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REVUE GÉNÉRALE

Facteurs environnementaux impliqués dans la maladie d'Alzheimer. Le mercure dentaire, probable déterminant majeur

Environmental factors and Alzheimer's disease: Mercury strongly under suspicion

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Abstract	Résumé
<p>Seen as a real sanitary curse in developed countries, Alzheimer's disease is about to create pandemonium on a worldwide scale. The outburst of this epidemic cannot only be explained by the ageing population and could, in decades to come, severely jeopardize the social security systems.</p> <p>The causes of this pathology are still largely unknown but epidemiological studies have proved the importance of environmental factors, whose effects depend on the presence of disease susceptibility genes. Numerous publications have underlined in particular the influence of toxic factors of chemical or physical kind: metals (mercury, lead, aluminum...), pesticides, electromagnetic waves... Among these risk</p>	<p>Véritable fléau sanitaire dans les pays développés, la maladie d'Alzheimer est en passe de devenir une pandémie mondiale. La flambée de cette épidémie ne peut s'expliquer uniquement par le vieillissement de la population et pourrait, dans les futures décennies, mettre en péril les systèmes de protection sociale.</p> <p>Si les causes de cette pathologie restent encore largement méconnues, des études épidémiologiques démontrent l'importance de facteurs environnementaux, dont les effets sont modulés par la présence de gènes de susceptibilité à la maladie. De nombreuses publications mettent notamment en évidence l'implication de facteurs toxiques de nature chimique ou physique : métaux (mercure, plomb,</p>

<p>factors, exposure to elemental mercury, whose main source is found in dental amalgams, seems to be particularly implicated. Indeed, scientific tests have clearly identified that inorganic mercury induces harmful biological effects in the brain that can be compared to those observed in Alzheimer's patients. Several mechanisms explaining these disturbances have now been clearly identified: induction of oxidative stress, destruction of neuronal cytoskeleton, inhibition of the activity of enzymes which play a vital role in brain functions, disturbances in glutamate -a neuromediator- metabolism, etc.</p> <p>Research must therefore be more orientated towards the identification of the causes of this illness and not only towards palliative therapies such as drugs and vaccination.</p> <p>The level of our exposure to mercury and other neurotoxic substances can only be reduced by rapidly applying the precautionary principle, therefore delaying cerebral ageing.</p> <p>Key words: Alzheimer disease, mercury, dental amalgams, gene-environment interactions, prevention.</p>	<p>aluminium...), pesticides, ondes électromagnétiques... Parmi ces facteurs de risque, l'exposition au mercure élémentaire, dont les amalgames dentaires constituent la source majeure, est particulièrement suspectée. En effet, des expérimentations mettent en évidence que le mercure inorganique induit dans le cerveau des perturbations comparables à celles observées chez les malades d'Alzheimer. Plusieurs mécanismes expliquant ces perturbations sont désormais clairement identifiés : déstructuration du cytosquelette neuronal, induction d'une agression oxydante, inhibition de l'activité d'enzymes jouant un rôle vital dans le fonctionnement cérébral, action sur le métabolisme d'un neuromédiateur, le glutamate, etc.</p> <p>La recherche doit par conséquent s'orienter davantage vers l'étiologie de cette maladie, et non seulement vers la mise au point de thérapies médicamenteuses ou vaccinales. Ce n'est qu'en appliquant rapidement le principe de précaution qu'on pourra réduire l'exposition de la population au mercure et aux autres substances neurotoxiques, et ainsi retarder le vieillissement cérébral.</p> <p>Mots clés : maladie d'Alzheimer, mercure, amalgames dentaires, interactions gènes-environnement, prévention.</p>
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➤ **Introduction**

Alzheimer's disease (AD) touches nearly 900000 people in France and is affecting about 225000 more French people every year. Projections are alarming: in France, 1 200 000 nationals should be diagnosed as having AD by the year 2020 and there should be more than two million victims by 2040. [1] Across the continent, about 6 millions Europeans are concerned today and they are expected to be more than 16 million by 2050. This degeneration is a real pandemonium, concerning 26 million people in the world, this number being expected to quadruple before 2050.

Although the elderly are the most affected by this neurodegenerative pathology, it does not spare the young: the latest Canadian statistics (Jan. 2009) reveal that the victims of AD are getting younger: 15% of people with AD are less than 65 years old. Because of its rapid progression the authors of the Canadian study consider that this epidemic might destroy the Canadian health care system. [2].

AD has therefore become a major public health issue costing not only human lives but also generating huge social costs and jeopardising health insurance systems. Will public health policies manage to slow down its unabated progression? Health authorities hope to delay the onset age of the disease by a few years to lower its prevalence. The French Alzheimer Plan (2008 – 2012) has high ambitions notably in the field of research. France would like other Member States to adopt the same strategy. However, no mention is made of a desire to do research on the environmental causes of this pathology.

