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Development of computerized Kana Pick-out Test for the neuropsychological examination

Masashi Inoue [a,*], Akihiko Suyama [b], Toshiaki Kato [c], Katsuya Urakami [d], Kenji Nakashima [e], Shunsuke Meshitsuka [a]

[a] *Department of Medical Environmentology, School of Medicine, Faculty of Medicine, Tottori University, 86 Nishi-machi, Yonago, Japan*

[b] *Department of Epidemiology, Radiation Effects Research Foundation, Nagasaki, Japan*

[c] *Department of Medical Science in Sports and Exercise, School of Medicine, Faculty of Medicine, Tottori University, Tottori, Japan*

[d] *Department of Biological Regulation, School of Health Sciences, Faculty of Medicine, Tottori University, Yonago, Japan*

[e] *Department of Neurology, School of Medicine, Faculty of Medicine, Tottori University, Yonago, Japan*

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[a] *Department of Medical Environmentology, School of Medicine, Faculty of Medicine, Tottori University, 86 Nishi-machi, Yonago, Japan*

[b] *Department of Epidemiology, Radiation Effects Research Foundation, Nagasaki, Japan*

[c] *Department of Medical Science in Sports and Exercise, School of Medicine, Faculty of Medicine, Tottori University, Tottori, Japan*

[d] *Department of Biological Regulation, School of Health Sciences, Faculty of Medicine, Tottori University, Yonago, Japan*

[e] *Department of Neurology, School of Medicine, Faculty of Medicine, Tottori University, Yonago, Japan*

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Abstract

The Kana Pick-out Test, which was developed in Japan and done with paper and pencil, is said to be suitable for inspecting higher-order brain function and to be a good method for screening persons with mild or slight dementia. We have developed a computerized version of the Kana Pick-out Test, which runs on a stand-alone computer, intended to be utilized for mass screening and self-administration. The program was developed with Microsoft Visual Basic 6.0 and runs under the Windows operating system on any IBM PC compatible computer. In this study, all subjects could use the system by interacting with the computer and it was found that the system seemed to have the capability of detecting cognitive status equal to the paper-based Kana Pick-out Test. Besides this, we developed a network-based Kana Pick-out game software which was intended to attract user's notice. The game program was written in JAVA language and runs on a web-browser supporting JAVA on any operating system. The program, a so called applet, is located on our web site (http://environ.med.tottori-u.ac.jp) and anyone can use the applet by accessing our homepage. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Dementia; Computerized screening system; Neuropsychological test

1. Introduction

In view of the increased population of the aged people, the number of persons who suffer from dementia is also increasing. This number is estimated to be 2.2 million by the year 2010 which amounts to 8.1% of all Japanese over 65 years of

* Corresponding author. Tel./fax: +81-859-34-8068.
E-mail address: masashi@grape.med.tottori-u.ac.jp (M. Inoue).

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age. Thus, many issues concerning the social support system for them are arising. Usually, cognitive decline progresses gradually through a slight memory deterioration [1]. It is said that the important task for the clinicians is to identify patients in early mild state [2]. Usually, neuropsychological tests [3,4] are used to get their diagnostic classification. However, neuropsychological tests sometimes take a long time and are troublesome, so the development of a more convenient method is required [5]. We have already developed a computerized screening system based on the Hasegawa Dementia Scale [4] and reported the results of a field test [6]. The Hasegawa Dementia Scale is suitable for classifying persons whose cognitive decline is advanced, but it is weak in detecting persons with a slight decline. Our system based on the Hasegawa Dementia Scale also shows a tendency to do the same thing. The Kana Pick-out Test [7], which was developed in Japan, is said to be suitable for inspecting higher-order brain function and to be a good method for screening persons with mild or slight dementia. The Kana Pick-out Test is done with paper and pencil and an examiner must mark the answer sheet after examination. When there are many sheets, it requires a long time to mark the sheets and even mistake of marking can easily occur. To solve this problem therefore, we have developed a computerized version of the Kana Pick-out Test, which runs on a stand-alone computer, intended to be utilized for mass screening and self-administration. Besides this, we also developed a network-based Kana Pick-out game software which was intended to attract user's notice. In this paper we present the system description and show the results obtained in the preliminary field tests.

2. The original Kana Pick-out Test

In the original Kana Pick-out Test [7], a paper sheet (Fig. 1) is used on which a short story is written in Japanese Hiragana characters, which are phonetic symbols consisting of 66 sound syllables, 5 of them vowels. The story consists of 406 symbols. Subjects are required to find as many of the 5 vowel symbols as possible in 2 min and also to retain the meaning of the story. Therefore, this test basically assigns two tasks simultaneously: finding the 5 vowel symbols and recognizing the substance of the story. These 5 symbols are located at 61 points in the story. While reading the story, the subject circles the symbols by pencil. If the subjects concentrate on only reading the story, they tend to become careless in finding the symbols. Inversely, if they concentrate on finding the symbols, they tend to forget the substance of the story. The test assesses subject's cognitive status based on the number of symbols selected correctly and retention of the substance of the story.

3. System description

The program for the stand-alone computer was developed with Microsoft Visual Basic 6.0 and runs under the Windows operating system on any IBM PC compatible computer. The computer must have an audio output device because the computer directs instruction by voice. We adopted a touch screen display as an input device so that even aged person can operate the system easily. All interactive operation can be done by touching the display without using a keyboard and mouse. At the beginning of the program, the computer instructs how to use the system by voice and text. We designed the program so that the selection of symbols could be done by touching the screen rather than by circling with pencil as in the original test. Therefore, the size of each symbol needed to be bigger than the tip of a finger. Moreover, we figured the bigger the symbols were, the easier aged people could read them. By considering the situation stated above, we decided that the area for each symbol should be 1.5×1.5 cm^2, and as a result only 117 frames could be arranged on our 15-in. display. Therefore, the original whole story was too long to be shown on the display simultaneously. At first we programmed to scroll the text manually or automatically in order to show the whole story, but this confused the users. So we gave up using the original story and created three new stories. Each story consists of 117 symbols and contains 18, 20 and 26 vowel symbols, respectively. The testing procedure consists of 3 windows which show the stories and senses the user's responses. As soon as the first window is presented, the computer asks the user to read the story and to find the 5 vowel symbols. While reading, the user must find the symbols and touch them to point out. When the computer senses the touch, it changes the color of the border of the symbol to indicate that the symbol has been selected. Pressing the selected symbol again can cancel the selection and the color of the border returns to its original color (Fig. 2). The first window disappears after 40 s, so the user is required to read the story, remember the substance and find as many vowel symbols as

