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Original article

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Neuropsychological and positron emission tomography correlates in idiopathic environmental intolerances

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Objectives It has been hypothesized that people with subjective hypersensitivity to chemicals may indeed suffer from neuronal damage due to widely distributed environmental toxins and that such deficits of diagnostic importance can be demonstrated with the help of functional neuroimaging even in single cases. In this study, a small group of well-characterized patients with idiopathic environmental intolerance were examined in order to identify such changes.

Methods Twelve patients with idiopathic environmental intolerance were investigated neuropsychologically and underwent cerebral F-18 fluorodeoxyglucose (F-18 FDG) positron emission tomography (PET). The imaging results were compared with findings from 17 healthy controls.

Results Six patients showed deficits in verbal learning and memory, and three of them also had a reduced information processing speed. In the individual analyses, 11 patients showed normal cerebral glucose metabolism. In the group analysis of the patients, no areas with significantly reduced glucose metabolism could be found.

Conclusions No consistent pathological cognitive performance and functional imaging pattern was found. It appears premature to claim specific neuropsychological or neuroimaging findings characteristic of idiopathic environmental intolerance. Therefore cerebral F-18 FDG PET should not be used to corroborate or rule out suspected idiopathic environmental intolerance, a syndrome whose potential biological underpinnings still need to be clarified.

Key terms controlled study; multiple chemical sensitivity; neuroimaging; neuropsychological performance.

Many people in Western civilizations consider themselves intolerant to environmental chemicals, a phenomenon known as multiple chemical sensitivity or idiopathic environmental intolerance. Idiopathic environmental intolerance has been defined as an acquired condition with multiple recurrent symptoms that are connected with exposure to diverse environmental chemicals well tolerated by most people and that cannot be explained by any known medical, psychiatric, or psychological disorder (1). There is a high comorbidity with psychiatric disorders such as depression, anxiety, and somatoform disorders (2–8).

Patients typically report impaired memory and concentration along with a wide range of nonspecific multisystem complaints. Cognitive performance has been tested in several studies to address the question of whether idiopathic environmental intolerance is associated with cerebral dysfunction. In a review article, Bolla (9) points out that neuropsychological test results must be interpreted with caution, as they are highly sensitive but not specific. Verbal and visual memory impairment in multiple chemical sensitivity patients has been described in two studies by Fiedler and her co-workers (7, 8). Bolla (10) evaluated neurobehavioral

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functioning in chemically exposed patients with and without symptoms of multiple chemical sensitivity and did not find evidence of impaired cognitive functioning in patients with multiple chemical sensitivity. Simon and his co-workers (5) found the immediate recall of verbal material to be significantly reduced in patients with idiopathic environmental intolerance when they were compared with control patients suffering from chronic musculoskeletal injuries. After control for the effects of anxiety and depression, the differences were no longer apparent. Similar results were reported in a more recent study (11), which found that verbal memory was worse in persons with multiple chemical sensitivity than in asthmatics, but neither patient group differed significantly from healthy controls, and the patients with multiple chemical sensitivity accompanied by comorbid depression performed significantly worse on the verbal memory test relative to asthmatics and nondepressed patients with multiple chemical sensitivity. In the first European study on neuropsychological performance in multiple chemical sensitivity, Österberg and his co-workers (12) found only subtle deficits in a complex attention test taken by Swedes with multiple chemical sensitivity when they were compared with healthy controls, and they interpreted the findings as representing no sufficient evidence of brain impairment. However, as several studies described minor neuropsychological changes in association with multiple chemical sensitivity, they recommended that larger samples of patients be investigated.

Cullen (13) suggested that a history of defined (occupational) exposure to neurotoxic chemicals may be a risk factor for the development of multiple chemical sensitivity. A study using single photon emission computer tomography (SPECT) (14) claimed reductions in the regional blood flow predominantly in the dorsal frontal and parietal lobe of the right hemisphere of persons exposed to pesticides or solvents. In another study on people with alleged chronic solvent-induced encephalopathy, Fincher and his co-workers (15) described significant changes in regional cerebral blood flow. Callender and his co-workers (16) described SPECT and neuropsychological abnormalities in a heterogeneous group of workers with a clinical diagnosis of toxic encephalopathy, who had been exposed to pesticides, solvents, and diverse other toxic chemicals. These studies have been criticized for methodological reasons (17, 18). While there are case reports of SPECT or PET (positron emission tomography) abnormalities in patients with a clinical presentation of idiopathic environmental intolerance (19–21), there are no controlled studies demonstrating evidence for neurotoxic damage in these patients.