➤ **Is Alzheimer's disease an unavoidable consequence of cerebral ageing?**

The rapid progression of AD's prevalence is constantly explained by the longer life expectancy that we benefit from today given that, most of the time, the illness affects the elderly: in developed countries approximately 20% of people over 75 and 30% of people over 90 have AD. The disease is therefore generally referred to as an almost unavoidable consequence of cerebral ageing for a large percentage of the population, particularly for those who show a genetic predisposition to it. This predisposition is linked to the existence of genes with several alleles whose presence can increase the risk or, on the contrary, give protection, depending on diverse environmental factors.

➤ **Environmental factors and genetic predisposition to Alzheimer disease**

We call environmental the determining factors that are not genetic such as dietary habits, risk prone behaviour (smoking, alcohol consumption, drug taking, sedentary lifestyles...) or exposure to toxic substances that are present in the air (at home, at the office or in any environment), in food, in medicine (vaccines, products for dental care) in beauty products and so on. To measure the extent to which environmental factors contribute to the development of AD we must focus on the evolution in time of AD's incidence, its geographical distribution and focus on the study of migrants from countries with very different results as to AD's prevalence. Throughout the years there seems to be an increase in AD prevalence and incidence for identical age groups. Indeed the Paquid study reveals that at the same age, prevalence is higher ten years after the beginning of the study (1998-1999) than at the inclusion phase (1988-1989). Also, an Italian prospective study brings to light the fact that in comparison to the results of previous studies AD's incidence rate is increasing. [1] This increase is clearly the case in China: over the last few decades AD's chronological prevalence has grown in a distinct manner [3]. However during the past 20 years there has been a change in the classifications and in methodologies that are used for surveys and investigations, which makes it difficult today to interpret all the available data [4]. In addition to this, the disease is extremely unevenly distributed throughout the world. Bearing in mind the population pyramid, the incidence of AD is high in developed countries (with the notable exception of Japan) and in Latin American countries, while it is much lower in developing and in least developed countries. What about the geographical distribution of genetic predispositions? The genetic predisposition to diseases of people in a given country is mainly due to the proportion of apolipoprotein E (APOE) alleles in the population of such a country. Indeed the APOE gene is the main genetic factor, useful to predict the development of the disease. It is particularly useful to determine whether symptoms might appear at an earlier or at a later stage in life. [5] APOE genes control the synthesis of apolipoproteins, which are abundant in the brain and help carry cholesterol and other lipids in the bloodstream. Genetic polymorphism is determined by the existence of three main alleles: APOE3 (or allele 3) the most common allele, APOE2 (which provides protection against AD) and APOE4 (which constitutes a genetic risk factor to the development of AD). A meta-analysis has shown that Caucasians who are homozygous for APOE2 have 25 times less chance of developing AD than Caucasians who are homozygous for APOE4 (in other words the figures are 0,6 versus 14,9) [6]. However, individuals who possess one or two APOE4 alleles do not necessarily develop dementia. Having APOE4 alleles is therefore an essential predisposing genetic risk factor which increases a person's risk of developing AD in developed countries. [7] If AD determinism was essentially genetic AD global prevalence should largely correspond to the global distribution of APOE4 alleles. However there is not necessarily a link between the presence of these alleles and the development of AD. In Asia, an APOE4 allele is not a common feature amongst the population (7 – 8% frequency) and AD prevalence is weak. In Africa, APOE4 alleles are very frequent but similarly to Asia, AD prevalence is very weak. [8] The comparison of two African populations who live in two very different environments (the Yoruba in Nigeria and Afro-Americans from Indianapolis) but who have a similar amount of APOE4 alleles (26 – 29%) shows that there is a 4.4 higher prevalence rate of AD for elderly Afro-Americans than for the Yoruba at the same age (6.24% versus 1.41%) [8]. It therefore seems as if environmental determinants, whether protective or risk-creating, play an important part in the development of AD: AD is a very rare

condition for the Yoruba even though they are prone to developing such a disease. However, American Caucasians who are subject to the same environment as Afro-Americans but who, on average, have fewer APOE4 alleles (13-16%) have 1.8 less chance of developing AD than Afro-Americans [9]. Studies on Japanese migrants also provide interesting information. Prevalence of AD is much lower in Japan than in other industrialised countries (approx. 2%) [10]. However, the prevalence is almost multiplied by three for Japanese people who emigrate to Hawaii (5.4%). The prevalence of AD for these emigrants is thus comparable to that of American or European Caucasians [8]. In addition to this, prevalence of AD for Japanese people who emigrate to Brazil is high (5.7%) compared to Brazilian nationals [11]. All this data make it clear that environmental factors have a major importance in the development of AD. In regions of the world where AD develops the most, as well as for Japanese migrants, when environmental factors are combined with genetic factors there is an increase in AD occurrence.