仮名ひろいテスト

被検者名
検査月日

次の文の中から、「あ・い・う・え・お」をひろい上げて、○をつけて下さい。
（なるべく速く、見落とさないように、物語りの内容も考えながら）

むかし　あるところに、ひとりぐらしのおばあさんが　いて、としを　とって、びんぼうでしたが、いつも　ほがらかに　くらしていました。ちいさなこやに　すんでいて、きんじょのひとの　つかいはしりを　やっては、こちらで、ひとくち、あちらで　ひとのみ、おれいに　たべさせてもらって、やっと　そのひぐらしを　たてていましたが、それでも　いつも　げんきで、ようきで、なにひとつふそくはないと　いうふうでした。

ところが　あるばん、おばあさんが　いつものように　にこにこしながら、いそいそと　うちへ　かえるとちゅう、みちばたの　みぞのなかに、くろい　おおきなつぼを　みつけました。「おや、つぼだね。いれるものさえあれば　べんりなものさ。わたしにゃなにもないが。だれが、このみぞへ　おとしてったのかねえ」と、おばあさんは　もちぬしが　いないかと　あたりを　みまわしましたが、だれも　いません。「おおかた　あなが　あいたんで、すてたんだろう。そんなら　ここに、はなでも　いけて、まどにおこう。ちょっくら　もっていこうかね」こういって　おばあさんは　つぼのふたを　とって、なかを　のぞきました。

採点　2分間　正（　）　誤（　）

Fig. 1. The paper sheet used in the original Kana Pick-out Test. On the sheet, a short story is written in Japanese Hiragana characters.

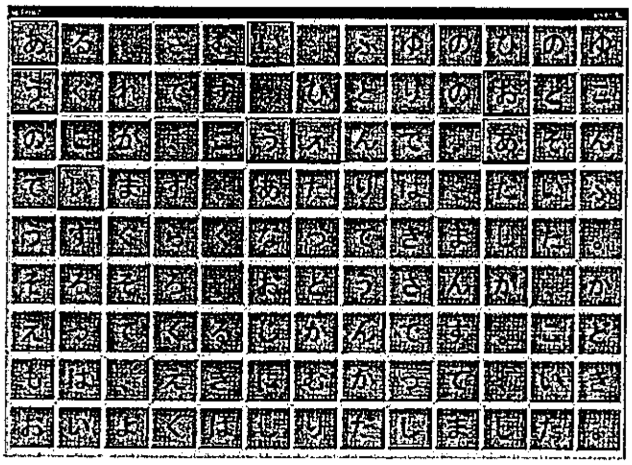

Fig. 2. One of interactive windows of the computerized test. It shows story and senses the user's responses.

possible within a limited time. After the first window disappears, the computer shows questions to examine whether the user remembers the substance of the story. Two questions and six choices for each question are displayed (Fig. 3). When the user answers two questions, the computer presents the second window in which the next story is shown and requires the same response as the first window. The same response is also required for the third story. Thus, the process is repeated three times in all. After the third set of questions are answered, the computer counts the number of

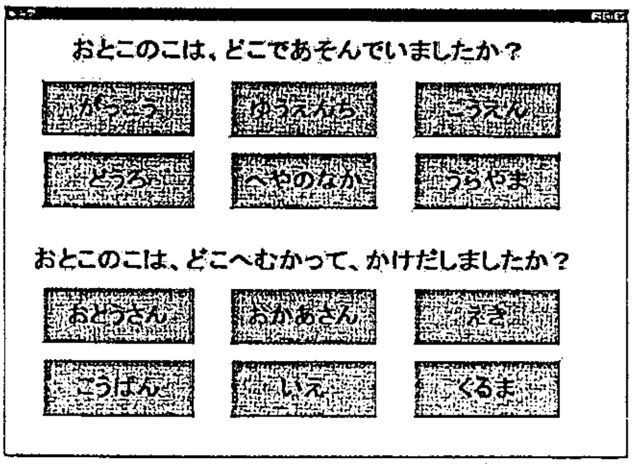

Fig. 3. A window showing questions to examine whether the user remembers the substance of the story. Two questions and six choices for each question are displayed.

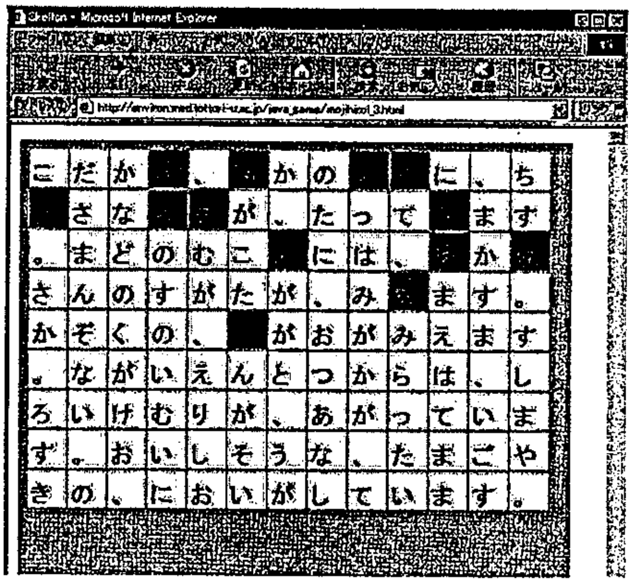

Fig. 4. One example of windows for the Kana Pick-out game. It runs on a web-browser supporting JAVA on any operating system. The program is located on our web site (http://environ.med.tottori-u.ac.jp) and anyone can use it by accessing our homepage.

symbols selected, the number of symbols correctly selected, the number of symbols incorrectly selected and the number of symbols missed. The computer also checks for the correct answers for the six questions. Then the results are shown. Before the actual test, users must practice an orientation task, which is aimed at assessing their manual motor ability and to determine whether the user can understand the operating procedure.

A network-based game program was written in JAVA language and runs on a web-browser supporting JAVA on any operating system (Fig. 4). The program, a so called applet, is located on our web site (http://environ.med.tottori-u.ac.jp) and anyone can use the applet by accessing our homepage. The design of the window and interaction are basically the same as that of the former system except for the size of each of the symbols. In the former system, the test consisted of three stories and the results are summed up. However, each story and its questions in the applet can be completed in one take. We provided 5 different stories and users can select one of these at their leisure. When the user completes one story and its questions, the applet shows the results. Users can select another story if they want to improve their score or for more practice.

4. Subjects and method

To evaluate the system's operational ability and performance, we recruited some subjects at a Health Promotion Event. The subjects were well informed for their consent and 55 persons accepted our proposal. They were all healthy adults and their age ranged from 25 to 79 years; 9 were males and 46 were females. The original paper-based test [7] was performed first and then computerized test was given about 30 min later. Before both tests, the orientation task was taken by each person. The paper-based test consisted of 406 total symbols containing 61 vowel symbols which should be selected. On the other hand, there were 351 total symbols and 64 vowel symbols on the computerized test. Therefore, in order to equally compare both results, we treated the percentage of the number of symbols selected correctly to the total number of correct symbols as a score.

