhir*, that “*Ibn-e Sarafiyun*, while discussing *Butlan-e Zikr* (loss of memory), says that this happens with the excess of *Burudat* (coldness) and *Ratoobat* (wetness) in brain which makes brain so cold that it prohibits absorption of things. The condition of brain is like melted wax which does not take the impression of stamp. In some people, excess dryness results in *Butlan-e Zikr* which does not protects memory. The brain becomes like hard wax which does not take the impression of stamp.’ (Razi, 2005, p. 92)

Sheikh-ur-Rais-Ibn-e-Sina (980-1037 AD), in his book *Al Qanoon Fit tib* (Vol. III, page no. 62), states:

”هو نظير الرعونة الا انه في موخر الدماغ لا نه نقصان في فعل من افاعيل موخر الدماغ او بطلان في جميعه و سببه الاول عند جالينوس هو البردا ما سا نجا او مع بيوسة فلا ينطبع فيه فان كان مع بيوسة دل عليه السهر و انه يحفظ الامور الماضية البتة و لا يقدر على حفظ الامور الحاليه الوقتية“

‘This disease resembles “*Ru‘unat*” (Egomania) but in *Nisyan*, pathology occurs either in posterior part of brain or as a whole all functions of brain gets altered”. He further adds that *Jaalinoos* (Galen) has listed *Sada Broodat* (plain coldness) or *Yabusat* (dryness) and preponderance of *Burudat* (coldness) and *Ratubat* (wetness) in brain as the early cause of this disease. Because of this, images perceived by the brain do not last for long. Therefore, when the excess of *Yabusat* (dryness) is there, it results in insomnia and old memory remains intact whereas there is no room for the more recent memory.’ (Qantoori, 1886, pp.78-79, Ibn-e-Sina, 1833, p. 62)

Ibn-e-Hobal Baghdadi (1122-1213), in his book *Kitab-al-Mukhtarat fit tib* (Vol. III page 36) has written:

”اما فساد التخيل و هو ان يرى الانسان ما ليس اولا يستحفظ صور المحسوسات الغائبه عن الحس و يرى منامات مشوشه و لا يستحفظها و غير ذلك ممايدل على ان الافة في البطن المقدم من الدماغ فينظر في سببه و يقصد علاجه و ان كانت اسبابه بعينها هي اسباب فسادالذكر و سببه الاول عند جالينوس هو



البرد اما مفرداً او مع يبوسة فلا ينطبع فيه المثل و يدل هذا النوع السهر و يبس مزاج موخر الراس و ان صاحبه يحفظ الامور الماضية و لا يحفظ الحاضرة و اما ان يكون البرد مع رطوبة و يدل عليه النقل و السبات و تذكرة الحاضرة و نسيان الغائب الا ان يفرط البرد فلا يذكر شيا و ان كان يبساً مع حر كان معد اختلاط الذهن“

‘Derangement in imagination refers to the condition in which either the person feels such things are not present or he is unable to retain things which get out of sight. Similarly, if he is not able to remember his dreams, this implies that a kind of disorder has occurred in the anterior part of brain. And this factor is also present in *Fasad-e-Zikr*. *Jaalinoos* has listed its first cause as the excess of *Burudat* (coldness) which might be present alone or along with *Yaboosat* (dryness). Because of this, brain is not able to retain what eyes have seen. Such patients will complain of insomnia and the sign and symptom of dryness of posterior brain will be present. In such cases, the patient will retain old memories but recent memory will be lost’ (Ibn-e-Baghdadi, 1944, pp. 36-38)

From the above descriptions, it can be concluded that deranged *mizaj* (temperament), caused by excessive coldness with dryness or excessive coldness with wetness, may result in the loss of memory in Alzheimer’s disease.

Signs and symptoms and classification

Abul Hasan Ahmed Bin Muhammad Tabri (11th Century) in *Al Moalajat-e-Buqratiya* has mentioned:

”هذه العلة غير علة النسيان لان النسيان ضرر يدخل علي التذکر وهلاك الذکر هو ان لا يذكر شيئا البتة وان كان حفظه وان استودعته ذكرا نسيه لان ذكره قد مات وهلك كما يقال ماتت القوة- وهو تنقسم الي قسمين لاثالث لهما فاحد القسمين ان يكون من استيلاء البرد والرطوبة علي القسم الموخر من الدماغ- والقسم الثاني ان يستولي عليه البرد واليبس فاما اذا استولت الحرارة والرطوبة فهي غير هذه العلة“
”ومن علامات هذه العلة اذا كانت من البرد والرطوبة ان ينام دائما ويكون كانه ان يغفل عنك ما تخاطبه به في الوقت ثم لا يمكن تذكره بعد ساعة ويسيل من مناخره ابداء الرطوبة ويجد ثقلا في موخر رأسه كانه يحبس الي اسفل ويعرض له ما يعرض للمشائخ الذين علت سبوهم وعمل فيهم الهرم“