➤ Environmental factors which could alter the risk of contracting Alzheimer disease

Little by little, the idea that environmental factors could be at the origin of AD or could at least worsen the condition of people affected by the disease has made its way through to health authorities, leading them to take primary preventive measures. The table below summarises the protective and risk factors that are recognised today (based on the Inserm's collective expertise (the French national institute for health and medical research) during the European symposium on AD prevention in Lisbon in May 2007 [4]). The factors are recognised as protective or risk-creating although sometimes with very little proof (Table 1). The expert group from the Inserm underlined that there were not enough epidemiologic studies taking into account all suspected risk factors. Easily accessible protective factors which make up primary prevention are measures such as the adoption of a Mediterranean type diet. This diet consists of having small quantities of wine, undergoing regular physical activity and banning smoking. Together with regular physical activity, a Mediterranean diet also reduces the risk of cardiovascular disease, of diabetes and to a lesser extent, it reduces the chances of depression because of the large quantities of omega 3 unsaturated lipids. However, despite scientific publications which bring to light the likely and possible contribution of these determinants to the development of AD, the Inserm does not mention any undesirable elements from our physical or chemical environment amongst the selected risk-creating factors. These mainly include exposure to pesticides, to aluminium present in drinking water, to mercury vapour releases from dental amalgams, to lead and to electromagnetic waves.

Table 1. Main identified or suspected protective and risk factors of Alzheimer's disease (AD)

Protective factors	Risk factors
A high level of education, A fulfilling social and intellectual life, Large quantities of omega3, of antioxidants (vitamin E, carotenoids, selenium) and of vitamin B: fish, fruit, vegetables, cereals in diet, 'Reasonable' alcohol intake Regular physical activity	Traumatic brain injuries Heavy smoking Sedentary lifestyles, obesity Depression, diabetes Hypertension (high blood pressure) Hypercholesterolemia Elevated homocysteine

➤ Does mercury from dental amalgams contribute to the development of Alzheimer disease?

It is a well known fact that mercury is a neurotoxin in all its forms (elemental mercury Hg⁰, inorganic mercury: mercurous ions (Hg⁺) and mercuric ions (Hg²⁺) and organic mercury: for example CH₃Hg⁺ methylmercury

cation) [22]. The expression to be "as mad as a hatter" illustrates the toxicity of mercury since it stems from the fact that hat makers used to handle mercury dissolved in nitric acid (nitrate mercurique) for stiffening felt. This led to mercury poisoning and to hat makers to lose their minds. Listed in the French chart of occupational diseases since 1919, hydrargyria (mercury poisoning or mercurialism) is an inorganic or elemental mercury intoxication which covers several illnesses and neurological syndromes such as acute encephalopathy, intentional shaking or cerebella ataxia. These past 20 years numerous publications have studied the possible links between exposure to inorganic or elemental mercury and AD.

- **The global distribution of Alzheimer disease corresponds to the distribution of dental caries**

The distribution of AD worldwide globally corresponds to that of tooth decay and to the use of dental amalgams. Similarly to AD prevalence, there is low prevalence of tooth decay for adults in Africa or Asia (including Japan where good dental hygiene used to be the rule because of the small amount of sugar that was eaten). However prevalence is high in developed countries and in Latin America where sugar intake is high and has been high for a long time. In Japan people still remember the Minamata tragedy, an incident which occurred in the 1950s. The choice was made not to use mercury for dental care. This is interesting to bear in mind since Japan is the only developed country where AD prevalence remains low even though tooth decay is rising due to the increasing sugar intake. Japanese people have long and healthy lives. Little data is available as to the possible links between tooth decay and AD. A small scale study has brought to light the fact that American patients with AD had seven to eight times more dental caries than people without AD (people with and without AD were grouped according to their age and level of education).

- **The brain as main target for mercury vapour releases**

Before they enter the market dental amalgams are not subject to tests in order to evaluate their toxicity and contain approximately 50% of elemental mercury. They constantly release mercury vapours (Hg^0). Elemental mercury is mainly inhaled and then transferred to 80% of the pulmonary alveoli before entering the bloodstream. The mercury located in the nasal cavity can also cross the nasal epithelium and be sent to the brain by the olfactory route (retrograde movement). In both cases it rapidly crosses the blood-brain barrier (BBB) thanks to its semi-lipophilicity. It is then oxidized and transformed into mercuric ions (Hg^{2+}) that are incapable of crossing the BBB. Due to mercury's affinity with thiol groups (-SH) the mercuric ions are then captured in insoluble form, together with sulphurated biological compounds (peptides or proteins). They build up in the brain little by little for years or even decades [13]. Mercury is therefore a bio-accumulative toxin just as lead, bismuth or cadmium which are generally grouped as toxic trace metals. It is the accumulation of mercuric ions in the brain that causes toxic effects after inhalation of mercury vapours – mercuric ions make up the ultimate toxin (elemental mercury is considered to be a protoxic). There is a correlation between the amount of mercury present in the brain and the number of dental amalgams [13]. A group of Italians have shown that people with over 12 dental amalgams have ten times more mercury in their pituitary gland and cerebral cortex than people with 3 dental amalgams or fewer [14]. Mercury from dental amalgams represents the main source of mercury exposure in developed countries [15]. For people living in developed countries mercury from dental amalgams contributes to approximately 2/3 of the mercury found in the body, most of it being present in the brain [16].

- **Presence of mercury in patients with Alzheimer disease**

There are higher levels of mercury in the brains of people with AD than in the brains of people not affected by AD [17], notably in the basal optic nucleus of Meynert. This is the part of the brain where there is the most neurone degeneration for people with AD [18]. People affected by AD also have higher mercury levels in their bloodstream compared to other non-affected people [19, 20]. Levels of mercury are on average three times higher for people with AD at the beginning of the disease. This could be due to high levels of amyloid peptides in the cerebrospinal fluid.

