Alzheimer disease and environmental exposure to neurotoxic factors: A controversy

Short title: Alzheimer disease and environmental neurotoxic factors

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Abstract

Background: Common neurodegenerative diseases including Alzheimer disease are a major public health issue because of their high prevalence and etiopathogenic complexity. Ageing, combined with a genetic predisposition and modifiable risk factors including cardiovascular factors, has been shown to be the main risk factor of Alzheimer and related diseases. The international scientific community suspects that physicochemical environmental factors may be involved. The lack of consensus justifies a general review of current knowledge on the role of environmental neurotoxic factors in the occurrence of some neurodegenerative diseases, particularly Alzheimer disease.

Methodology: A literature search was conducted on PubMed using the keywords dementia, dementia syndrome, Alzheimer disease, Alzheimer type dementia, exposure, neurotoxicity aluminium, mercury, pesticide. After reading all of the abstracts and ruling out irrelevant articles, only relevant articles in English or French were selected. We read more than 600 abstracts and based on these we selected and read 352 articles, 176 for each of the two authors. Finally, our bibliography includes 78 articles.

Results: The neurotoxicity data from animal experiments are old, and in the professional environment there is no evidence regarding the gradient of environmental toxicity. Synergistic, multiple-factor neurotoxicity is complex and difficult to document epidemiologically as it is due to a cumulative toxic continuum rather than a dose/effect relationship. Within this recognized multi-causal model of neurodegenerative diseases, particularly Alzheimer disease, chronic exposure to neurotoxic products has a real pathogenic effect on the central nervous system though certain aspects of this effect are not entirely proven.

Conclusion: The lack of overall agreement about precautions for heavy metals does not mean that latent and prolonged exposure to these products is safe, especially with regard to the potential risk of worsening neurodegenerative diseases.

Keywords: Environment; exposure; Alzheimer disease; neurodegenerative disease; neurotoxicity.

1. INTRODUCTION

Ageing is recognized as a major determinant of neurodegenerative diseases (NDD), notably Alzheimer disease (AD). However, the etiopathogenicity of AD is still relatively unknown. Most authors agree on the multifactorial nature of the causes of sporadic forms, which account for 99.4% of cases of AD [1]. The exponential increase in cases of AD worldwide since the end of the 90s suggests an environmental cause, even though there is no consensus on this point. Worldwide, the prevalence of AD is estimated at between 24 and 26 million cases, with a new case diagnosed every 7 seconds [2,3]. The prevalence of AD in France is 800,000 to 1 million cases, with an incidence estimated at 225,000 new cases annually [2,3]. Even more alarming is that the prevalence is set to quadruple in the 50 years to come [4]. The PAQUID study published in 2003 [3] reported 769,000 people with AD in France and 135,000 new cases annually, corresponding to a doubling since 1994 with progression in every age group [5], including people younger than 60. Data in the literature show a lower prevalence of AD in Japan (2%), though the prevalence of AD in Japanese people who migrated to the United States is higher than that in those who stayed in Japan [6,7]. The causative role of ageing, as put forward by the medico-scientific community, is still a matter of debate. In addition, ageing alone cannot explain the clinical manifestations of AD or the increase in mortality due to the disease [8]. The multi-causal model of AD is becoming more and more widely accepted, and it is clear that in industrialized countries environmental factors, the effects of which are modulated by the presence of a genetic predisposition for the disease, play a role [9]. Less than 10% of AD cases are caused by genetic mutations in three genes, namely amyloid-ß protein precursor (APP), presenilin 1 and presenilin 2, which are involved in the production of amyloid-ß peptide. A vast research effort has been made to study amyloid-ß peptide overproduction and/or Tau hyperphosphorylation, but their contribution to the onset and pathogenesis of this devastating disease is still controversial. The interaction

between oxidative stress and mitochondrial dysfunction probably forms a vicious downward spiral that amplifies the deficits and probably plays an important role in the pathogenesis of AD [10].