5. Results and discussion

Computerized neuropsychological tests have already been developed and their usefulness has also been reported [8–10]. The major advantages of computerized tests are said to be precision, speed and reliability. We believe our system also presented these advantages. The system provides speedy and precise procedure. Also it keeps a time limit and marks answers more precisely than by human checking. It took about 30 min for one examiner to mark 55 sheets in the event, but the system could present the result as soon as a test was finished. Results were not only shown on the display but were stored on the hard disk, so it was easy to use the results for statistical analysis afterwards. An important consideration in designing a computerized system is the user-computer interface because most of the aged persons seem to be threatened by the novelty of new technology [11]. We intended to design the system to be applied not only for mass screening but also for self-administration. In this study, all subjects could use the system by interacting with the computer and this means that our aim has been achieved. The program is available in Japanese and in the form of CD-ROM for wide distribution and application, for example, for the preliminary examination at the hospital or for the health examination held by public organization. Moreover we think to put the system at the public place, for instance, the lobby in the city hall or community health center and expect that visitors will use it freely and check their own cognitive status.

The methodology of the Kana Pick-out Test can be applied to languages other than Japanese with or without modification. There may be no further modification in syllabic languages like Cherokee for example. In the case of alphabetic languages such as English, on the other hand, some modifications are required to apply the test. Some words like pronouns, articles and prepositions are suggested to be used instead of vowel symbols.

Almost all subjects got a higher score on the computerized test than on the paper-based test and the mean scores were 77 and 58%, respectively, for computerized and paper-based tests. We think the reason is that the computerized test was done after the paper-based test; therefore subjects seemed to become more accustomed to the testing procedure in the later test. Fig. 5 shows the relationship between the results obtained from

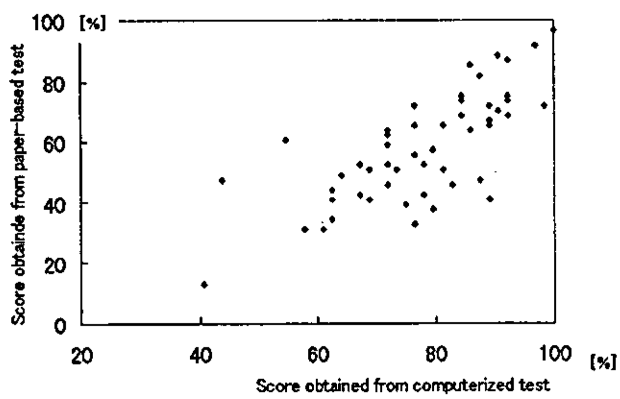

Fig. 5. Relationship between the results obtained from the paper-based test and the computerized test. A coefficient of correlation of 0.76 ($P < 0.01$) was obtained.

both tests and a coefficient of correlation of 0.76 ($P < 0.01$) was obtained. The tendency is that the person who got a high score on the computerized test also got a high score on the paper-based test and vice versa. It means the system seems to have the capability of detecting the cognitive status as equal as the paper-based test.

The criteria assessing the score on the paper-based test has already been established [12]. That is, the cut-off score to classify normal and suspected persons has been decided for the age groups within the same decade. At the present time we do not have enough data to establish a criteria for the computerized test, therefore, as a first step we adopt the cut-off score of paper-based test for the computerized test as follows; 50% for twenties, 46% for thirties, 36% for forties, 26% for fifties, 20% for sixties, 15% for seventies and eighties, respectively. In addition to the score, we have to consider the number of correct answers to the questions of substance of the story. In this computerized test, there were 26 people whose score were 80% or more, but 6 people among them answered merely four or less out of six questions correctly. We do not treat these 26 people as the same cognitive status. Following the criteria of the paper-based test, we regard each fails of the questions as a score of minus 5%. We think further investigation is required to build better criteria for the computerized test.

Nowadays the internet has become available and many homepages offer information concerning health care and medicine. Though these pages are enlightening and educational, the page must also provide information tailored at each user in order to make it more attractive. For example we have developed a network-based Kana Pick-out game. It is just a game and not an automated diagnosis program, but we think it can inspire a user to be more attentive and improve their motivation.

The Kana Pick-out Test is not perfect. Therefore, we have to use it as one type of neuropsychological tests and combine it with other tests for the medical diagnosis. However, we are sure that the system can produce a more precise and rapid examination and enable medical staff to adopt a more personal role in test sessions and to devote more attention to clinical observation.

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Heavy metal analysis of groundwater from Warri, Nigeria

DAVID A. AREMU[1]*, JOSHUA F. OLAWUYI[2], SHUNSUKE MESHITSUKA[1], MYNEPALLI K. SRIDHAR[2] and PAUL A. OLUWANDE[2]

[1]*Department of Medical Environmentology, Tottori University Faculty of Medicine, 86 Nishi-machi, Yonago, 683–8503, Japan,* [2]*Division of Environmental Health, College of Medicine, University of Ibadan, Ibadan, Nigeria*

The levels of some ions of heavy metals known to be associated with petroleum industry operations, including Pb, Ni, V, Cr, Cd, Zn and Fe, were studied in untreated groundwater from Warri area, Nigeria, by atomic absorption spectroscopy. Warri area is characterized by petroleum industry activities including a Refinery. With this in mind, the residential area was divided into Effurun junction, Waterside, Ekpan village and the Refinery's vicinity. The concentrations of Pb, Ni and Fe measured (in mg l^{-1}) in the groundwater samples of all areas studied ranged from 0.06 to 0.44, 0.008 to 0.19 and 0.315 to 2.753 respectively, while V, Cr, Zn and Cd were present in very low concentrations, 0–0.85×10^{-3}. The levels of Pb, Ni and Fe exceeded the threshold limits (0.01, 0.02 and 0.3 mg l^{-1}, respectively) set by the WHO health-based guideline for drinking water and this could portend environmental hazards.

Introduction

Water pollution by heavy metals resulting from anthropogenic impact is causing serious ecological problems in many parts of the world (Chapman and Kimstach 1992, Van Oostdam *et al.* 1999). This situation is aggravated by the lack of natural elimination processes for metals. As a result, metals shift from one compartment within the aquatic environment to another, including the biota. These metals are concentrated by the food chain and pose the greatest danger to organisms near the top of the chain (Peavy *et al.* 1985, Kotze *et al.* 1999, Van Oostdam *et al.* 1999). A similar experience is the Minamata mercury poisoning episode in Japan (Nitta 1970). In the case of groundwater, the volume and location reduce the contaminant's dilution factor and thereby further compound the problems of pollution.

