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Long-term effects of defoliant exposure on brain atrophy progression in humans

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Highlights

- TCDD is the most toxic dioxin and a group 1 human carcinogen.
- The chronic effects of TCDD exposure on the nervous system are still controversial.
- We investigated the long-term effects of TCDD on the progression of brain atrophy.

Abstract

As the most toxic dioxin, 2,3,7,8-tetrachlorodibenzo-p-dioxin is classified as a group 1 human carcinogen. We investigated the long-term effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin exposure on the progression of brain atrophy in humans. We retrospectively selected 546 patients exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (exposed group) and 1353 patients not exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (control group). The patients in both groups underwent brain T1-weighted magnetic resonance imaging (MRI) twice. We divided the patients into two propensity score-matched groups, analyzed voxel-wise whole brain atrophy in the MRI images of each patient,

and compared the progression of brain atrophy between the two groups. The exposed group showed significant brain atrophy progression in the bilateral frontal and temporal lobes, compared with the control group. The ventrolateral prefrontal area in the frontal lobe and whole temporal lobe were the main atrophic regions in the exposed group, compared with the control group. The neurotoxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin can damage the brain, even in patients exposed to it over 40 years ago. Humans exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin should thus be evaluated for progression of brain atrophy.

Introduction

The United States Department of Defense has developed many tactical herbicides for use in military operations; these herbicides were used during the Vietnam War. Agents Green and Pink contained 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and were sprayed in Vietnam from 1961 to 1963. Agents Purple and Orange contained a mixture of two phenoxy herbicides: 2,4-dichlorophenoxyacetic acid and 2,4,5-T. Agent Purple was sprayed between 1962 and 1965, and Agent Orange was sprayed between 1965 and 1970 (Young and Cecil, 2011). All dioxins, including those found in Agent Orange and other herbicides, are not manufactured commercially but are formed as a byproduct in the synthesis of 2,4,5-trichlorophenol, which is a 2,4,5-T precursor. The formation of 2,4,5-trichlorophenol from tetrachlorobenzene is a hydrolysis reaction that is carried out under alkaline conditions at high temperatures and pressure. Increasing amounts of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) are formed when these conditions are not carefully controlled (Milnes, 1971). The mean TCDD concentration in Agent Orange was close to 13 ppm. Moreover, it is estimated that 366–1000 kg of TCDD was sprayed in Vietnam between 1961 and 1971 (Stellman et al., 2003). During the Vietnam War, which lasted from 1961 through March 1973, South Korea sent 312,853 soldiers to support the Republic of South Vietnam (Young and Cecil, 2011). It is assumed that many Korean Vietnam veterans were exposed to toxic tactical herbicides, including TCDD.

TCDD is the most toxic dioxin and is classified as a group 1 human carcinogen by the International Agency for Research on Cancer, with a toxic equivalency factor of 1, according to the World Health Organization (Van den Berg et al., 1998). The well-known early and mid-term symptoms of dioxin exposure are chloracne, porphyria, and transient hepatotoxicity (Bertazzi et al., 1998, Pelclová et al., 2006). Because the plasma half-life of TCDD is 8 years, TCDD exposure has long-term effects on the human body (Pelclova et al., 2009). Long-term epidemiological studies have demonstrated a strong link between TCDD exposure and certain types of diseases, such as atherosclerosis, hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, retinopathy, and cancers of the gastrointestinal, lymphatic, hematopoietic, soft tissue, and respiratory tract systems (Kim et al., 2003, Pelclova et al., 2009, Pelclová et al., 2006, Urban et al., 2007).

The effects of TCDD exposure on the nervous system are controversial. Several studies have expressed doubts that TCDD causes neurological damage because it does not penetrate well into nervous system tissue, despite its low molecular weight and highly lipophilic character (Pelclová et

al., 2006, Sweeney et al., 1993). Conversely, other studies have reported adverse neurological effects associated with TCDD exposure. Peripheral neuropathy after TCDD exposure has been reported in veterans of the Vietnam War (Kim et al., 2003), chemical workers (Klawans, 1987, Thömke et al., 1999), and accident victims (Bertazzi, 1991). The effects of TCDD exposure on the central nervous system are more contentious, especially regarding the brain. Abnormal findings associated with the brain have been detected, using single photon emission computed tomography (SPECT) and visual evoked potentials, long after exposure to TCDD (Pelclova et al., 2009, Pelclova et al., 2018, Urban et al., 2007). Abnormal symptoms associated with the brain have also been demonstrated using motor dysfunction tests (tremor and dystonia) (Goetz et al., 1994, Klawans, 1987) and neuropsychological examinations (psychomotor speed, attention, and memory) (Goetz et al., 1994, Pelclova et al., 2009, Pelclova et al., 2018, Urban et al., 2007).