The aim of this article was therefore to take stock of the role of environmental neurotoxic factors in the onset of AD.

2. METHODOLOGY

A search of the literature was conducted on PubMed using the following key words: dementia, dementia syndrome, Alzheimer disease, Alzheimer dementia, exposure, neurotoxicity, aluminium, mercury, pesticide. All of the abstracts revealed by this search were read by the authors and articles that were off the subject were rejected. The remaining articles were read thoroughly. Only studies in English or in French were retained. We read more than 600 abstracts, which represent about 60% of relevant articles published on the topic on PubMed. Based on these abstracts, we selected and read 352 articles, 176 for each of the two authors. Finally, our bibliography includes 78 articles (Figure 1).

3. RESULTS

Active epidemiological research is being conducted around modifiable risk factors for NDD, particularly those bearing on the way of life and cardiovascular risk factors in particular during midlife. However, few authors have shown an interest in the effects of exposure to substances present in the environment and at the workplace [11]. Over the past few years, the existence of protective factors and risk factors that could be easily accessible for primary prevention has come to light [11]. These environmental protective or risk factors include any factor involved in disease onset that is not genetic, for example, diet and attitudes to risks

such as smoking, alcohol consumption or drug use and a sedentary lifestyle [11]. Having a healthy diet and an intake of dietary vitamins C and E have been shown to decrease AD risk [12]. Moreover, studies have shown that deficiency in antioxidant vitamins (including vitamins C and E) alone is sufficient to induce neurological deficits similar to those in AD, thus suggesting that oxidative imbalance plays a role in the pathogenesis of AD [10]. In the above studies, however, no mention was made of exposure to toxic substances present in the air (at home, at work or in the environment), or to healthcare products (drugs, vaccines, dental materials...) [13]. The link between exposure to neurotoxic substances in childhood and the onset of NDD in adulthood has nonetheless been raised in a wide range of international studies since the 90s, and since 2006, a number of highly-regarded experts have revived interest in such links [14,15], for example, concerning the interaction between genetics and the environment in AD

[16]. Research in toxicology has revealed that pollutants and/or toxic substances present in the environment may have a detrimental effect, in particular when exposure occurs at the prenatal stage. These substances include metals (aluminium, mercury, lead, cadmium...), tranquillisers, pesticides, polychlorobiphenyls (PCB), perfluorinated compounds (Polytetrafluoroethylene), brominated flame retardants (Polybromodiphenylether), bisphenol A and phtalates. Our review of the literature will focus on the toxic impact of two heavy metals, namely aluminium and mercury, and pesticides, all of which are widely distributed in the environment and for which recent data seem to be in agreement.

3.1. The most common neurotoxic substances

3.1.1. Aluminium

Aluminium is the most common neurotoxic metal on earth [17,18]. It is present in drinking water, and in industrial foods. Dietary intake accounts for 95% of the level of aluminium in the body [17,19]. Aluminium is widely used every day and exposure of humans to the metal varies according to the situation and source. On average, dietary intake stands at less than 30 mg per day, but in urban areas, however, this intake may exceed 100 mg per day because of the presence of additives and/or colorants [20]. Paradoxically, aluminium was shown to be a neurotoxic substance in animals as well as in humans in the study by Dolken in 1897 [17,21,22]. Since the first studies by Perl and Brody in 1979 [23], aluminium has been shown to be a factor in the onset of AD in studies in animals and in humans and in epidemiological data [17,18,24,25]. Certain studies concluded that aluminium had multiple neurotoxic effects [21] involving complex neurobiochemical mechanisms that are still poorly understood [16]. A correlation between neurofibrillary degeneration, revealed by histopathological examination and high intracerebral levels of aluminium has been reported by many authors, not only in animals [25], but also in patients with AD [24]. However, depending on the study, these observations are inconsistent, even in cases of exposure to high levels of aluminium because of low absorption and high excretion [17,18]. *In vitro* studies have found aluminium in senile plaque, as well as altered Tau protein and more rarely neurofibrillary degeneration, which is characteristic of AD, in patients exposed to aluminium [26]. However, some authors interpreted these as artefacts [18]. Walton put forward the hypothesis that aluminium played a role as a cofactor with hyperphosphorylated Tau protein in the onset of neurofibrillary degeneration [27]. Aluminium's oxidative properties contribute to neurotoxicity, with early damage during the prodromal phase of AD [19]. In healthy animals exposed to long-term ingestion of aluminium, the metal has been shown to accumulate preferentially in AD-affected regions of the brain, particularly in the hippocampus, in the absence of any genetic predisposition [16,19]. In addition, aluminium seems to exacerbate the formation of reactive