The ability of a water body to support aquatic life as well as its suitability for other uses, however, depends on many trace elements. Some metals, e.g., Mn, Zn and Cu, present in trace concentrations are important for the physiological functions of living tissue and regulate many biochemical process. The same metals, however, discharged into natural waters at increased concentrations in sewage, industrial effluent or from mining operations, can have severe toxicological effects on humans and aquatic ecosystems. Toxic metals on the other hand are harmful to human and other organisms even in small quantities. Cumulative toxins such as

Correspondence: David A. Aremu, Department of Medical Environmentology, Tottori University Faculty of Medicine, 86 Nishi-machi, Yonago, 683–8503, Japan. Tel.: +81-859-34-8285; Fax: +81-859-34-8068; E-mail: aremuda@grape.med.tottori-u.ac.jp

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arsenic, cadmium, lead and mercury, are particularly hazardous (Peavy *et al.* 1885, Zadorozhnaja *et al.* 2000).

Generally, trace amounts of metals usually found in freshwater are from the weathering of rocks and soils. However, significant concentration in water can usually be traced to mining, industrial, or agricultural sources (Chapman and Kimstach 1992). Vanadium, Ni, Fe and Cu are the most significant among abundant metals in crude oil (Sychra *et al.* 1981, Olajire and Oderinde 1993, Asuquo *et al.* 1995, Sasaki *et al.* 1998). Pollutants in produced water of drilling operations include Pb, Cr, Ni, Zn and Cd among others. Refinery oil waste, on the other hand, contains a range of metals such as V, Pb, Zn and Cu (Shailubhai 1986). Discharge of such waste into freshwater environments could, apart from being deleterious to aquatic organisms, ultimately leach to the groundwater. This is highly probable since dynamic equilibrium maintained by gravity and capillarity exists between the surface waters and groundwater within the land (Trett 1989). Unfortunately, Warri River according to Osibanjo *et al.* (1988) is among rivers grossly polluted by oil and organic pollutants. This is because the River receives discharges from all sorts of petroleum industry operations. Refinery effluent in Warri has also been reported not to satisfy European and USA effluent standards and have polluted adjacent soils and receiving water bodies including bottom sediments with oil (Osibanjo *et al.* 1988).

This work reports the levels of V, Pb, Fe, Ni, Cr, Cd and Zn in untreated groundwater from 22 hand-dug wells in four different locations in Warri. This was with the view to generating baseline data for future work in an area that is growing rapidly in population and petroleum industry activities.

Materials and method

The present work was carried out in 1997, and Warri was divided into four areas, Effurun junction (an area presumed to be relatively far from petroleum activities), Waterside (as the name implies, the area is very near to Warri River), Ekpan village (an area within 3 km radius from the refinery) and the Refinery's vicinity (an area within 200 m radius from the refinery's premises.

Cross-sectional samples of raw groundwater from hand-dug wells were collected for analyses in the month of June (rainy season). The samples were acidified to a $pH < 2$ to minimize the adsorption of the trace metals to the inner surfaces of the containers. To avoid contamination during sampling and sample preparation, all bottles, beakers and other laboratory tools were pre-washed thoroughly in distilled water, soaked with 0.1 N HCl, then washed again with deionized–distilled water in a similar manner to that described by Sabri *et al.* (1993).

To digest a sample, a suitable volume (100 ml) was transferred to a beaker. Five ml of concentrated HNO_3 were added and the sample evaporated on a hot plate to the lowest volume possible (about 15–20 ml) before precipitation or salting out occurs. Another 5 ml of concentrated HNO_3 were added to the sample and a gentle re-fluxing carried out by covering the beaker with a watch glass. Heating and addition of concentrated HNO_3 continued until sample was light colored. One to 2 ml of concentrated HNO_3 were added to dissolve the residue on the wall of the beaker. The beaker walls and watch glass were thereafter washed down with deionized–distilled water. Digested sample was filtered and made up to 50 ml. A blank sample (deionized–distilled water) was treated to the same procedure. The digested sample was then analyzed using atomic absorption spectrophotometry (AGW-AES model 200A by Analysengerate GMbH, Germany). Checks on contamination and instrument accuracy, using standard solutions, were carried out prior to sample analysis in a similar manner to that described by

Abaychi and Douabul (1985). Wilcoxon two-sample test, a non-parametric test for asymmetrically distributed data like water quality data sets (Demayo and Steel 1992), was employed to test for any significant difference between two groups of samples.

Results and discussion

The summary statistics of the concentrations of metal ions in the groundwater samples from different locations in Warri is presented in Table 1 as minimum, median and maximum values as well as range. Figure 1, on the other hand, compares the mean concentrations of the metal ions in the samples from different locations of the study area. The Refinery's vicinity recorded the highest mean value of 1.13 mg l^{-1} for Fe while that of Pb, 0.29 mg l^{-1}, was from samples from Waterside. The highest mean value of Ni on the other hand was from Effurun junction, 0.15 mg l^{-1}. The mean values of V, Cr, Cd and Zn were generally low during the present study. However, the highest mean values of Cr and Cd were from the Refinery's vicinity with 3.3×10^{-6} mg l^{-1} and 5.2×10^{-4}, respectively. The highest mean values of V (1.4×10^{-8}) and Zn (5.1×10^{-4}), on the other hand, were from Waterside. Although, the concentrations of these metals are considerably low, the Refinery's vicinity and Waterside recorded the worst values, followed by Ekpan Village.

The recorded levels of Fe, Pb, and Ni in the groundwater of Warri were generally high. The concentrations of Fe in all wells from all locations in the study area were higher than the 0.3-mg l^{-1} WHO (1996) guideline for aesthetic purposes. A sample from the Refinery's vicinity was as high as 2.75 mg l^{-1}. The concentrations of Pb and Ni were also generally higher than the guidelines of WHO for drinking water, which are, respectively, 0.01 and 0.02 mg l^{-1} (WHO 1996). It is alarming to note that the levels of Pb in the study area are even higher than the maximum allowable concentration of 0.05 mg l^{-1} proposed by Alloway and Ayres (1993) without any exception. With the exception of a sample from Ekpan Village, all the samples studied exceeded the 0.02-mg l^{-1} provisional health guideline for Ni (WHO 1996) and this calls for a serious concern. The concentrations of Cr, Cd, Zn and V, on the other hand, were generally lower than the WHO (1996) guidelines for drinking water which are, respectively, 0.05. 0.003 and 3 mg l^{-1}, an exception is V, which as yet has no guideline value. Nevertheless, the values of V in this study fell within the range quoted for fresh water by Alloway and Ayres (1993), that is 0.01–20 ng m^{-3} (i.e., 1.0×10^{-8} to 2.0×10^{-5} mg l^{-1}). It is interesting, however, to note that Zn, which is an essential trace element (Parisic and Vallee 1969, Krachler *et al.* 1999), falls seriously short of the recommended value. Moreover, the Zn/Cd ratio in the present study does not correlate with other findings (Barcellos and Lacerda 1994, Jensen *et al.* 1999).

