



Chronic Environmental exposure to *Alternaria tenuis* may manifest symptoms of neuropsychological illnesses: A study of 12 Cases.

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ABSTRACT: Toxicogenic mold exposures are shown to lead to illnesses most of which are just being unraveled. This paper reports the findings in cases of 12 white female office workers who presented with symptoms of neuropsychological illnesses, most likely, due to indoor environmental toxicogenic mold exposures. Their major complaints were: weakness and numbness in legs, dizziness, loss of memory, light-headedness and vertigo, fatigue, getting lost in familiar territory, and confused thoughts. The subjects were evaluated by testing immunologic, basic EEG, and comprehensive neuropsychological tests. Abnormal antibodies to *Alternaria tenuis*, *Pullularia pullulans*, and *Epicoccum nigrum* antigens were found in all the subjects' serum, and they were quite different from the abnormal levels of *Aspergillus*, *Stachybotrys*, and *Penicillium*, *Cladospirium* genera found in their indoor environment. EEG examination was abnormal all the subjects with 10 Hz posterior dominant activities in 6 out of 12, which were synchronous, symmetrical and attenuated on eye opening and eye-closure. There was an evidence of tremor of the extremities in 3 subjects. These particular subjects' reflex was abnormal, and they had accommodation paresis. Gross neuropsychological abnormalities including those observed in the brain-damaged population and significantly below non-brain damaged functioning was observed. These findings seem to indicate that chronic exposures to *Alternaria tenuis*, *Pullularia pullulans*, and *Epicoccum nigrum* might have neuropsychological effects, and that most likely, only one abnormal antibody to toxicogenic mold antigen could have the most dominant adverse toxic exertion leading to the observed neuropsychological effects. It is concluded therefore, that chronic exposures to certain toxicogenic molds might lead to neuropsychological manifestations and that although, it is acknowledged that the contaminations of the indoor environment by toxicogenic molds are directly related to the adverse health effects on the occupants, there could be a situation where such relationship does not exist. @JASEM

Indoor environmental air quality has taken a center stage in public health discussions to which chronic exposures to toxicogenic molds share greater concerns than other indoor environmental contaminants. Hence, there is increasing evidence of health risks associated with damp buildings and homes in which high levels of toxicogenic molds are found to grow. Pieces of evidence are also accumulating that support the views that certain toxicogenic molds are particularly a risk factor for adverse human health through exposure and inhalation of fungal spores (Jarvis, 2002). Several residential homes are contaminated by these toxicogenic molds consequent upon which illnesses such as pulmonary hemosiderosis in infants have been reported (Jarvis et al., 1996; Flappan et al., 1999). It is also believed that such illnesses are due, at least in greater part, to the mycotoxins produced by the toxicogenic molds. Although, the extent to which mycotoxins affect the human health is still emerging, certain mold mycotoxins could be contributory to a significant number of neuropsychological illnesses than one would have imagined.

For infants, the elderly, and persons living or working in "at high risk" urban areas the occurrence of illnesses due to toxicogenic mold exposures may be high, depending on the type of mold and the individual health variations. However, what makes a

full understanding of the processes that lead to the action mechanism of mycotoxins in humans very difficult is the fact that there are several species of toxicogenic molds that produce different toxic metabolites that are capable of exerting different toxicological effects.

Cases of 12 white female office workers aged between 24 and 52 years, who presented with symptoms of neuropsychological illnesses, most likely, due to indoor environmental toxicogenic mold exposures were comprehensively investigated. They all complained of weakness and numbness in both legs and had some episodes of vagal experiences with exertion. She described symptoms of dizziness and loss of memory, light-headedness and vertigo, fatigue and a general cognitive dysfunction. Four out of 12 subjects had seen therapists in the past for depression. Eight out of 12 complained of getting lost in a familiar territory and had troubles getting words out at times and putting their thoughts together. Initial clinical impression was subjective memory dysfunction and possible aphasic symptoms without obvious abnormality and pseudodementia.

In the year 2000, she moved into a home that was found to contain abnormal levels of toxicogenic molds that included: *Aspergillus*, *Stachybotrys*, and

Penicillium, and Cladosporium genera. A private environmental laboratory that used microscopic, culture, and chemical techniques performed the toxigenic mold exposure characterization and quantification. What was very unique about the patient was that all the members of her family including their pet dog manifested similar behavioral changes. On the advice of Insurance Carrier and the company that tested the home, she consequently moved out of her home almost 2 months later. She was initially placed on Wellbutrin and later she was tried on Topomax to which she complained of feeling dizzy and so, stopped the medication. Although, she found a temporary relief at that time, her major conditions persisted with increasing loss of memory, neuropsychological problems, and allergic reactions.