oxygen species *in vivo* and *in vitro*, accompanied with elevated mitochondrial activity and glutathione depletion, in glial but not neuronal cell lines [28]. Glial proliferation, macrophage activation and the excessive production of inflammatory cytokines have been described and confirmed not only experimentally in animals subjected to continuous absorption of aluminium, but also in patients who died as a result of aluminium encephalopathy [17]. Some recent genetic data on aluminium and its effects on micro-ribonucleic acid (miRNA) abundance in a highly relevant transgenic animal model for AD show strong parallels between miRNA profiles found in AD brain. These findings suggest that miRNA-induced mechanisms may be present in two important *in vitro* and *in vivo* models for AD and in AD itself [29]. The role of aluminium has also been raised in conformational modifications and in the more pronounced aggregation of amyloid-ß peptide 1-40 [30]; these changes exacerbate the toxicity of the peptide. Other authors have reported that people with AD show greater intestinal absorption of aluminium and higher levels in the brain even though there is no underlying disease [31]. It is in the professional environment that the link between exposure to aluminium and neurodegenerative diseases has been most thoroughly studied [32,33]. However, these studies contain certain inherent uncertainties because of co-exposure to other toxic substances [20], or are weakened by small sample sizes [34,35]. Since 1989, many international studies in the population at large have shown a link between AD and the presence of aluminium in the water, especially when there are low levels of silicon [18,27,36-38] or between AD and the consumption of aluminium-rich antacids [20,39]. Most of these studies, however, suffered from methodological limitations [20], and other studies found no link [16]. The study by Dartigues et al., which was carried out in 1996 and included 2,698 people older than 65, reported that the number of cases of AD doubled when the concentration of aluminium in the water was 100 µg/L. The acceptable level in European legislation is a maximum of 200 µg/L [37]. In 2009, this analysis was refined in a larger

cohort, with a more precise estimation of daily water consumption and the inclusion of protective factors such as the presence of silicon in the tap water. However, no definitive conclusions could be drawn [20,38]. The deleterious impact of aluminium on neurocognition was documented by a meta-analysis published in 2007. This study confirmed a correlation between cognitive performance and the concentration of aluminium in the urine [17,40].

3.1.2. Mercury

Mercury is also an abundant heavy metal and its impact on human health is quite worrying [41]. The neurotoxicity of mercury as an element or an inorganic compound has long been known, and mercury poisoning has been on the list of occupational diseases since 1919 [41]. This neurotoxicity is particularly due to long-term often underestimated exposure to mercury in the environment. This exposure is often related to industry [41] and to dental amalgams which contain the metal [42]. As well as exposure to particulate mercury, exposure to mercury is also related to food, where it is mainly in the form of organic mercury compounds (methylmercury) essentially found in fish. The daily dietary intake of mercury in France is estimated at 2 to 20 µg [41].