Thus, with the exception of Fe, Pb and Ni during the month of June, almost all other values recorded in the present study were lower than the maximum allowable limits set by the WHO standard for drinking water. Although, the fact that the values of all the metals were generally higher at Waterside and Refinery's vicinity seems to suggest that the refinery and Warri river might be possible sources of these metals, the present study is not enough to implicate them, the more so because most of the metals were below the prescribed levels. However, in a similar work by Nikumbh *et al.* (1998), higher concentrations of metals in excess of prescribed limits, like those of Fe, Pb and Ni, have been attributed to occurrence of anthropogenic origin rather than geochemical sources. Although these metals in the present study are known to be associated with petroleum industry operations (Sychra *et al.* 1981, Shailubhai 1986, Olajire and Oderinde 1993, Asuquo *et al.* 1995, Sasaki *et al.* 1998) that are unrestrained in this area, there were no significant differences between samples from Effurun junction and Ekpan village and Refinery's

Table 1. Summary statistics of the concentrations of metal ions in the groundwater samples from Warri. The minimum, median and maximum values as well as the range were used to report the parameters studied from four different locations in Warri

Characteristics	*Effurun Junction*	*Ekpan Village*	*Waterside*	*Refinery's Vicinity*
Iron (Fe) (mg l^{-1})				
Minimum	0.375	0.383	0.335	0.315
Median	0.393	0.901	0.658	1.04
Maximum	0.525	2.068	1.32	2.753
Range	0.15	1.685	0.985	2.44
Lead (Pb) (mg l^{-1})				
Minimum	0.158	0.105	0.155	0.058
Median	0.19	0.241	0.305	0.265
Maximum	0.293	0.443	0.39	0.363
Range	0.135	0.338	0.235	0.305
Nickel (Ni) (mg l^{1})				
Minimum	0.098	0.008	0.093	0.023
Median	0.178	0.1	0.138	0.088
Maximum	0.178	0.188	0.178	0.128
Range	0.08	0.18	0.085	0.105
Vanadium (V) (mg $l^{-1} \times 10^{-8}$)				
Minimum	0.5	0	0	0
Median	0.5	1.5	1.5	0.75
Maximum	2	2.5	3.5	4
Range	1.5	2.5	3.5	4
Chromium (Cr) (mg $l^{-1} \times 10^{-6}$)				
Minimum	0	0	0	0
Median	0.5	1.5	1	0.75
Maximum	0.5	9	1.75	1.9
Range	0.5	9	1.75	1.9
Cadmium (Cd) (mg $l^{-1} \times 10^{-4}$)				
Minimum	3.5	0.75	1.5	1.7
Median	4.5	3.5	3.5	6
Maximum	4.5	7	8	8.5
Range	1	6.25	6.5	7
Zinc (Zn) (mg $l^{-1} \times 10^{-4}$)				
Minimum	0	0	0	0
Median	0.5	0.2	0.05	0.4
Maximum	0.5	0.5	1.8	0.75
Range	0.5	0.5	1.8	0.75

vicinity on one hand, and Waterside on the other. Therefore, the present observation is more likely to be due to the geological nature of the catchment area (Sabri *et al.* 1993, Robson and Neal 1997, Sadiq and Alarm 1997). However, in view of the fact that the levels of these metals could portend serious environmental hazards, and the uncertainty that surrounds their possible sources in the present study, it is imperative to establish their source(s) in subsequent investigations. A comparative study of an area which falls within the same ecological zone but

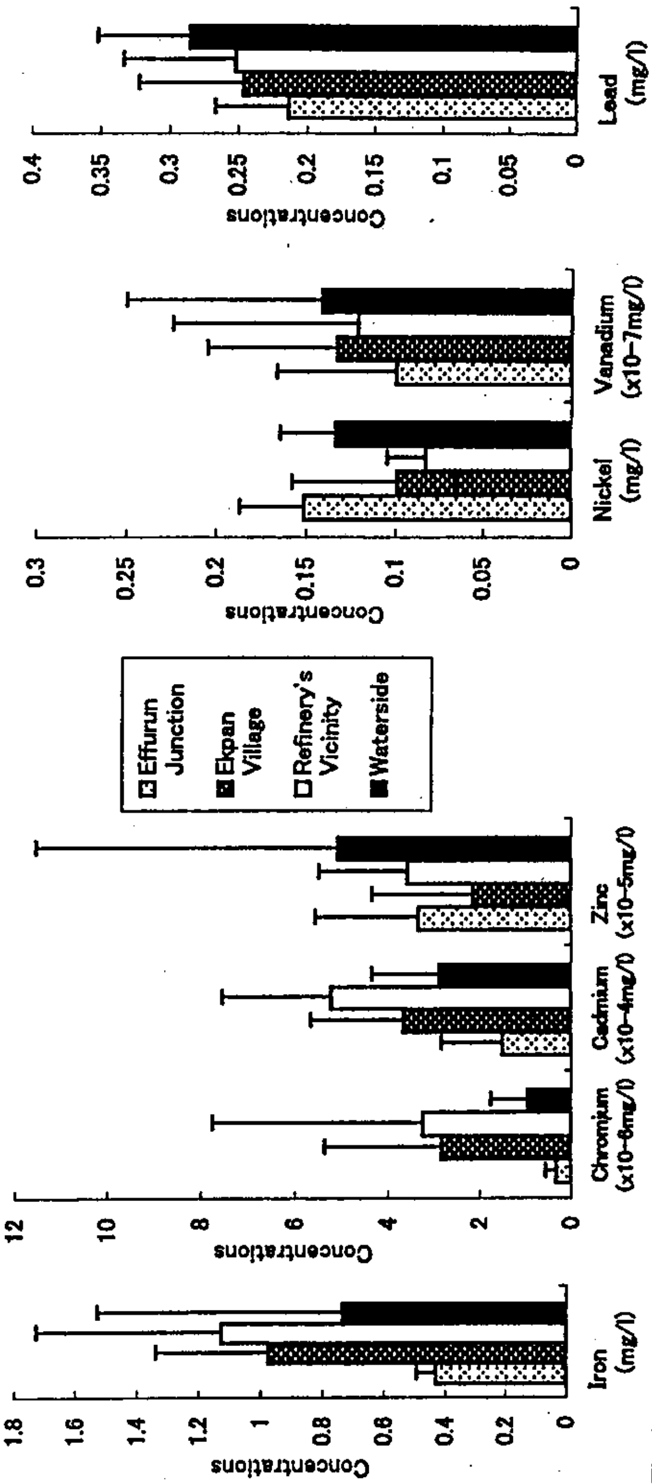

Fig. 1. Comparisons of the concentrations of metal ions in the groundwater from different locations in Warri. The mean concentrations ± SE of the metal ions in the groundwater from different locations in Warri were used to plot the histogram. The grouping of the metals was to ensure evenness in the height of the bars. Vanadium, Cr, Cd, and Zn occurred in very low concentrations while Fe, Pb and Ni occurred in high concentrations. There was no significant difference between any two locations using Wilcoxon two-sample test.

without similar petroleum industry activities should be carried out so as to check the trend if the metals are from anthropogenic sources. This will also allow an effective monitoring of the groundwater quality in an area with petroleum industry activities that has a rapidly growing population.