- **Cerebral dysfunction due to exposure to small doses of inorganic mercury**

- **A summary of the biochemical characteristics of Alzheimer disease**

The development of AD corresponds to a process of neuro-inflammation and cerebral degeneration. The three main characteristic features of AD are the hyperphosphorylation of the Tau protein followed by neurofibrillary degeneration (intracellular lesions) as well as the creation of senile plaques because of the accumulation of amyloid peptides (extra-cellular lesions).

- **Oxidative damage: an important mechanism, part of mercury's toxic process in the central nervous system [21, 22]**

The brain tissue of a person affected by AD shows levels of oxidative damage that are much higher than for a person without AD [23]. Exposure to small quantities of inorganic mercury also leads to oxidant stress in the brain.

The main mechanisms of oxidative damage caused by mercury

When mercury releases vapours and is inhaled it takes three main forms in the brain: elemental mercury (Hg^0 – mercury that has crossed the BBB), mercurous ions (Hg^+) and mercuric ions (Hg^{2+}) which constitute the stable and the reactive form of mercury. These ions (Hg^+ and Hg^{2+}) are generally soluble in water and cause toxic reactions. They are balanced between the reduced and oxidized forms of mercury (Fig.1). In turn these play a fundamental role in mercury's toxic processes.

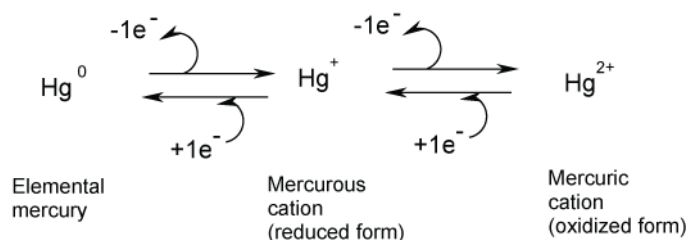


Figure 1

Redox couples of mercury and its ionised forms

In glial cells (the cells which provide nutrition for neurones), enzyme reactions involving a single electron allow elemental mercury to be transformed into mercuric ions. This happens in the presence of a peroxydase, the catalase, which uses hydrogen peroxide (H_2O_2) as oxidative reactant. Not only do mercuric ions have the capacity to oxidize and cause oxidative damage to a certain number of biological constituents (proteins, peptides, unsaturated lipids, nucleic acids and so on), the two redox couples also reduce dioxygen into several forms of reactive oxygen species (ROS) and in the end into hydroxyl radical ($H-O$). Hydroxyl radical is very short-lived (10-6s) and is extremely reactive. It can immediately destroy any organic biological molecule such as DNA. Oxidative damage to cellular constituents starts with an attack on unsaturated lipids. Such membrane peroxidation then leads to the oxidative degradation of proteins and of DNA. If this kind of oxidative damage is not regulated at the neuronal level by the antioxidant system, cell degradation occurs. This leads to neurone degeneration and can lead to dementia as in AD. Other toxic mechanisms can also take place and disrupt defence mechanisms – in particular the mechanisms related to reducing sulphurated molecules such as glutathione (G-SH) a tripeptide which is indispensable to help protect cells from oxidative damage. Indeed, insoluble mercuric compounds inhibit molecules such as glutathione. Thus, the exposure of neuroblastoma cultures to small doses of mercuric ions causes glutathione concentrations to decrease and oxidative damage to rise [24]. At the cellular level and after being stocked in lysosomes, mercuric ions will mainly interact with mitochondria, where reduced oxygen species which are responsible for cell ageing are produced. While the toxicity of a mercuric ion is mainly linked to the ion's strong affinity with protein or peptide thiol functions (for

example tubulin or glutathione respectively) it is likely that oxidative damage can have important consequences depending on the affected organ (CNS – central nervous system, kidneys...).

Fig.2 summarises the impact of mercuric ions on the biological molecules of neurones and glial cells.