‘*Halakat-e-Zikr* is different from *Nisyan* in the sense that in *Nisyan* only *Quwwat-e-Tazkarah* (Faculty of memory) gets disturbed, whereas in *Halakat-e-Zikr* complete memory loss occurs. That is to say, the faculty of memory stops functioning.

On the basis of the etiology, this disease has been classified into two types:

1. The first type results from the excess of *Burudat* (coldness) and *Ratubat* (wetness) in posterior brain region.

2. The second type results from the excess of *Burudat* (coldness) and *Yabusat* (dryness)

In the first type, the patient sleeps excessively; if he is addressed at a particular time, he understands that sentence, but if he is asked to recall it after a while, he cannot do so. There will be nasal discharge, discomfort in posterior part of head and difficulty in climbing down the stairs.

In the second type, the patient will suffer from chronic insomnia, dryness of nostrils, and difficulty in talking rapidly. In certain moments, the patient will feel suffocation and complain of heaviness in head, and excess sleep. The patient is able to remember things



while they are present in front of his eyes and forgets as soon as they disappear. In case of the excess of *Burudat* (coldness), he is not able to remember anything. If there is *Hararat* (hotness) and *Yabusat* (dryness), then admixture of thoughts occurs. The treatment of *Fasad-e-Zikr*, resulting from *Hararat* and *Yabusat*, is easier than the treatment of *Fasad-e-Zikr*, resulting from *Burudat*.’ (Tabari, 1215, pp. 389-390)

Hakim Mohd Azam Khan (19th century), in his book *Rummoz-e-Azam* states that:

”نسیان- و آن عبارت است از وقوع فساد در ذکر یا فکریا تخیل فساد ذکر آنست که هر چند ببیند و شنود زود فراموش کند و فساد فکر آنکه هر چند بفکر آید فاسد باشد یا بر تفکر اشیاء قدرت نه بود و فساد تخیل آنست که در ضبط صورتهایی محسوسه قاصر باشد و آنچه در خواب ببیند فراموش کند و جمله سبب این مرض استیلابی سردی و تری و سردی و خشکی است بر موخر دماغ در فساد ذکر و بر وسط دماغ در فساد فکر و بر مقدم دماغ در فساد تخیل“

‘*Nisyan* is name of that disease in which derangement of *Hafiza* (Memory), *Fikr* (Thinking) and *Takheel* (Imagination) occur. Sign and symptom of derangement of *Hafiza* is that patient forgets whatever he sees or hears. In derangement of *Fikr*, the patient has bad thoughts and his/her thinking power rate declines to zero. Derangement of *Takheel* is that whatever a patient feels and perceives is not retained and whatever he sees in dreams, he forgets. As a whole, its cause is the excess of coldness and moistness or coldness and dryness which in cases of *Fasad-e-Zikr*, it occurs in posterior brain. In cases of *Fasad-e-Fikr*, it occurs in mid brain and in cases of *Fasad-e-Takheel*, it occurs in anterior brain.’ (Khan, 1902 pp. 47-50)

Management

Since Alzheimer's disease is caused by changes in the temperament of the brain of the patient towards cold and moist or cold and dry conditions, therefore, Unani medicine advocates the removal of causative element accumulated in the brain. Hippocrates has advised plain enema for this purpose. After giving enema, the brain is invigorated by various brain tonics which help in restoring the memory. Regimenal therapies are also prescribed for restoring the normal temperament of the brain.

Natool (irrigation) on the head, application of *Zimad* (thick paste of selected drugs), *Takmeed* (Hot Fomentation), *Naswar* (Snuff) and *Shamoom* (inhalers) are prescribed. Formulations made from *Kundur* (*Boswellia serrata*), *Filfil Daraz* (*Piper longum*), *Saad Koofi* (*Cyperus rotundus*), *Filfil Siyah* (*Piper nigrum*), *Zafran* (*Crocus sativus*), *Mur Makki* (*Commiphora myrrha*), *Waj* (*Acorus calamus*) *Halaila Siyah* (*Terminalia chebula*), *Injeer* (*Ficus carica*) etc. are claimed to be effective in the management of the disease.