Although there are many studies on the acute neurotoxicity of TCDD in humans and laboratory animals, studies on the long-term effects of TCDD exposure on the brain are limited. Previous studies on the long-term effects of TCDD are limited by the lack of a comparison group with serial data on the progressive effects on the brain. One study using brain MRI showed that TCDD exposure in adulthood, indicated by blood levels, is associated with low gray matter volume in the left fusiform gyrus and the left medial temporal pole (Vu et al., 2021). Another study using SPECT of the brain highlighted focal reduction of perfusion in various brain locations 50 years after TCDD exposure (Pelclova et al., 2018). This suggests that the neurotoxic effects might have occurred decades after the people were exposed to TCDD, since they had no prior diagnosis of any central or peripheral nervous system disease.

The chronic effects of TCDD exposure are non-specific and multifactorial. For TCDD to reach the brain, it must pass through the blood-brain barrier. The etiology of brain damage from TCDD exposure might be associated with blood-brain barrier disruption and vascular impairments (Hassoun et al., 2003, Urban et al., 2007). Investigations into the mechanisms of TCDD neurotoxicity have shown that TCDD exposure leads to oxidative stress and apoptosis in the brain (Filbrandt et al., 2004, Hassoun et al., 2000). Meanwhile, research has shown that brain atrophy progresses more rapidly with increasing age (Davatzikos et al., 2009) and that accelerated longitudinal atrophy in aging cortical gray matter in the brain is more vulnerable to oxidative stress because of its higher oxygen requirements relative to white matter (Kirkness, 2005). With these considerations in mind, we investigated the long-term effects of TCDD exposure on the progression of brain atrophy. Specifically, we examined whole brain atrophy in a defoliant-exposed group of Vietnam War veterans based on serial brain magnetic resonance (MR) images and compared the findings to those in a control-matched group.

Section snippets

Participants

This study retrospectively collected brain magnetic resonance imaging (MRI) data and reviewed the medical records of veterans who had been exposed to a defoliant during the Vietnam War and had undergone brain MRI between January 2007 and December 2017. The inclusion criteria were (i) participation in the Vietnam War for more than 100 days between July 1964 and March 1973 and registration with the Korea Veterans Health Service for exposure to the defoliant, (ii) underwent brain T1-weighted MRI …

Group characteristics

The mean ages at the first MRI examination of the exposed and control groups were 65.4 ± 4.7 and 65.6 ± 7.7 years, respectively. The mean intervals from the first to the second MRI examination in the exposed and control groups were 1175.0 ± 805.0 and 1193.3 ± 723.4 days, respectively. The average duration of service in the Vietnam War in the exposed group was 420.7 ± 181.6 days. The exposed group had a significantly higher prevalence of disease, including hypertension, atherosclerosis, and …

Discussion

This study investigated the long-term effects of defoliant exposure on the progression of whole brain atrophy. We found that defoliant exposure results in significant brain atrophy in both the frontal and temporal lobes. The long-term neurotoxic mechanisms of TCDD may consist of direct and indirect damage to the nervous tissue: direct damage to the brain neurons from TCDD neurotoxicity and indirect damage to the brain neurons from vascular impairment caused by the presence of hypertension, …

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Ethics approval

The local institutional review board approved the procedures and protocols of this study on March 17, 2020 (approval no. 2020–03–006). …

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

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Consent to participate

The institutional review board committee waived the requirement for informed consent because of the retrospective nature of the study. …

CRediT authorship contribution statement

Hyun Ah Lee: Conceptualization, Writing – original draft. **Dae Hyun Kim:** Conceptualization, Methodology, Formal analysis and Investigation, Writing – review and editing, Funding acquisition, Supervision, Resources. **Sohyun Kyeong:** Methodology, Resources. …

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2024, Journal of Hazardous Materials

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