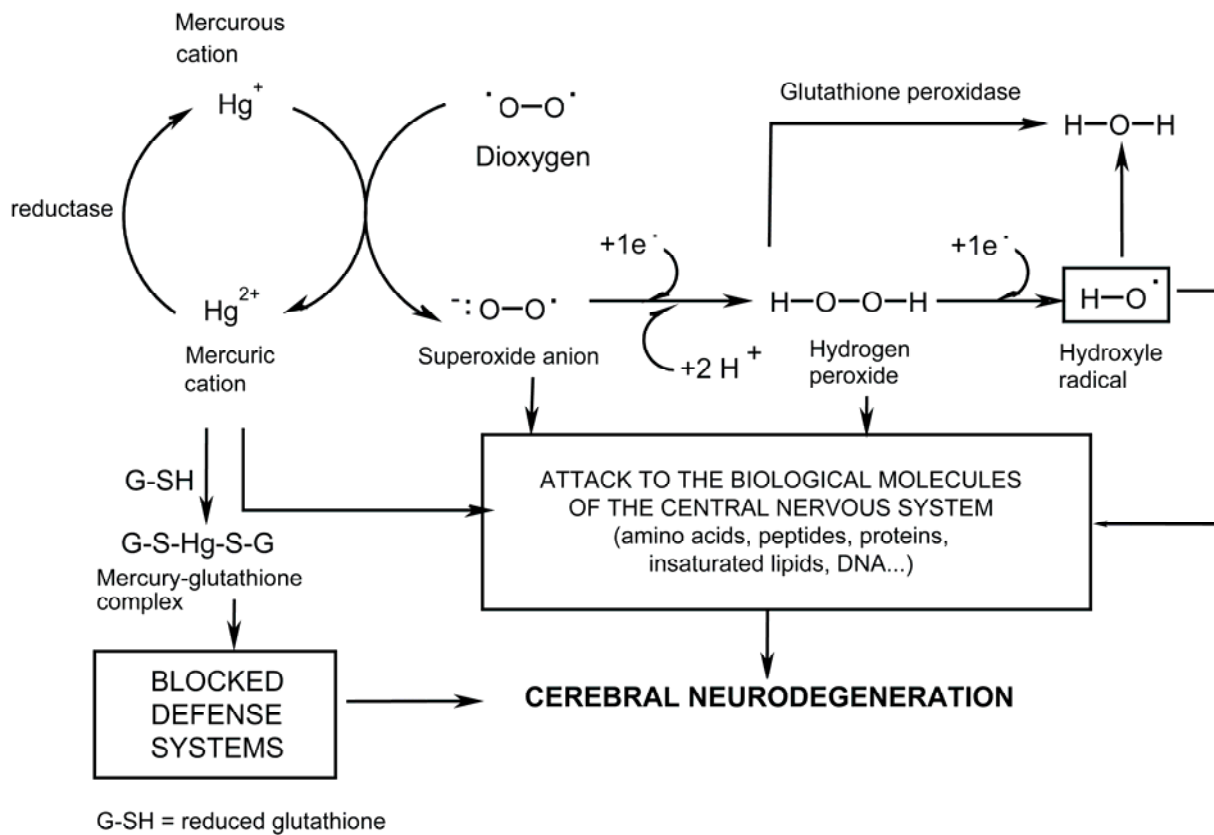


Figure 2

Degradation mechanisms of the biological molecules of the central nervous system by the mercuric cation and the reduced entities of dioxygen (ROS) (22b,c,d)

The **protecting role of selenium** regarding mercurial intoxications may be linked to its action in defense systems, as for glutathione peroxidase, an enzyme containing selenomethionine, and which role is (with the catalase) to neutralize the hydrogen peroxide (H_2O_2) formed during the reduction of dioxygen. Fish are rich in selenium and consuming contaminated fish seems to protect from AD, in spite of the intake in methylmercury.

- Perturbations linked to the strong affinity of the mercuric cation towards the thiol groups of proteins

The very strong affinity of the mercuric cation towards the thiol functions of peptides and proteins (in the manner of lead) explains for the most part their formidable neurotoxicity.

The neuronal cytoskeleton assures, among other things, the axoplasmic transport of numerous molecules, a vital process for neurons. It is made of microtubules assembled by the polymerization of a protein called **tubulin**, which has several cysteines with sulphurated thiol functions, essential for the polymerization. **Mercuric cations** stop this process by blocking the thiol groups, resulting in **neurofibrillary tangles** that are **toxic** to the neuron and lead to its necrosis.

Thus, tubulin constitutes an extremely vulnerable target to mercury, as demonstrated by numerous experiments [7].

Very weak doses of inorganic mercury inhibit the tubulin phosphorylation by guanosine triphosphate (GTP) in human nervous cells [25]. The same mechanism has been observed in rats. These cerebral molecular disturbances are identical to the ones observed post-mortem in the brains of 80% of AD patients, and the importance of the lesions is correlated to the mercurial concentration in the brain. It was also demonstrated that the ADP-ribosylation of tubulin and actin is strongly inhibited, in vivo and in vitro in rats, by very weak quantities of mercury [27]. The blocking of the functions of tubulin can lead to apoptosis and to the formation of chaperone heat shock proteins [28]. Finally, adding very weak quantities of inorganic mercury (10^{-7} mol) in a cell culture of growing neurons causes the depolymerization of tubulin, leading to the **destruction of the cytoskeleton**, the **degeneration of the axons** and then to the **formation of neurofibrillary tangles**. This effect is not observed with other neurotoxic metals (Al, Pb, Mn...) and the authors of this study conclude that this biochemical data clearly demonstrate the **implication of mercury as a potential etiologic factor in neurodegeneration** (the video of the experiment is available at the website of the Faculty of Medicine at the University of Calgary <http://commons.ucalgary.ca/mercury/>) [29]

Enzymes such as **glutamine synthetase** (see below) and **creatine kinase** (CK), which plays a key role in the regulation of the neuronal adenosine triphosphate level, are particularly **vulnerable to mercuric cations** due to their large number of thiol functions. And **CK activity is clearly reduced in the cerebral regions particularly affected by AD** [30].