The patient reported that she had marital difficulties and that the family business where she worked was sold without her knowledge and felt she did not have any meaningful occupational satisfaction. She had sleep disturbances and was stressed out significantly as a consequence. She reported being tested at the age of 30 for learning disability. She had problems with muscular weakness, muscle and joint ache, twitching muscles, painful lymph nodes and short of breath. It was not inconceivable at that time she might have had mild cognitive impairment associated with an early dementing illness or metabolic encephalopathy. MRI investigation found herniated disc with no other explanation, although, there was an indication of significant damage to the parietal and frontal lobes of the brain.

MATERIALS AND METHODS

The patient was given comprehensive examinations to make sure that their health conditions were fully evaluated. These examinations included: the review

of the patients' medical records, basic EEG examinations including awake and asleep, photic stimulation, and hyperventilation. Immunologic examination of the patient's blood samples was done, using enzyme-linked immunoabsorbent assay (ELISA) methods, (Johanning et al., 1996). The psychological evaluation was administered using a number of tests within the following cognitive and neuropsychological domains (Wechsler 1981; 1987; Rosenberg et al., 2002): the Wechsler Adult Intelligence Test-III, Wechsler Memory Scale, Luria-Nebraska Neuropsychological Battery, Trail making B Test, Stroop Neuropsychological Test, Rey Auditory Memory Test, Mental status Examination, Beck Depression Scale, the Minnesota multiphasic personality inventory (MMPI), and Test of Proverbs. The reason for the comprehensive test battery was to measure the intellectual functioning yields (verbal), performance (nonverbal), and Full-Scale IQ scores. The outcomes of these tests played a greater role in ascertaining whether the patient's condition was due to an underlying biogenic brain abnormality or attributable to the chronic toxigenic mold exposures alone.

RESULTS

Immunologic examination: Most of the immunologic parameters, though, outside the purpose of this paper, were abnormal. However, abnormal IgG antibodies to *Alternaria tenuis*, *Epicoccum nigrum*, and *Pullularia pullulans* antigens, but none of the toxigenic molds found indoor were observed. Hence, there was no correlation between the toxigenic molds found indoor with the abnormal antibodies to the three toxigenic mold antigens found in the patient's serum (Table 1). IgG titers greater > 1600 found in the patient were suggestive of chronic exposure to all the three fungi.

Table 1. Abnormal antibodies to *Alternaria tenuis*, *Pullularia pullulans*, and *Epicoccum nigrum* mycotoxins mold antigens found in the patient with neuropsychological impairments. Antibodies to all other toxigenic molds were within normal values.

Test for antibodies	Abnormal values	Reference Range
IgG <i>Alternaria tenuis</i>	4800	0-1600
IgG <i>Epicoccum nigrum</i>	10600	0-1600
IgG <i>Pullularia pullulans</i>	2700	0-1600

Physiological examination: EEG examination showed 10 Hz posterior dominant activities, which were synchronous, symmetrical and attenuated on eye opening and eye-closure. Neither lateralized and generalized background slowing, nor spike or sharp wave discharges foci were identified. Also, hyperventilation did not alter the background rhythm. Stage I sleep was recorded and the Awake EEG was apparently normal. Her grip meter readings were L = 29; R = 30 and she was unable to hold steady against the grid. There was an evidence of tremor of the

extremities. Her reflex was abnormal, and she had accommodation paresis, arthralgia/joint pain, cough, fatigue, headache, immune mechanism disorder, memory loss, mycosis, severe muscular weakness, mood swing, intolerance to alcohol, personality changes, anxiety, attention disturbances. She had speech disturbances, frequently saying the wrong word, depression, dizziness, nausea, and blurred vision.

Neuropsychological Evaluation: Summary of the patient's neuropsychological performance is presented in Tables 2 and 3. Patient had average intellectual abilities, which were about what could be expected from her academic background and work role. Her working memory on the intelligence test indicated a problem with short term and immediate recall. Her memory score was significantly below other index scores, and indicated some deterioration.

Her processing speed was her highest index score. Extreme anxiety and agitation was observed throughout the tests. The Luria-Nebraska evaluation indicated impairment in intellectual process, which reinforced the belief that her general functioning was within that observed in the brain damaged population and was significantly below non-brain damaged functioning.