This study was an attempt to identify potential functional brain changes and neuropsychological abnormalities characterizing idiopathic environmental intolerance.

Study population and methods

Study population

We selected 12 persons, 7 women and 5 men aged 31 to 61 [mean 44 SD 11.1)] years, with idiopathic environmental intolerance according to the aforementioned definition (1) who attended a university-based outpatients' department for environmental medicine. Patients with unstable medical or psychiatric disease states, possible pregnancy, and age under 30 years were not included. The exclusion of unstable medical diseases was made after thorough physical and routine laboratory investigations, including patients' case histories taken by experienced internists at the outpatients' department of environmental medicine. The psychiatric examination was performed by experienced and trained psychiatrists (SB and CH) using the Structured Clinical Interview for DSM-IV (22).

The patients reported chronically impaired health with recurrent symptoms in multiple organ systems in response to low-dose chemical exposures. An average number of 12 (range 8–17) symptoms per patient was recorded. All of the patients suffered from subjective cognitive impairment (problems with concentration, memory, orientation, verbal fluency, anomia), along with diverse other complaints, including nausea, difficult breathing, itching of the skin and nasal mucosa, erubescence, headache, pain in different parts of the body, anxiety, cardiac arrhythmia, dizziness, a feeling of imminent fainting, regurgitation, burning of the tongue and eyes, paresthesia, lightheadedness, nervousness, flu-like symptoms, nasal congestion, cough, swelling of the face, gingival hemorrhage, bloody mucus, tremor, muscle weakness, fatigue, aggressivity, dyspepsia, diarrhea, dysphagia, paralysis, ringing in the ears, sweating, and problems with accommodation. All of the patients had been ill for several years (range 2–20 years). They showed typical illness behavior with frequent visits to the doctor, a self-concept of bodily weakness and health fears, and they had a health belief model typical of patients with idiopathic environmental intolerance, namely, being especially sensitive to environmental chemicals. However, several patients attributed their symptoms not only to chemicals, but also to other "environmental" influences, such as foods, smells, medication, alcoholic beverages, coffee, noise, crowded places, and general pollution of the environment. Of the 12 patients, 7 had been disabled for at least 1 year prior to the investigation; 2 of these received pension payments and 2 had applied for a pension due to incapacity to work. Only 5 patients were still working.

The control group for the F-18 fluorodeoxyglucose (F-18 FDG) PET examination consisted of 17 healthy persons (health professionals from our hospital and their

relatives), 9 women and 7 men aged 43 to 65 [mean 57 (SD 5.5)] years with no history of neurological and psychiatric disorders.

In the neuropsychological investigation, the results of the patients were compared with the normative values of the instruments.

Procedure

The neuropsychological test battery consisted of tests measuring global verbal intelligence [Mehrfachwahl-Wortschatztest (MWT-B) (23)], cognitive and psychomotor processing speed [Zahlen-Verbindungs-Test (ZVT) (24)], a test comparable to, but more reliable than, the Trail Making Test A, Digit Symbol Test [from the German version of the WAIS-II (25)], a selective attention [test "d2" (26)], and verbal learning and memory [CVLT (27), German version (28)]. The battery took about 50–60 minutes to complete and was carried out during the day between 1000 and 1500. The participants did not receive any instructions (eg, to refrain from consuming coffee) before the test day.

All of the patients and controls underwent cerebral positron emission tomography (PET) with F-18 FDG. Under standardized resting conditions, the patients received an injection of 370 MBq F-18 FDG. PET scans were started 30 minutes after the tracer application. A sequence of one frame of 10 minutes and two frames of 5 minutes was started and later combined into a single frame. Acquisitions were made in 3D mode with a total axial field of view of 15.5 cm.

An automated analysis of the individual F-18 FDG PET images (comparison with a normal database) was carried out using an established routine (3D-SSP, Neurostat, MI, USA) to detect significant abnormalities in individual cerebral glucose metabolism (29–31).

Further statistical analysis on a voxel-by-voxel basis was conducted using SPM99 (Wellcome Department of Cognitive Neurology, London, UK).

Data analysis

We used individual analyses and a group comparison between the controls and patients (2 sample t-test) to identify the brain regions with significant hypometabolism in the patient group.

Since there was no a priori hypothesis for possible abnormalities of the cerebral glucose metabolism in idiopathic environmental intolerance, changes in the whole brain were measured using a threshold of significance of $P \leq 0.05$ (corrected for multiple comparisons).