- **The exposure of nervous cells to inorganic mercury leads to the apparition of the disturbances typical to Alzheimer disease**

We have seen that **neurofibrillary tangles**, a marker of AD, appear in neurons exposed to small quantities of mercury [29]. The apparition of the two other markers of the disease, the **hyperphosphorylation of Tau proteins** and the **increase in the secretion of β -amyloid peptides**, is observed in a neuroblastoma cells culture subjected to weak doses of inorganic mercury [24]. Copper and zinc, two metals essential to neuronal life and entering in dental amalgams composition, would also be involved in the formation of **amyloid plaques**, in relation to disturbances in the neuronal cellular homeostasis [31].

- **Inorganic mercury disturbs glutamate transport and glutamine synthetase (GS) activity**

Glutamate, a neurotransmitter involved in learning and memory, is essential to the synthesis of gamma-Amino butyric acid (GABA), and glutathione [32]. AD patients show an **excessive activity of glutamate**, an excitatory neurotransmitter that becomes neurotoxic if in excess. And **mercuric cations disturb the metabolism of glutamate**, even at micromolar doses. When this neurotransmitter is released in the synaptic cleft, they bind to the thiol functions of its proteic transporters and inhibit its recapture by the astrocytes [33]. This leads to an increase in the extracellular glutamate, leading to neuronal death by necrosis. In addition, the **GS level** is a lot higher in the cerebrospinal fluid of AD patients, which could constitute a marker of the disease [34]. This enzyme is essential to the production of glutamine (used into neurotransmitters synthesis) from the glutamate captured by the astrocyte. And **the mercuric cation inhibits in a dose-dependent manner the activity of the GS in the astrocytes** a lot more than the methylmercuric cation, even at very weak dose: a concentration of 5 μ M of inorganic mercury during 6 hours leads to a fall in the activity of the GS by 74 % [35].

Exposure to mercury vapors emitted from dental amalgams may therefore lead to **the inhibition of cerebral GS**, leading to an **increase in the glutamate level**, becoming **excitotoxic** and resulting in the necrosis of the astrocytes and disturbing the glutamatergic and GABAergic neurons. **Therefore weak doses of inorganic mercury (Hg^{2+}) inhibit the activity of 3 proteins, one structural protein, tubulin, and two enzymes essential to cerebral functioning, creatine kinase and GS. These cellular disturbances are observed in AD.**

- **APOE alleles, risk of Alzheimer disease and exposure to mercury**

The major impact of the $\epsilon 4$ allele of the apolipoprotein E gene on the risk to develop AD and the protective effect of the $\epsilon 2$ allele are known. But apolipoprotein E do not take place only in the excretion of lipids, including cholesterol, out of the central nervous system. **These proteins can also bind to mercuric cations**

thanks to their thiol groups which have a very strong affinity towards this element (and towards other metallic cations such as lead cations): **the mercury** stored in the brain is transported by these proteins and then, it can cross the hematoencephalic barrier and get excreted by the kidneys [7; 36]. But the apolipoprotein E2 has two cysteines, therefore two thiol functions (-SH), whereas the apolipoprotein E3 has only one and the apolipoprotein E4 has no one. **Therefore APOE2 homozygotes have a great capacity of excreting mercury out of the brain, which is not the case of APOE4 homozygotes.** Other categories have intermediate detoxication possibilities within these two extreme probabilities [7]. Therefore some researchers emit the hypothesis that this mechanism explains the susceptibility to AD given by APOE4 genes: carriers of one or two APOE4 genes would have **more risk to contract AD due to their difficult mercury elimination.** Without exposure to mercury (case of the Yoruba people of Nigeria and Japanese people), APOE4 carriers therefore have little risk of getting affected by AD. On the other hand, if exposed to important quantities of mercury (from dental amalgams), Japanese migrants would increase their risk of developing the disease. The frequent presence of $\epsilon 4$ alleles gives a very high risk of having the disease for the African American population ("historic migrants") whereas the risk for the Yorubas, who are not exposed, is independent from the APOE haplotype [37].

There are **other genetic susceptibilities** to AD, such as a greater or lesser capacity to synthesize **metallothioneins** in answer to an exposure to mercury. These small sulphurated proteins, whose main function is the transport of zinc and copper, are able to bind strongly to mercuric cations in the brain, and thus allow their elimination. This genetic variability can also explain the inequality in front of a comparable exposure to mercury [38]. A polymorphism called *Brain-derived neurotrophic factor* (BDNF) **seems also to play a role in the vulnerability to long-term exposure to mercury** [39].

In addition, some scientists show an increasing interest in the mercury responsibility for **modifying the expression of genes (epigenetic process)**, and in particular for long term effects of an early exposure to mercury and its possible transgenerational consequences.

Figure 3 shows the main biological genetic and environmental determiners that can increase or decrease the risk of developing AD one day

- **Alcohol, mercury and Alzheimer disease**

A regular consumption of wine (2 to 4 glasses/day) is associated to a four times lower risk of AD [40]. This beneficial action could be linked to a competition between the oxidation of the ethanol and the oxidation of the elemental mercury into mercuric cation [41]. Some specialists explain the protective effect of alcohol against AD by its inhibitive effect on the oxidative bioactivation of mercury that decreases the mercurial impregnation of the central nervous system.