Conclusion

Apart from Fe, Pb and Ni, other metals reported in the present study are below the prescribed limits. However, the sources of the metals in higher concentrations are still uncertain, even though they are known to be associated with the petroleum industry operations rampant in this area. In view of the likely environmental hazards and effective monitoring, a comparative study is necessary to ascertain whether their sources are anthropogenic or geochemical. Nevertheless, the results here will serve as baseline data for future investigations.

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REVIEW

A Risk of Alzheimer's Disease and Aluminum in Drinking Water

Shunsuke Meshitsuka,[*1] **David A. Aremu,**[*1] **and Takayuki Nose**[*2]

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[*1]Division of Medical Environmentology, Department of Social Medicine, Tottori University Faculty of Medicine
[*2]Division of Health Administration and Promotion, Department of Social Medicine, Tottori University Faculty of Medicine

Reprint requests to Shunsuke Meshitsuka, Division of Medical Environmentology, Department of Social Medicine, Tottori University Faculty of Medicine, 86 Nishimachi, Yonago, Tottori 683-8503, JAPAN.

Key words: sporadic Alzheimer's disease, aluminum, drinking water, epidemiology

Abstract: The epidemiological studies on the relation between Alzheimer's disease and aluminum in drinking water are reviewed. In descriptive studies, case-control studies, and also cohort studies aluminum in drinking water turned out to be positive for the senile dementia of Alzheimer type. Negative results were obtained in the studies of presenile dementia or alminum levels lower than 0.1 mg/L. Aluminum is the third abundant element on earth, therefore, exposure to aluminum is inevitable in daily life. It is known that as over 95% of cases with Alzheimer's disease are sporadic, some environmental factors are expected to be etiological. Aluminum has been so far studied as a candidate for a neurotoxic factor. It is not known why attention has been given to only aluminum in drinking water as the cause of the neuro-degenerative disease other than aluminum in foods or medications, and how aluminum acts as a toxicant in brain. Nonetheless, reduction of aluminum in drinking water is recommended, as well as investigations on the mechanism of neurotoxicity of aluminum to find out the way to be free from the fear of aluminum.

Introduction

The formation of senile plaque from amyloid protein, the neurofibrillary change from phosphorylated tau protein in neurons, and the subsequent loss of neurons are the characteristic features in brains of Alzheimer's disease patients. Recently, it has been revealed that mutations of the amyloid precursor protein gene, presenilin 1 and presenilin 2 genes, and polymorphism of apolipoprotein E were related to Alzheimer's disease. The results of the genetic research give us the impression that the cause of Alzheimer's disease is clarified. However, these are the causes of familial Alzheimer's disease. The cause of sporadic Alzheimer's disease that accounts for 95% or more of the total Alzheimer's disease patients is not known yet. It is indisputable that aging is the most important factor because most of the sporadic Alzheimer's disease is diagnosed from the specific symptoms at the age of 65 or more. Because an inherited factor is not found at the present time, environmental factors are assumed to play an important role in the etiology of the sporadic Alzheimer's disease.[1,2]

A similar phenomenon to neurofibrillary change was seen when aluminum was administered to rabbit's brains.[3] In addition, because it was shown that aluminum was the cause of the dialysis encephalopathy,[4] the relation between senile dementia and aluminum was given attention. With such a background, it has become an important subject to clarify whether aluminum is a causative agent of Alzheimer's disease. The neurofibrillary change in the brain of the animal, to which aluminum was administered, was a single fiber formation, but that which was seen in Alzheimer's disease was a paired helical filament. Moreover, the neurofibrillary change in the brain of the patient of dialysis encephalopathy was different from that of Alzheimer's disease despite the aluminum accumulation.[5] The definite features related to Alzheimer's disease were not reproduced in a lot of animal experiments where the neurotoxicity of aluminum was reported.

In these circumstances, research effort directed at humans has been intended, thus, epidemiological investigations have been paid attention to. Epidemiology, established as a method for the research of infectious diseases, is applied to non-infectious diseases such as cancers and lifestyle-related diseases successfully. In addition, when geographic distribution of the patients corresponds to the polluted area, the patient who has a certain symptom has some relief being a certified patient with pollution-caused diseases. In pollution trials such as Minamata disease, Itaiitai disease, and Yokkaichi asthma, an epidemiological causal relation was adopted as evidence though a strict causal relation for each person could not be proven.

It is difficult to prove a causal relation in a strict sense for the materials abundant in the environment. There is ambiguity in estimating a small amount of polluted material in the environment going back in the past. A chronic disease caused by a long-term exposure of material such as aluminum in the environment is difficult to be studied in the animal experiment. From these points of view, epidemiological investigations of aluminum in the environment undertaken in some countries of the world are very valuable.

Methods of Epidemiology for Environmental Factors

It is necessary to recognize the advantages and the limitations of the methods of epidemiological studies to choose subjects and to analyze data. Epidemiological research is classified into three types.[6] The first is descriptive epidemiology, which is useful for clarifying the nature of subjects by the description of the collected data. The second is analytic epidemiology, which is divided into a case-control study and cohort study. The case-control study is subdivided into cross-sectional and longitudinal studies. In the cross-sectional study, analysis of the data of a complete survey in population, or the data of a random sampling is undertaken to clarify the feature of the case group and the control group. In the longitudinal study, the control group is matched based on the environmental conditions as much as possible with the case group, the effects of the environmental factors in the past on the persons who belong to each group are analyzed (retrospective study). For example, the past exposure to an amount of aluminum as an environmental factor is presumed, the influence of aluminum on Alzheimer's disease can be obtained as an odds ratio which has a similar meaning to a relative risk. However, the weaknesses of a retrospective study include the arbitrariness in choosing the control group, and the limited reliability in the estimation of the amount of the exposure in the past.