The study and its consent forms were approved by the local ethics committee. All of the participants had full capacity to give their informed consent, and they signed consent forms.

Results

Medical and psychiatric findings

The case histories of 10 patients revealed at least one medical disorder. Five patients had been diagnosed with chronic bronchitis, and several had asthma and conventional allergies (not against chemicals), in addition to other diagnoses (table 1).

For all but one patient at least one psychiatric diagnosis was made. The most frequent diagnoses were somatoform and mood disorders (table 1). The patients did not receive any treatment for their psychiatric conditions during the study.

In no case were medical or psychiatric disorders severe enough to justify exclusion from the study.

Neuropsychological testing

The mean (corrected for age and gender) z-scores and 95% confidence intervals (95% CI) indicated a tendency towards subtle verbal learning and memory deficits in the idiopathic environmental intolerance patient group. The results (z scores: normal range $-1 \leq z \leq +1$) of the whole group of patients are presented as means and 95% confidence intervals (95% CI) in table 2.

Table 1. Psychiatric and medical disorders in the patient group (N=12). (DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition)

Psychiatric disorders (DSM-IV)	Number of patients
Major depression episode	7 (2 partially, 2 fully remitted)
Dysthymia	2
Somatization disorder	7
Undifferentiated somatoform disorder	2
Pain disorder	1
Panic disorder with agoraphobia	2
Panic disorder without agoraphobia	1 (partially remitted)
Agoraphobia without panic disorder	1
Obsessive–compulsive disorder	1
Generalized anxiety disorder	1
Claustrophobia	1
Alcohol abuse	1 (fully remitted)
Benzodiazepine dependence	1 (fully remitted)
Benzodiazepine abuse	1 (fully remitted)
Avoidant personality disorder	1
Depressive personality disorder	1
Obsessive–compulsive personality disorder	1
Medical disorders	
Chronic bronchitis	5
Bronchial asthma	2
Degenerative diseases of the spine	5
Fibromyalgia	2
Atopic eczema	2
Conventional allergies (pollen, etc)	3
Contact allergy	1
Urticaria	1
Hypertension	2

Table 2. Neuropsychological test results for the group of patients with idiopathic environmental intolerances. [95% CI = 95% confidence interval, MWT-B = Mehrfachwahl-Wortschatz-Intelligenz-test (multiple choice vocabulary intelligence test), ZVT = Zahlen-Verbindungs-Test (figure connecting test), WAIS = Wechsler Adult Intelligence Scale, CVLT = California Verbal Learning Test)

Neuropsychological tests or subtests	Mean value (z score)	95% CI of the z score
MWT-B	0.43	-0.24–1.11
ZVT	-0.68	-1.32–-0.05
WAIS Digit Symbol	-0.20	-1.15–0.75
d2 quantity	-0.42	-1.08–0.25
d2 quality	0.54	0.004–1.08
d2 composite score	-0.17	-0.79–0.46
CVLT		
List A total	-1.76	-2.94–-0.57
Short delayed free recall	-1.00	-2.18–0.18
Short delayed cued recall	-1.33	-2.39–-0.27
Long delayed free recall	-1.08	-2.28–0.11
Long delayed cued recall	-1.50	-2.52–-0.47
Recognition hits	-1.25	-2.43–-0.06
Discriminability	-1.25	-2.27–-0.23

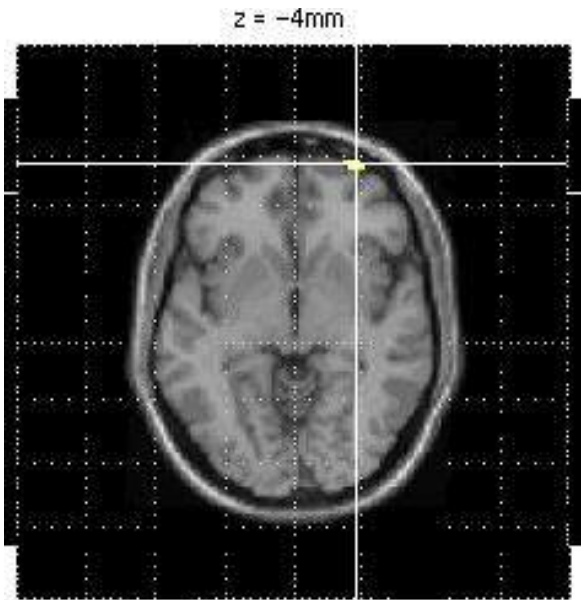

Figure 1. Group analysis of the F-18 FDG PET data of 12 patients with idiopathic environmental intolerance. The group analysis showed an area with a trend towards hypometabolism in the right superior frontal gyrus (Brodmann area 10), but without statistical significance (P_{corr}=0.08). (F-18 FDG = F-18 fluorodeoxyglucose, PET = cerebral positron emission tomography)

On closer examination, the distribution of the z-scores of the individual patients showed that four had completely normal test results. Six patients showed marked deficits in verbal learning and memory (acquisition, free recall and recognition). Three of them also showed a reduced speed of information processing. Two patients had a reduction in their processing speed only.