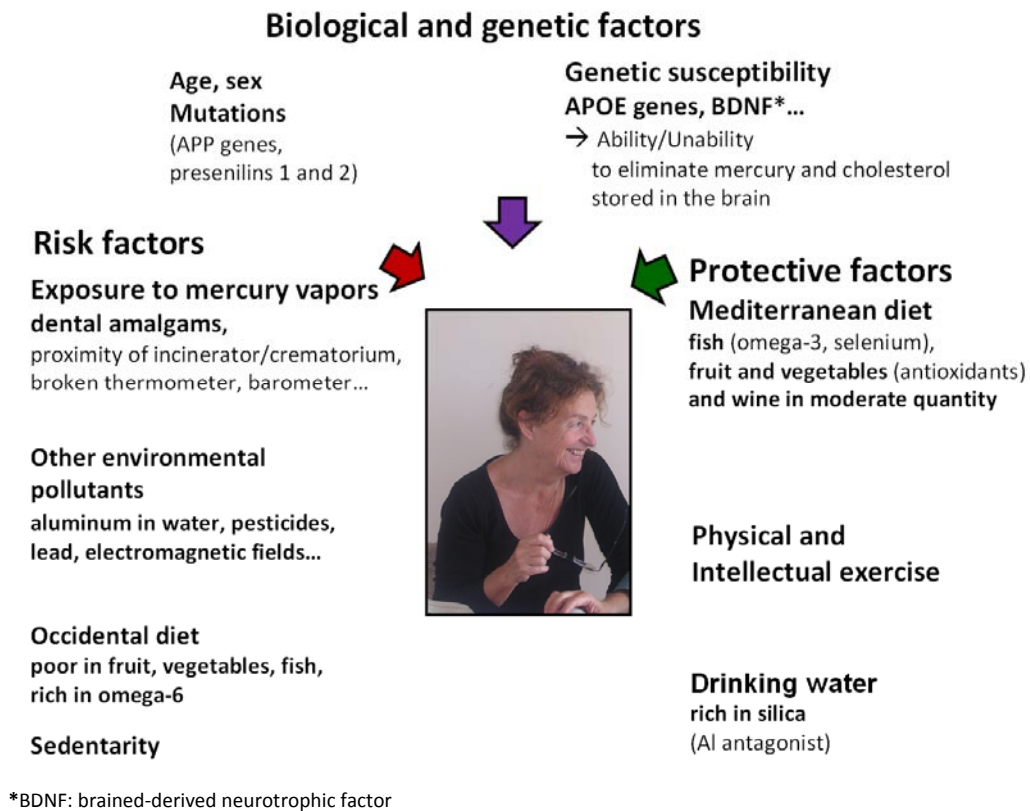


Figure 3

Main genetic and environmental determiners of Alzheimer disease (AD)

- **Exposure to mercury vapors, olfaction deficiency and Alzheimer disease**

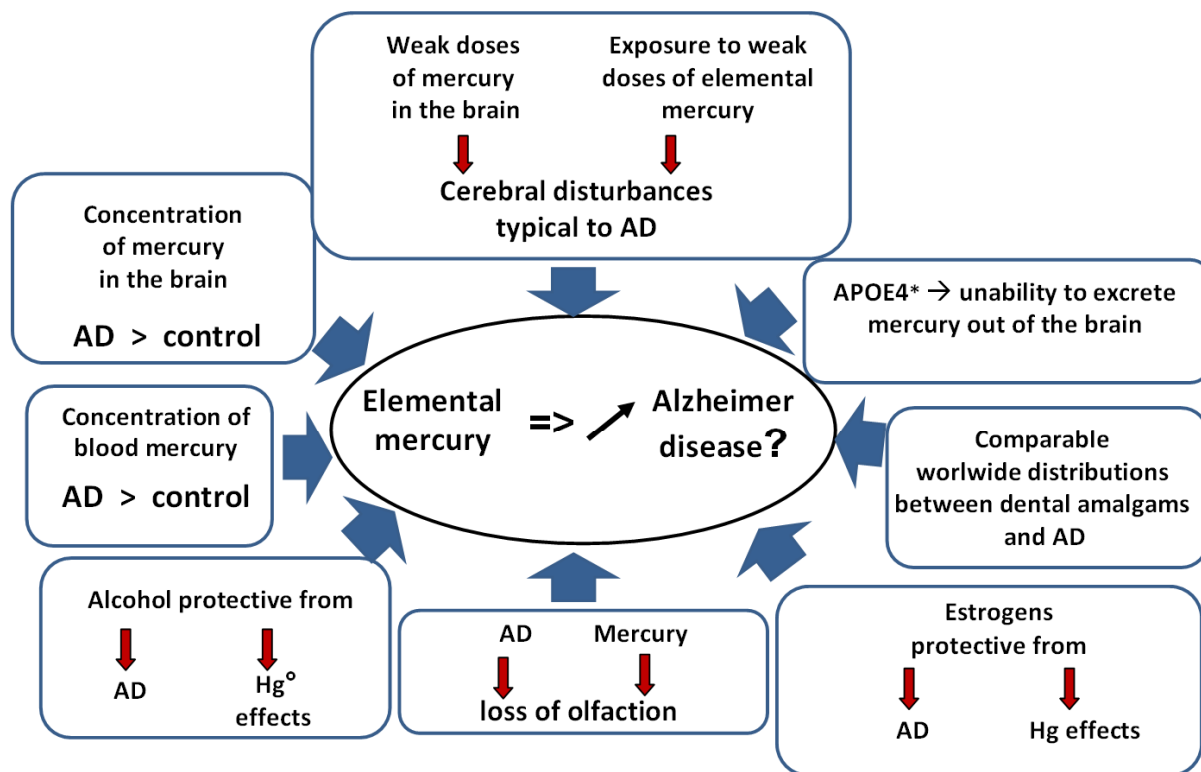
The elemental mercury present in the nasal cavity can cross the nasal epithelium and be transported up to the brain by the olfactive tract: **the mercury accumulates preferentially in the olfactive bulb, leading to olfactive deficiency** [42]. And **one of the frequent early signs of a beginning AD is the loss of olfaction**, which could be used as a early marker of the disease in case of a minor cognitive deficiency [43].