Renowned Unani physicians, like *Khauz*, *Ibn-e-Masawiyya*, *Abu Juraej*, *Fahleman*, and *Ibn-e-Masa* have advised the use of *Baladur* (*Semecarpus anacardium*) in the prescribed dose for enhancing memory. (Majoosi, 2005, pp. 255 -256, Razi, 2005, p. 92, Qantoori, 1886, pp.78-79, Ibn-e-Sina, 1833, p. 62, Ibn-e-Baghdadi, 1944, pp. 36-38)

Unani physicians have given detailed dietary recommendations for the management of Alzheimer's disease. The diet should be taken in proper quality and quantity regularly on time. Eating easily digestible, and energetic food, such as chicken, dry fruits,



Fundug (*Corylus avellana*) are recommended. Meat of wild birds, honey water and radish are also said to be very beneficial. Alcohol and the use of onion (*Allium cepa*), *Kishneez* (*Coriandrum sativum*), *Baqila* (*Vicia faba*) *Lobia* (*Vigna catiang*), *Masoor Dal* (*Lens esculenata*), *Karnab* (*Brassica oleracea*) and *Karafs* (*Apium graveolens*) have been restricted for the patients suffering from this disease.

Apart from this, it is advocated that balance should be maintained in six essential prerequisites of life which are air, food, drinks, sleep and wakefulness, bodily movement and repose, psychic movement and repose, excretion and retention.

Recent studies, carried out on the medicinal plants recommended in Unani classical literature for the management of Alzheimer's disease, generated credible evidence to substantiate their use. Aqueous infusions of *Boswellia serrata* (*Kundur*) were investigated in a study on Aluminium Chloride induced Alzheimer's disease in rats. The results showed that the aqueous infusion of *Boswellia serrata* increased acetylcholine level and reduced anti-cholinesterase (AChE) activity in brain homogenates. This indicates that aqueous infusions of *B. serrata* significantly reduce neurodegeneration in Alzheimer's disease (Nemat et al. 2013, pp. 1–11). In another study, carried out in animal model of Alzheimer's Disease, *B. serrata* infusion extract showed increase in the brain acetylcholine levels and marked reduction in brain acetylcholine esterase levels, in a dose-dependent manner (Mahboubi et al 2016, p. 681). The anti-inflammatory and anti-apoptotic effects of *B. serrata* methanolic extract were investigated on neurodegeneration associated with Alzheimer's disease in rat model. The analysis of data showed that there was significant improvement in the biochemical parameters in rats treated with *B. serrata* methanolic extracts. Significant improvement was also observed in histological features of the brain. (Ahmed et al 2014, pp. 384-392).

As the oxidative stress plays an important role in pathogenesis of Alzheimer's disease, a study was carried out to evaluate the protective effect of *Cyperus rotundus* (*Nagarmotha*) as an antioxidant on amyloid β ($A\beta$)-induced memory impairment. Treatment with *C. rotundus* extract was found to be protective against $A\beta$ -induced memory impairment (Mehdizadeh et al 2017, pp.249-254). Another study showed that *C. rotundus* extract repaired spatial memory impairment through increased neurogenesis in the hippocampus, which could be related to the flavonoid components in the extract (Shakerin et al 2020, p. 17). The effect of ethanolic extract of *C. rotundus* tubers (CRT) was studied on motor activity in nucleus basalis of Meynert (NBM) -lesioned rat model of Alzheimer's disease and intact rats' Cholinergic deficiency of the cerebral cortex and decrease in the cholinergic neurons of the NBM were showed to be associated with memory dysfunction observed in Alzheimer's disease. The results of this study suggested that ethanolic extract of CRT would be useful in NBM-induced lesion rats via inducing some changes in acetylcholine levels in the brain (Rabiei, Gholami, and Hojjatil 2014, pp. 43-54).