According to the World Health Organization, the mercury contained in the dental amalgams of millions of people is the principal source of exposure to mercury in the developed world. Elemental mercury is reported to be cytotoxic, genotoxic, immunotoxic and neurotoxic even at low doses [43]. Mercury is a pro-oxidant that causes oxidative stress, thus diminishing the brain's antioxidant activity, increasing AβPP expression, and inducing glial cell reactivity [42]. Inorganic mercury, as well as having a direct neurotoxic effect on axons [44], also induces the hyperphosphorylation of Tau protein [45] as well as the production of insoluble Beta-amyloid 40 and 42 [46]. In addition, it could also disrupt glutamatergic metabolism [47]. Apolipoprotein E is involved in the transport and elimination of mercury at the level of the

central nervous system [48]. However, this detoxification mechanism depends on the binding of mercury cations to the thiol groups in apolipoprotein E2 (2 thiol groups) and E3 (1 thiol group). These ions, however, bind less well to apolipoprotein E4. People with apolipoprotein E4 thus have difficulty excreting mercury, and are therefore more prone to AD [42,48].

Findings from animal and experimental studies suggest that mercury is a causative factor in a number of NDD, in particular multiple sclerosis (MS) [49-51] and AD [44,45,52-54]. There is still, however, some debate on this matter because of the absence of sufficient post-mortem and epidemiological evidence [41,55-58]. The current low prevalence of AD in Japan, which withdrew mercury from dental amalgams after the Minamata accident in the 1960s, is, however, strong evidence of the toxicity of mercury [7].

Nonetheless, mercury is still used as a preservative in many multidose vaccines (notably against H1N1 influenza), though its use in vaccines for children has been restricted by the AFSSAPS in France since 1999 [59].

3.1.3. Pesticides

The neurotoxicity of pesticides has been suspected for many years, but the findings vary depending on the authors, the studies and the products [14,60-63]. For certain authors, the link between exposure to pesticides, including rotenone, organochlorine pesticides, paraquat and dithiocarbamate and certain NDD [64,65] such as Parkinson disease has been corroborated by data from autopsies [66,67] and proven by experimental data [68,69]. It has been demonstrated that mitochondrial electron-transport-chain complex inhibitors such as rotenone, 1-methyl-4-phenylpyridinium, and 3-nitropropionic acid cause fragmentation of the mitochondrial network and increased production of reactive oxygen species. This mechanism perhaps plays an important role in the oxidative imbalance in AD [10]. Other studies, notably the prospective analysis by Baldi et al [71], have shown a possible correlation between

pesticides and AD [65,70]. The overall risk of pesticide-related neurotoxicity is thus not exclusively occupational but also environmental [61,70-72]; this risk, however, is not taken into account by European legislation, which came into force on 14th June 2011 (Regulation CE n°546/2011 of the Commission dated 10th June 2011). The Commission suppressed the use of paraquat in 2007, but still authorises the use of neurotoxic fungicides such as ethylene bis dithiocarbamate [73].

3.2. Environmental neurotoxicity

Concerns about the neurotoxicity of the heavy metals mentioned above and pesticides put forward by the National Research Council in the United States and by the French health authorities led to the creation of an agency for health and safety in the environment and at work (Afsset) in France in 2006. This agency lists neurotoxic agents that are available to the public. These include aluminium, inorganic arsenic, bismuth, bromides, organic compounds of tin, lithium, manganese and mercury, inorganic compounds of lead and thalium, organochlorine and organophosphate pesticides, carbamate and anticholinesterase pesticides and organic solvents. However, invasive neurotoxicants, such as fluorines, polybromodiphenylethers (PBDE), perchlorates, camphor and sweeteners are absent from the list. Certain drugs including alcohol and tobacco are also absent.

This effort to classify neurotoxicants has allowed an overall analysis of risk, but has not led to unanimous regulatory measures for withdrawal and or general standards for protection, and has not yet led to the implementation of a health alert system, at either the international or national level, that is independent of industrial lobbying [43,54,74].