- **Mercury and estrogens**

Protective effects of estrogens against AD are becoming well studied. A preliminary treatment of a culture of nervous cells by estrogens before exposure to mercury prevents from the oxidative aggression process [44].

- **Hopes brought by metal chelating treatments**

Several research programs are interested in the use of metal chelators to slow down the evolution of the disease by solubilizing the **β-amyloid peptides** [45]. Some phase II clinical tests are in progress, in particular with Clioquinol, a chelator of copper and zinc [4] and also mercury [46].



* APOE4 : gene coding for an apolipoprotein without thiol function

Figure 4. Mercury (Hg) and Alzheimer disease (AD): a bundle of presumptions

➤ Conclusion

There is a **significant scientific corpus showing the probable implication of elemental mercury in the initiation of neurodegenerative diseases, in particular AD**, as Figure 4 shows. Moreover, some scientists suspect an early exposure to mercury and to other neurotoxics (in utero or during small childhood) may increase the risk of developing, decades later, a neurodegenerative disease [47]. In fact, the developing brain is extremely vulnerable to the effects of neurotoxics and it is known that degeneration mechanisms start at a relatively young age: **the optimal strategies of prevention from dementias should consist in avoiding exposure to toxic substances from the youngest age** [48].

The long prospective study necessary to prove the cause-effect relationship between AD and an exposure to long term and to weak doses of mercury is difficult to consider, due to the difficulty to find a large enough control population that would never have been exposed to mercury, and due to the great interindividual variability of the sensitivity to mercury. Some scientists deplore the **too high level of proof required before deciding on the interdiction of a chemical substance** and its substitution, even though its neurotoxic effects are well-known [49]: it would be time to consider the data of the cellular and molecular toxicology to take decisions allowing decreasing the exposure to neurotoxic metals. The frequent interpretation by the experts of the sanitary instances of the uncertainty to retain the null hypothesis (absence of risk) leads to huge sanitary and societal costs on the long term range [50]. The example of lead well illustrates it: 50 years have passed between this metal neurotoxicity has been admitted and its suppression as an additive in petrol with tragic consequences on the developing brain during two generations [51]. To slow down AD epidemic, it is therefore **urgent to get concerned by its environmental causes** and to quickly set up **preventive strategies**. If it is important to promote a **Mediterranean diet** and a regular **physical activity**, is it essential to **decrease the exposure of the population to neurotoxic substances by improving the physico-chemical environment**. Some

simple measures can quickly be taken: **stop using dental amalgams**, as have already decided Norway, Denmark and Sweden, **stop using aluminum salts in water treatment**, **obligation to use filters** that are effective for “heavy metals” (crematoriums, thermal power plants).

Up to now, the efforts of research have been concentrated on therapies that have not proved yet their efficiency. From now on, **tackling the causes of the disease should be a priority: this is definitely the surest way to get durable and satisfying results in the fight against cerebral ageing.**

For practical purpose, to limit exposure to elemental mercury:

- ask for dental obturators made from materials alternative to amalgam (composites, ionomeric glass, ceramic) and avoid proximity between gold crowns and dental amalgams in the mouth (situation of a maximum corrosion);
- in case of intervention on a dental amalgam (place of a crown) or removal of a dental amalgam: impose a strict protocol to limit the inhalation of toxic vapors (by example the IAOMT protocol [1]) ;
- limit, for dental amalgam carriers, exposure to electromagnetic fields (use a free hand kit phone): they increase dental mercury emission [52] and hematoencephalic barrier permeability ;
- do not keep at home a mercury thermometer or barometer, and avoid breaking low consumption light bulbs (they contain mercury);
- use recycling channels (light bulbs, thermometers, barometers...).

[1] <http://iaomt.org/articles/files/files288/Safe%20Removal%20of%20Amalgam%20Fillings.pdf>

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