Subedee et al. (2015) studied the preventive effect of *Piper nigrum* (Filfil Siyah) (PN) on the histopathological, biochemical and behaviour changes associated with Alzheimer's Disease in rat model. The standardized extract of PN exhibited anticholinesterase activity, prevented nerve degeneration and significantly improved learning and memory deficits. Further, neuropsychological symptoms were alleviated in the animal models of Alzheimer's disease by PN. The therapeutic effect of treatment with PN may be due



to its anticholinesterase and anti-oxidant activity and it may also be attributed to its inhibition of the formation of amyloid plaque and oligomerisation of tau protein. (Subedee et al. 2015, pp.1-4). In another study, memory-enhancing potential and antioxidant proprieties of the methanolic extract of PN fruits were analyzed in animal model of Alzheimer's disease. It was observed that administration of the plant extract significantly improved memory performance and exhibited antioxidant potential. The results suggested that amyloid beta (1-42)-induced spatial memory impairment was ameliorated by the plant extract through attenuation of the oxidative stress in the hippocampus of the rat (Hritcu et al 2014, pp. 437-449). Methanolic extracts of PN have also exhibited potent anti-inflammatory effects against neuroinflammation, associated with Alzheimer's disease. (Ahmed et al 2013, pp. 437-446)

Three new cadinane-type sesquiterpenes, Commiphoin A-C (1-3), together with two known cadinane-type sesquiterpenes (4 and 5), were isolated from the resinous exudates of *Commiphora myrrha* (*Mur Makki*). Compounds 1 and 3-5 were screened for anti-Alzheimer's disease activities and the results showed that they all had significant anti-Alzheimer's disease activities (Yu et al 2020, p. 142).

Co-administration of total ginsenosides and volatile oil of *Acorus tatarinowii* (Syn. *Acorus calamus*) (*Waj Turki*) exhibited an effect on improving the ability of learning and memory and inhibiting apoptosis in Alzheimer's disease induced by D-galactose and aluminium chloride in mice model (Deng, Huang and Fang, 2015, pp. 1018-1023).

In Sancheti et al.'s study, the methanolic crude extract of the fruits of *Terminalia chebula* (*Halaila*) exhibited inhibitory effects on anti-cholinesterase (AChE) and butyrylcholinesterase (BChE) (Sancheti et al. 2010, p. 285-288). In addition to the effects of gallotannins on AChE inhibition, a potential inhibitory effect on AChE was also exhibited by tannic acid, an active component of *T. chebula* (Upadhyay and Singh 2011, pp. 1095-1100).

A phase II study, carried out by Akhondzadeh et al in 2010, provided preliminary evidence of a possible therapeutic effect of *Crocus sativus* (*Zafran*) extract in the treatment of patients with mild-to-moderate Alzheimer's disease. Saffron was found to be effective similar to donepezil in the treatment of mild-to-moderate Alzheimer's disease in this 22-week, multicenteric, randomized, double-blind clinical trial. (Akhondzadeh et al. 2010, p. 637-643). A one-year single-blind randomized, with parallel groups, clinical trial was carried out to examine the efficacy of *Crocus sativus* in patients with amnesic and multi domain MCI (aMCI_{md}). The results exhibited that patients who were treated with saffron had improved Mini-Mental State Examination scores (Tsolaki et al. 2016, pp. 129-133). In a one-year double-blind randomized clinical trial, the administration of saffron extract capsules to patients with moderate to severe Alzheimer's disease reduced cognitive decline which was comparable with memantine (Farokhnia et al. 2014, pp. 351-359).

Conclusion

Mental health remains the most important aspect of a person's well-being. Diseases affecting brain functions are posing a greater threat to the medical world. Alzheimer's disease is one of the important components of health news column. No doubt, thanks to



the technology revolution, it is now easier to monitor living brain function and pinpoint the pathology of the Alzheimer's disease. However, the exact cause of this disease is still obscure and treatment of this debilitating disease remains a big question mark. The literature survey of Unani classics has revealed that although there is no direct reference to Alzheimer's disease in the classical literature, similar conditions, like *Fasad-e-Zikr* and *Nisyan*, which are characterized by loss of memory, resembling Alzheimer's disease, have been described vividly, highlighting their etiology pathogenesis, signs and symptoms. The management of Alzheimer's disease described in the classical texts includes the use of single drugs, compound formulations, regimental therapies and dietary advices. Many of the drugs recommended for its treatment have been tested in experimental and clinical studies and found to exhibit protective as well as therapeutic effects.

The growing evidence of risk factors for dementia suggests that lifestyle modifications and effective implementation of other interventions have the potential to delay the onset of dementia and reduce the future number of patients having dementia (Livingston et al. 2017, pp. 2673-2734; Elwood et al. 2013, p. e81877).

The dietary measures, drugs and formulations described in the treatment of dementia by Unani physicians are based on their observations and experimentations. Further research is required to be carried out, in conjunction with modern technology, to come up with promising results and provide better treatment for the Alzheimer's disease.

Acknowledgements

The authors thank Hakim Abdul Hannan Former Joint Director, CCRUM Hqs for assistance in Arabic translation.

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