Another method of analytic epidemiology is called a cohort study in which the same group is observed over a long period, and the relation of the item suspected as a factor of the disease is analyzed from the information on the incidence of and the death by the disease. A detailed investigation is executed from both sides of the health conditions and the environmental qualities in cooperation with the participants, who are examined regularly (prospective cohort study). The contraction of diseases and changes of environmental factors are recorded in detail. Occasionally, when there exists an item, which can be used in a cohort study set for other purposes, the data are analyzed in the process of going back in the past (retrospective cohort study). Because all the data have been collected in the past, it is not possible to change the content and the quality of the investigation, and this is a limitation in a retrospective cohort study. An area where there is limited movement of population is suitable for a cohort study.

The third method is called intervention study. The effect of intervention is determined for a group that was given a specific method of treatment or prevention and observed as a cohort, and the causal relation is proven. The cause of a disease can be associated with an environmental factor by analyzing the incidence and the death rate of the disease by comparing the cases with and without the environmental factor. It is necessary to receive the agreement and the cooperation of a lot of people. A definite result is obtained when an intervention study can be executed.

Epidemiological Studies of Aluminum and Alzheimer's Disease

A. Descriptive epidemiology

Vogt[7] and Flaten[8] reported that there is a geographic relation between the mortality rate with senile dementia and the concentration of aluminum in drinking water in Oslo in Norway. There was a methodological weak point in the estimation of the mortality rate of the people with senile dementia because they used the death record in their investigations. However, thereafter the contents of aluminum in drinking water was given attention. Frecker pointed out that the mortality rate of senile dementia was high in New Foundland in Canada, and aluminum in drinking water of this region was also high.[9]

B. Case-control study

So far, the case-control studies of the relation between aluminum in drinking water and Alzheimer's disease have been carried out in some regions of the world. These studies are classified by the methods of collection of the records of the patients of Alzheimer's disease such as the postmortem examination, the diagnosis when leaving the hospital, and the certificate of death. The reported investigations are summarized according to the districts and countries as follows.

1) Ontario (Canada)

Ontario is well suited for epidemiological study of this kind because drinking water is processed from geochemically diverse ground and surface sources overlying paleozoic sedimentary rock and glacial deposits in the south and the precambrian shield in the north, resulting in waters of widely different mineral content, and aluminum content of public drinking water supplies varies over a wide range, 4 to 203 μg/L.

Neri and Hewitt presented epidemiological evidence that may implicate aluminum in drinking water as an etiological factor in Alzheimer's disease.[10] All patients discharged from general hospitals in the Province of Ontario were obtained from Statistics Canada. In 1986, 2,344 patients aged 55 or over, who had a diagnosis of Alzheimer's disease or presenile dementia were matched by age and sex with patients with non-psychiatric diagnoses. Repeated admission of the same individual was eliminated. The members of each case/control pair were residents of a locality, for which reliable water quality data were available, including a measure of aluminum concentration in the finished water of the municipal supply system. The relative risk was estimated to be 1.46 in the patients who had water with aluminum levels higher than 0.20 mg/L, compared with those with levels of aluminum less than 0.01 mg/L.[10]

McLachlan et al. reported a possible relation between aluminum concentration in public drinking water and Alzheimer's disease on the basis of strict neuropathologic criteria.[11] The subjects consisted of 830 from whom tissue had been offered to the Canadian Brain Tissue Bank. Using the case/control odds ratio as an estimate of relative risk and aluminum concentration>0.1 mg/L as the cutoff point, elevated risks for histopathologically verified Alzheimer's disease were associated with higher aluminum concentration. Comparing all Alzheimer's disease cases with all controls, and using the aluminum concentration of public drinking water at last residence before death as the measure of exposure, the estimated relative risk associated with aluminum concentration>0.1 mg/L was 1.7 (95% CI: 1.2-2.5). Estimating aluminum exposure from a 10-year weighted residential history resulted in estimates of relative risk of 2.5 or greater.[11] It is noteworthy that the cases were selected by certified diagnosis of autopsy and the residence history of 10 years in the areas of the concentration of 0.1 mg/L or more of aluminum in water supply.

2) Quebec (Canada)

Gauthier et al. confirmed the association between aluminum exposure and Alzheimer's disease, estimating aluminum species and genetic characteristics.[12] The study participants were selected from a random sample of the elderly population (≥70 years of age) of one region of Quebec. Sixty-eight cases of Alzheimer's disease diagnosed according to recognized criteria were paired for age (±2 years) and sex with nondemented controls. Aluminum speciation was assessed using established standard analytical protocols along with quality control procedures. Exposure to Aluminum forms (total Al, total dissolved Al, monomeric organic Al, monomeric inorganic Al, polymeric Al, Al^{3+}, AlOH, AlF, $AlH_3SiO_4^{2+}$, $AlSO_4$) in drinking water was estimated by juxtaposing the subject's residential history with the physicochemical data of the municipalities. The markers of long-term exposure (1945 to onset) to aluminum forms in drinking water were not significantly associated with Alzheimer's disease. On the other hand, after adjustment for education level, presence of family cases, and ApoE ε4 allele, exposure to organic monomeric aluminum estimated at the onset of the disease was associated with Alzheimer's disease (odds ratio 2.67; 96% CI 1.04-6.90). On average, the exposure estimated at the onset had been stable for 44 years.[12] The important points of the Quebec study are that the participants were over 70 years old on account of the study of the senile dementia, a precise chemical speciation was carried out, and a long-term history of the exposure was estimated.

3) England

Martyn et al. reported that the risk of Alzheimer's disease was 1.5 times higher in districts where the mean aluminum concentration exceeded 0.11 mg/L than in districts where concentrations were less than 0.01 mg/L in a survey of 88 county districts within England and Wales.[13] Rates of Alzheimer's disease in people under the age of 70 years were estimated from the records of the computed tomographic (CT) scanning units. Aluminum concentrations in water over 10 years were obtained from water authorities and water companies. There was no evidence of a relation between other types of dementia, or epilepsy, and aluminum concentrations in water.[13]

Martyn et al. carried out a case-control study to explore further the relation of Alzheimer's disease to aluminum in drinking water in eight regions of England and Wales.[14] Subjects were identified from the records of neuroradiology centers, and diagnoses were confirmed by a review of hospital case-notes. Exposure to aluminum in drinking water was estimated from the residential history of 106 men with Alzheimer's disease, 99 men with other dementing illnesses, 226 men with brain cancer, and 441 men with other diseases of the nervous system. There was little association between Alzheimer's disease and higher aluminum in drinking water when cases were compared with any of the control groups. However, the subjects in this study were between 42 and 75 years of age.