F-18 FDG PET of the brain

Individual findings of the PET scans revealed normal cerebral glucose metabolism in 11 of 12 patients. One 32-year-old man showed an nonhomogeneous pattern and mild hypometabolism in the posterior temporal and occipital regions on both sides, insufficient to suggest a specific diagnosis. Individual and group analyses of the controls showed a normal metabolic pattern. A group analysis of the 12 patients with idiopathic environmental intolerance versus the controls did not show any significant differences in glucose metabolism. Only one small area in the right superior frontal gyrus (Brodmann area 10) showed a trend towards hypometabolism (P_{corr}=0.08) (figure 1).

Discussion

To our knowledge, this is the first controlled study that combines neuropsychological testing of cognitive performance with brain PET assessment in patients with idiopathic environmental intolerance.

The patients reported a variety of multisystem complaints occurring in response to low-level exposure to chemicals. However, at least some of the symptoms may also be explained by diseases of the respiratory system, such as chronic bronchitis, asthma, and traditional allergies. Irritating chemicals would then, at best, serve as triggers of symptoms of an underlying airway disease. However, most of the complaints in the patient group concerned various other organ systems and did not correspond with the diagnosed medical diseases.

All of the patients complained of impaired concentration and memory, but not everyone had subnormal test results. Objectively, verbal learning and memory was slightly impaired in several patients with idiopathic environmental intolerance, and this impairment accounted for the subnormal results of the group as a whole.

It can be discussed whether this objective cognitive impairment can be interpreted as an early sign of beginning neurodegeneration. Most neurodegenerative diseases occur later in life, and our patients were only about 40 years of age. Still one might argue that, in vulnerable persons, neuronal damage (induced by chemicals) may appear earlier. However, as has already been mentioned, evidence for neurotoxic damage in patients with idiopathic environmental intolerance has not been demonstrated to date.

An alternative explanation could be that the reduced cognitive performance observed was functional and reversible. Depressed persons typically show a reversible pattern of cognitive deficits characterized by difficulties in attention and concentration, executive function, and immediate memory or memory encoding (32). In a

Finnish study, somatizing patients showed reduced neuropsychological performance with regard to attentional processing, semantic memory, verbal episodic memory and visuospatial tasks (33); these findings correspond to our findings with respect to idiopathic environmental intolerance. Due to the large proportion of patients with idiopathic environmental intolerance satisfying the diagnostic criteria of somatoform disorders (34), and the overlap of the latter and idiopathic environmental intolerance with regard to symptom profiles and psychological features, it has been argued that idiopathic environmental intolerance itself can be interpreted as a somatoform disorder (35, 36). Memory deficits in both conditions can be plausibly explained by the fact that these patients are often preoccupied by their bodily sensations, by which their attention is distracted. This possibility has also been identified as a cause of memory impairment in normal aging (37).

A third alternative may be that the reduced cognitive performances in our patient group were a result of other medical conditions. The most prevalent were chronic bronchitis, atopic diseases (allergy, asthma, eczema), degenerative diseases of the spine, and pain syndromes. There is little information in the literature about the possible effects of chronic bronchitis and atopic diseases on cognitive performance. van Boxtel and his colleagues (38) found that somatic morbidity as a whole contributes only modestly to the total variance in cognitive function in elderly people. However, they observed a negative association between chronic bronchitis and cognitive performance speed. There are several reports on the impairment of attention, processing speed, psychomotor speed, and working memory in patients with chronic pain (39–41). Patients with rheumatoid arthritis have shown reduced performance in tests of visuospatial ability (42). For patients with chronic fatigue syndrome, reduced attentional capacity, information processing speed, verbal learning, and memory have been described (43, 44).

Cognitive deficits in chronic illness can be either due to the disease process itself or to comorbid depression or medication, or they may reflect the patients' preoccupation with symptoms and health-related concerns.