In France, research in toxicology has been in steady decline. Pezerat, who alerted the authorities about the dangers of asbestos and lead, and the neurotoxicity of aluminium, was

one of the last representatives of the profession [75]. In the same vein, in Japan, 50 years elapsed between the accidental exposure to methylmercury in Minamata and compensation of the victims [74].

4. DISCUSSION

Evidence concerning the neurotoxicity of certain chemical pollutants in the environment has been accepted by the international scientific community [15,18], and qualified by certain authors as a neurotoxicity pandemic [14]. However, the fact that this view is still a matter of debate [65] reflects a very probable underestimation of their toxicity. The subclinical impact of these substances is more and more widely recognised and confirmed in the professional world by robust data and/or by prospective epidemiological studies notably in children [14,18]. In addition, aluminium, mercury, lead and pesticides have a synergistic toxic effect on the nervous system [46]. The link between these substances and the onset of NDD has been suggested by many epidemiological studies [17,18], but not proven with certainty [20]. The multi-causal, but not yet fully elucidated character of these NDD, including AD, is a major methodological difficulty as is the lack of prospective epidemiological studies [7,21,74]. All of the hypotheses for the onset of AD, including the amyloid cascades, have supporters and detractors [19]. The appearance of AD is not a normal process of aging. Other factors are therefore involved in initiating and/or amplifying oxidative stress during the onset and progression of the disease [10]. Among these potential initiators/sources, mitochondria probably play a critical, if not central, role because of their primacy in energy metabolism and redox homeostasis. Defects in mitochondrial dynamics, due to either the response to genetic deficits or metabolic/environmental alterations, will make mitochondria less versatile in responding to the changing needs of cells. This lack of versatility probably has particularly debilitating effects on neurons. The resulting mitochondrial dysfunction and ensuing oxidative

stress, and the interactions between these have the potential to form a vicious downward spiral that becomes a ubiquitous causative feature of cell malfunction and degeneration [10]. Oxidative imbalance could be one of the earliest manifestations of AD, actually preceding the classic appearance of amyloid-ß deposits and neurofibrillary tangles [12].

The level of proof for the cellular and molecular toxicity of substances or metals studied in this article, which are recognized as not being essential for life, is still a matter of debate, because of the lack of reliable autopsy data [42,58]. The result is that the principle of precaution is not being applied at the international level [74]. The poor estimation of the toxic effects is due to a number of factors that vary depending on the substance implicated and is classically related to the considerable biochemical complexity of certain metals, notably aluminium [16,20], the neurotoxicity of which has been highlighted by a large amount of experimental evidence [18]. It has been established that this neurotoxicity is above all a consequence of long-term exposure to small doses in a population that in most cases is unaware of this exposure [16,18]. The implication of aluminium in AD has not yet been confirmed [6,18,20,23], even though the recent work of Walton has shown the cumulative neurotoxic effect of low doses of aluminium over the long term with neuropathological signs characteristic of AD [16]. The analysis indicates that chronic aluminium intake is not only the environmental cause of AD but also triggers the hallmarks of AD assumed by many to cause AD [19].

Another shortcoming in the methodology is not taking into account the genetic predisposition. This problem has been raised by many authors. These genetic factors explain the variability in detoxification in similar conditions of exposure to toxicants. In the course of AD, the relationship between mercury and apolipoprotein E4 is informative [58]. Any study designed to assess the link between AD and any environmental factor needs to take apolipoprotein E into account [7,16,58].

The imprecise nature of reference values for certain biomarkers and reference thresholds for toxicity could lead to major epidemiological biases concerning exposure and thus lead to the possible underestimation of any dose/effect relationship [43].