In another related study, Foster et al. reported that no significant relationship between exposure to aluminum in water supplies, tea, and antacid was found.[15] A family history of dementia was confirmed as a risk factor in presenile dementia of the Alzheimer type. Cases were 109 patients clinically diagnosed to have presenile dementia of the Alzheimer type under 65 years old and 109 controls were matched for age and sex. In addition, Parkinson's disease, maternal age, medical history, and cigarette smoking were not significant.[15] It has been revealed that presenile dementia is caused mainly by inherited factors, therefore, dementia in less than 65 years old is expected to include patients with causes unrelated to environmental factors. Thus, the lack of association between dementia and level of aluminum in the two English studies above may be due to the inclusion of presenile cases in the study.

4) Swiss

Wettstein et al. suggested the aluminum concentration of drinking water is not an essential factor in the pathogenesis of senile dementia.[16] The residents who lived for over 15 years in districts with high (98 μg/L) or low (4 μg/L) aluminum concentrations in drinking water were evaluated in a population survey of 800 residents aged 81 to 85 by Mini Mental Status test.[16] It is thought that the pathogenesis of Alzheimer's disease could not be specified, since all kinds of dementia were included in this survey.

C. Cohort Study

1) Ontario longitudinal study on aging

Forbes et al. reported that men living in areas where drinking water aluminum concentrations were high, and fluoride concentrations were low were about three times more likely to have some form of mental impairment, compared with those living in areas where aluminum concentrations were relatively low and fluoride concentrations high (odds ratios of 1.00 and 0.37, respectively).[17] The subjects of this investigation were the remaining men (n=782) who were 76 years of age in the Ontario longitudinal study on aging, in which some 2,000 males were followed up for about 30 years.[17]

2) Paquid study

A prospective cohort study to investigate the effect of aluminum and silica in drinking water on the risk of dementia and Alzheimer's disease started in southeastern France in 1988 with an intermediate report in 1994.[18] The subjects of this study were 3,401 healthy people who lived at home at 65 years of age or older and were extracted from the electoral poll at random. There were 383 people who had died before the first examination of cognitive function and 320 people who had refused to participate in the follow-up investigation. Rondeau et al. reported the subsequent analysis of data (a total of eight year follow-up) of 2,698 subjects in the Paquid study.[19]

Prevalent and incident cases of dementia were detected by a two-step procedure. First, after the psychometric evaluation, the psychologist systematically completed a standardized questionnaire designed to classify the criteria of dementia. Second, subjects, who were positive for dementia, were examined by a senior neurologist who confirmed the diagnosis and applied the criteria for Alzheimer's disease or other type of dementia. Subjects were then re-evaluated with the same procedure as for the baseline screening 1, 3, 5, and 8 years after the initial visit to diagnose incident cases of dementia.

After investigation of the water distribution network, the samples were divided into 77 drinking water areas. Concentrations of aluminum, calcium and fluorine, and pH were measured. To evaluate the past exposure of the subjects, the history of the water distribution network over the previous 10 years was retraced.

A total of 253 incident cases of dementia (with 17 exposed to high levels of aluminum), including 182 Alzheimer's disease (with 13 exposed to high aluminum levels), were identified. The relative risk of dementia adjusted (a Cox proportional hazard model) for age, gender, educational level, place of residence, and wine consumption was 1.99 (95% CI: 1.20, 3.28) for subjects exposed to an aluminum concentration greater than 0.1 mg/L. This result was confirmed for Alzheimer's (adjusted relative risk=2.14, 95% CI: 1.21, 3.80). These findings support the hypothesis that a high concentration of aluminum in drinking water may be a risk factor for Alzheimer's disease. However, a dose-response relationship between aluminum and the risk of Alzheimer's disease was not observed.

Because a cohort study is a long-period observation of many people, the reliability of the investigation is high. However, 182 persons were diagnosed for the senile dementia of Alzheimer type, and number of patients who were exposed to aluminum at a high concentration was only 13. A cohort study of a larger scale is expected to confirm the relation between the risk of Alzheimer's disease and aluminum in drinking water.

Aluminum in Drinking Water and Concomitant Substances

WHO is recommending that the concentration of aluminum in drinking water should be less than 200 μg/L. In some countries including the United States the standard for the concentration of aluminum in drinking water is less than 200 μg/L. In Japan, 200 μg/L is also determined as the additional standard concentration without the obligation to measure every time. It has been pointed out that not only the concentration of total aluminum in drinking water, but also the concomitant substances influenced the absorption of aluminum through the intestinal tract. It is known that there is possibility of the absorption of aluminum to be disturbed by silicon. In the cohort investigation in France (Paquid study), the corrected relative risk of senile dementia in the people who used the drinking water, which contained silicon at a concentration of 11.25 mg/L or more was 0.74.[19)] It has been reported that absorption of aluminum by intestinal tract is affected also by fluoride ions.[17, 20)]

Chemical Species and Daily Intake of Aluminum

A long-term exposure of aluminum in a variety of chemical forms in drinking water in Quebec state of Canada has been mentioned earlier.[12)] The proportion of organic aluminum monomers in the original water of water supply was 36, 37, and 54% in the river, lake, and underground water, respectively. The aluminum ions bound to organic compounds may be absorbed easily by the living body. There are a lot of reports on the content of aluminum in foods. The dietary intake of aluminum is 5 to 10 mg/day.[21,22)] The daily intake of water is about 2 liters and the amount of aluminum in drinking water is only 10% or less, compared with a total dietary intake of aluminum. It is unlikely that aluminum in drinking water is a risk factor of the Alzheimer's disease based on this value alone. If however, aluminum in drinking water is absorbed easily, then it may serve as a risk factor of the Alzheimer's disease. The reason why only aluminum in drinking water could be seen as the cause of neurodegenerative disease is not clear so far. Advanced research of chemical speciation of aluminum such as the chemical species absorbed easily and chemical species accumulative in the brain after passing across the blood-brain barrier will be required.

Conclusion

The present survey of results of the epidemiological investigations concerning the relation between risk of Alzheimer's disease and aluminum in drinking water can be summarized as follows:

1) When the concentration of aluminum in drinking water is 100 μg/L or more, aluminum in drinking water is a risk factor for the senile dementia of Alzheimer type (WHO standard: 200 μg/L).
2) Alzheimer's disease of 65 years old or less are unrelated to aluminum in drinking water.
3) As for the chemical species of aluminum, the aluminum complexes with organic compounds are more probable risk factors.
4) Silicon and fluorine seem to have antagonistic effects on aluminum toxicity.

It has been shown that Alzheimer's disease of the presenile type is due to inherited factors, so there is no relation with aluminum in the water supply.[15)] Moreover, when cerebrovascular dementia is included in the epidemiological study of senile dementia, the relation to aluminum