If the neuropsychological deficits of our idiopathic environmental intolerance patients were due to neurodegeneration, the latter would have probably been detected in the brain F-18 FDG PET scans. Only one patient showed PET abnormalities; the abnormalities were not typical of any specific disorder, however. The group comparison revealed no significant differences, and this finding is a strong argument against the neurodegeneration hypothesis. This conclusion is in contrast to that of a few publications claiming brain SPECT abnormalities suggestive of neurotoxic effects in patients with chemical sensitivity (20, 21). Heuser & Wu (19) found hypometabolism in cortical structures and hypermetabolism in subcortical regions; they associated these findings with the theory of limbic kindling (45). These previous studies have been criticized because of the unwarranted interpretation of highly nonspecific findings as signs of neurotoxic damage (46). In a recent PET activation study the baseline regional cerebral blood flow of patients with multiple chemical sensitivity was normal (47).

Transient hypometabolism, particularly in the left frontal lobe, linked with a perceived decline of cognitive performance, has been observed in patients with depression, but also in normal sadness (48). Mayberg (49) has given a description of abnormal PET findings that can be observed during depressive episodes. Like functional cognitive deficits, functional brain changes have not only been described in psychiatric disorders with an organic or "endogenous" origin, but also in conditions perceived as "psychogenic", such as somatization disorder. Hypoperfusion in several brain regions (cerebellum, temporoparietal, frontal, and prefrontal areas), predominantly in the nondominant hemisphere, was demonstrated in SPECT imaging of 11 patients with somatization disorder (50). A F-18 FDG PET study of 10 female patients with severe somatization revealed reductions in glucose metabolism in the caudate nuclei on both sides, in the left putamen, and the right precentral gyrus (51). In 12 out of 26 patients with chronic fatigue syndrome, a condition closely related to both somatization disorder and idiopathic environmental intolerance (studied with F-18 FDG PET), bilateral hypometabolism in the cingulate gyrus, and adjacent mesial cortical areas, in some patients additional decreases in the orbitofrontal or frontobasal cortex could be demonstrated (52). Our results do not parallel these findings, although this outcome might have been expected under the assumption held by some researchers that idiopathic environmental intolerance is a somatoform disorder with symptom attribution to the environment.

In summary, our study argues against degenerative brain processes or structural neurotoxic damage in association with idiopathic environmental intolerance. No specific pathological cognitive performance and functional imaging pattern was found. The neuropsychological deficits in idiopathic environmental intolerance patients found in this study are nonspecific and similar to findings described for patients with chronic medical illnesses such as chronic bronchitis and allergy, chronic pain, and other states of illness with medically unexplained symptoms. Even if subtle deviations in cerebral glucose metabolism had been detected, it would not argue against the hypothesis that idiopathic environmental intolerance may be a variant of somatoform disorders. The study by Bailer and his co-workers (53) provides support for this hypothesis, as cases of idiopathic environmental intolerance and somatoform disorders were

shown to overlap, not only in regard to symptoms, but also with respect to certain behavioral and psychological features characteristic of somatization, such as somatic attribution of symptoms, negative affectivity, trait anxiety, a self-concept of bodily weakness, and heightened vigilance toward bodily sensations. The results of our study are also in line with more complex explanatory models of idiopathic environmental intolerance that propose that it could be the result of an interaction between environmental influences, individual predispositions, such as an organic disease and personality traits, psychological influences, and cognitive processes (36, 53).

The absence of clear neuropsychological and neuroimaging findings seriously calls into question the validity of the "diagnosis" idiopathic environmental intolerance as reflecting a real and consistent neurobiological entity. If it really exists, functional neuroimaging does not appear to be a suitable instrument for diagnosing it. However, if idiopathic environmental intolerance is conceptualized as a state of illness with definable neurobehavioral, neurophysiological, and cognitive characteristics (54), as suggested by recent research, it could possibly be subsumed as an entity under the category "functional somatic symptoms and syndromes", which has been proposed as a new classification of the disorders currently referred to as somatoform (55).

This study has some limitations. First, the F-18 FDG PET control group was about 13 years older than our patients. The given age difference between the groups should be taken into consideration in the interpretation of our findings. However, age-related changes in cerebral glucose metabolism would not be expected to occur in exactly the same brain regions in which patients with idiopathic environmental intolerance possibly exhibit abnormalities. Therefore, it appears improbable that the absence of significant differences in the group comparison was due to a leveling of the same pattern of changes resulting from ageing in the control group or from unexplained pathological physiology taking place in the patients with idiopathic environmental intolerance.

Second, the validity of our study was limited by the small sample size. Before further conclusions are drawn, larger patient samples ought to be investigated.

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