The phenomenon of latency between exposure and the clinical effect means that routine toxicology tests cannot identify links. This factor may also lead to underestimation of the toxicological risk [23]. Studies involving intentional chronic exposure are rare for ethical reasons [19]. Too often, the usual scenario is unfortunately the discovery of occupational toxicity in adults. From such cases, it is possible to detect infraclinical functional disorders in the population at large, and these are later confirmed by prospective epidemiological studies [76]. The continuum of accumulative dose-dependent subclinical toxic effects means that these phenomena unintentionally escape from public health statistics [14]. The prodromal phase of AD, with its long clinically-silent period is striking similar to the early manifestations of chronic aluminium neurotoxicity [19]. Preclinical AD might correspond to a compensatory period during which the brain is able to maintain cell vitality and minimize oxidative stress and consequently preserve cognitive function. Further investigations aimed at the cellular consequences of oxidative RNA damage and compensatory mechanisms might provide insights into the process of aging and the pathogenesis of age-associated neurodegeneration [77]. However, the absence of evidence is sometimes intentional and due to the refusal to publish environmental toxic effects. This was the case in the 35-year delay in the publication of a population-based study conducted in 1971 in Japan after the accidental exposure of the population of Minamata to methylmercury, even though this exposure led to neurological symptoms and foetal abnormalities [74]. In 2006, the International Committee of Experts concluded that low doses of aluminium had a possible effect on the reproduction system and neurological development in humans [18]. In contrast, in France, the Institut de Veille Sanitaire (surveillance agency for health risks) ruled out any toxic role of aluminium in

drinking water given the low levels, but failed to provide any risk gradient according to the concentration of aluminium as shown in several studies [37]. Concerning mercury, the worldwide consumption of which has fallen by half since the 80s [41], efforts have centred on prevention in the workplace, essentially with regard to acute intoxication. However, the controversy surrounding the problem of dental amalgam remains, even though it is the principal source of exposure to mercury in the developed world [42]. Many publications show a certain degree of alarm because of the delay in implementing preventive strategies, which are nonetheless already available, and measures to remove neurotoxic metals [14,18,74] or even to initiate chelating treatments [49]. Aluminium chelation seems to be the only therapy to date that has proven to be effective in AD, particularly if treatment can be commenced at a relatively early stage [19].

Moreover, the use of aluminium in drinking water could be limited within the more general aim of removing heavy metals by improving ultrafiltration. Current knowledge has led to the elimination of toxicants like lead and methylmercury [43], and justifies the precautions recommended for pregnant or breast-feeding women [41]. The United States seems to have taken on board the environmental risks of pollution with regard to certain groups such as children [15], and this as early as 1993, long before Europe. It was American experts who proposed the generalization of « developmental neurotoxicity tests » going beyond the old paradigm "the dose makes the poison", established by Paracelse 400 years ago, so as to be closer to current understanding of environmental toxicology, "the timing makes the poison". This concept is still little known and needs to be promoted [78].

However, we must temper our suppositions on the cause and effect relationship between environmental neurotoxic factors and AD. Indeed, the data gathered should be confirmed by other changes observed in experimental studies and/or during the clinical course of AD.

This work does have limitations. First, only articles in English or in French were selected. Moreover, as the literature search was conducted exclusively on PubMed, the vast majority of articles selected for this study were obtained from this search engine.

5. CONCLUSION

The requirement of a maximal level of evidence to forbid or replace a chemical substance known to be neurotoxic is thus a possible aggravating factor in NDD, especially AD, and exacerbates social and health-related risks not only in the youngest but also in the oldest given that chronic diseases and particularly neurological diseases manifest themselves during old age.

As the true effects of these different substances on health are still uncertain, in the absence of proof to the contrary, they are considered innocuous. This maintains doubt in face of the explosion in AD and NDD in general. Everyone agrees, however, that these diseases are heterogeneous and multifactorial.

Apart from the fact that toxicological, cellular and molecular data are simply not taken into account, the absence of any international consensus on primary prevention concerning substances qualified as neurotoxic is a major brake on the generalisation of measures to protect populations.

AUTHORS' CONTRIBUTIONS:

Hélène Sordet-Guépet: study concept, acquisition of data, interpretation of data, preparation of manuscript

Patrick Manckoundia: study concept, interpretation of data, preparation of manuscript

CONSENT:

Not applicable

ETHICAL APPROVAL:

Not applicable

ACKNOWLEDGEMENTS:

The authors are grateful to Mr. Philip Bastable

COMPETING INTERESTS

Neither of the authors has any competing interest for this article.

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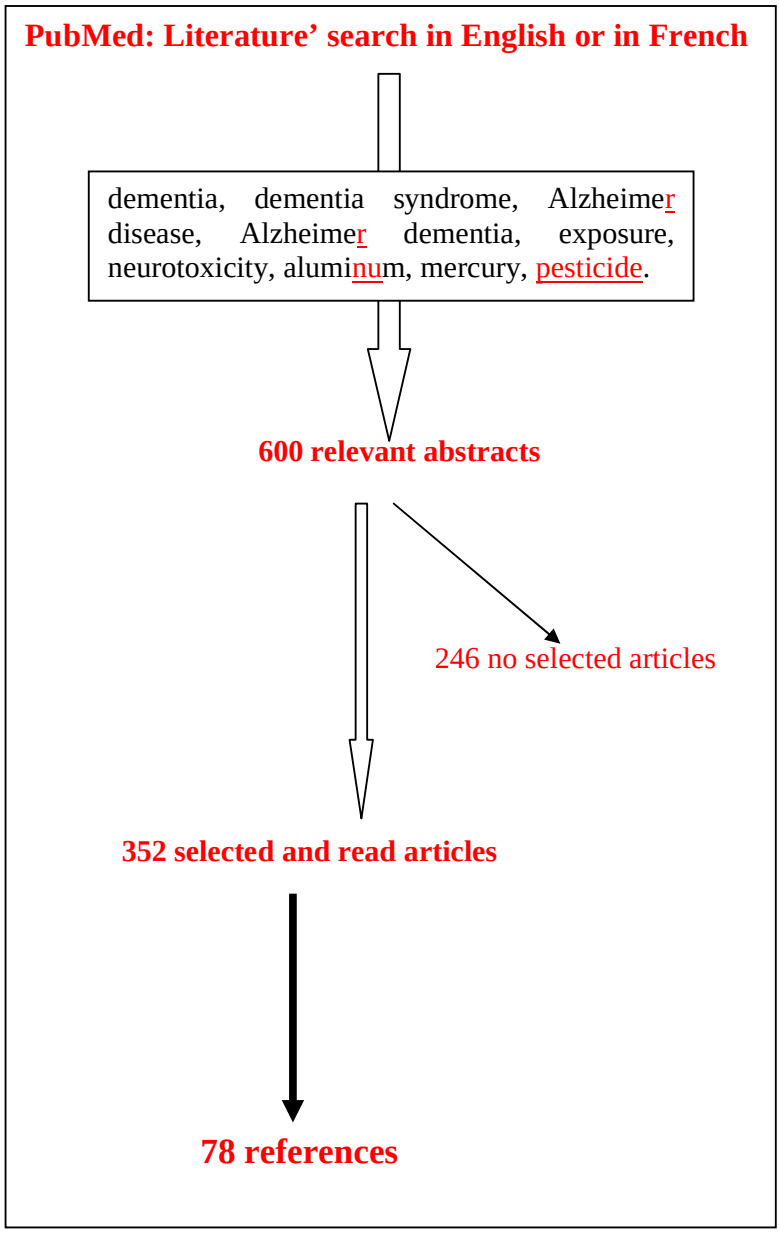
Legend:

Figure 1: Detailed schematic drawing of our bibliographic research.

Figure 1.


PubMed: Literature' search in English or in French
dementia, dementia syndrome, Alzheimer disease, Alzheimer dementia, exposure, neurotoxicity, aluminum, mercury, pesticide.
600 relevant abstracts
246 no selected articles
352 selected and read articles
78 references