Table 2: IQ measures for the patient with chronic exposures to *Alternaria tenuis*, *Pullularia pullulans*, and *Epicoccum nigrum* mycotoxins

<i>IQ Measures</i>	<i>Scores</i>	<i>%</i>
Verbal	101	53
Performance	104	61
Full-Scale score	102	55
Processing speed	108	70
Verbal comprehension	105	66
Perceptual Oriental	101	53
Lowest working memory	92	30

She indicated a general impairment, which demonstrated that she had not compensated or adjusted appropriately for her cognitive impairment. She demonstrated a probable arithmetic learning problem and an indication of not being very academically oriented. There was specific localization of injury found. Her memory quotient was 76, which was extremely poor and indicated significant impairment. It was significantly below her intellectual abilities in general. Her scores on other memory tests were both good and poor and indicated an intermittent lapse of memory rather than a consistent problem. She was capable of learning given repetition. Hence, her impairment appeared to be more attention and concentration oriented and thus might be more of frontal, than temporal lobe of the brain in nature. However, she indicated mild frontal lobe impairment primarily with attention, concentration, mental agility and abstract reasoning.

She appeared to have a major depressive affective disorder of a moderate to severe nature. She was agitated, with lagging attention and has unusual beliefs that were unconventional. She presented with difficulty concentrating and thinking. She had some unique somatic and bodily delusions and was immobilized by multiple symptoms. She had chronic relationship problems and was an underachiever for most of her life. It seemed as though she was her own worst enemy. She presented with some symptoms such as dizziness, light-headedness, which could be both medical and psychological in nature. She presented with other anxiety symptoms that gave credence to a functional diagnosis. Although it was believed that she had an early dementia and major depression of unknown etiology, pseudo-dementia was probably ruled out. Her weakness and dizziness could also be a product of molecular encephalopathy.

Table 3: The summary of the neuropsychological findings in the patient with chronic exposures to *Alternaria tenuis*, *Pullularia pullulans*, and *Epicoccum nigrum* mycotoxins [(+++)= very high; (++)= high; (+)= relatively low]).

<i>Test Measures</i>	<i>Overall Outcome</i>	<i>Ranking</i>
WAIS-III	Significant general impairment	+++
Luria-Nebraska	Intellectual process impairment	+++
MMPI	High level of impairment	+++
Stroop	Language impairment	++
Trait Making B Test	Multiple errors (70 sec)	+++
Beck Scale	Moderate depression	++
Test of Proverbs	Impaired abstract reasoning	+++

Behavioral observations: The patient presented as a cordial and outgoing individual, well groomed, and appeared to be significantly anxious with indications of mild to moderate depression. Her thought

processes appeared vague at times, and was high strung with agitation. She indicated good cohesion between ideas and thoughts, and her judgment and decision-making appeared appropriate. There was an

indication of short term and immediate recall problems and she appeared to have a concentration and attention deficit. She did not make connection between her emotional state and physical symptoms and appeared depressed with accompanying agitation and anxiety to warrant a psychological diagnosis. She appeared somewhat "dazed" and disconnected during some of the testing.

The patient was probably of average intellectual abilities and had some difficulty with abstract reasoning and higher order thinking. Her visual memory and perception was hampered with mild indication of word loss. The patient may have a learning disability of a hyperactive nature and appeared impulsive and easily distracted. There was an indication of dyslexic behavior involving sequencing events in a picture story right to left instead of left to right. The mini-mental status examination yielded a mild to moderate problem thinking clearly and reasoning in a rational fashion.

Intelligence tests: The WAIS-III indicated a verbal IQ of 101 at the 53%. Her performance IQ was 104 at the 61% and her full-scale score was 102 at the 55%. There was no significant difference between the verbal and performance scores. All scores were within the average range of scores. Her highest index score was in processing speed at 108 and the 70%. Verbal comprehension was 105 at the 66%, perceptual orienting was 101 at 53% and the lowest was working memory at 92 and the 30%. Her working memory was significantly lower than other index scores and indicates a problem with short term and immediate recall. The working memory score is significantly below other index scores. The average scaled score is 10. The patient scored 103 on verbal and 10.6 on performance. Both scores are at or slightly above the national average. Her IQ scores are about what could be expected given her academic background and occupational track.

Intellectual processes: The patient indicated her scores discriminate between brain damaged and non-brain damaged individuals. Generally her score fell within the brain damaged category. It is heavily influenced by left hemisphere activity. She generally performed below those without brain damage. However, her performance supported the MRI observation of a possible damage to the parietal lobe or frontal lobe of the brain.

Working memory: The Wechsler Memory Scales indicated a memory quotient of 76. This is extremely poor and indicates a score within the borderline category. This score is significantly below her intellectual abilities and thus indicates a cognitive

impairment. She indicates problems with mental control, logical memory, digit span, and visual memory. The Rey Verbal Learning Test indicated no impairment in auditory learning. Her scores were all average in immediate and short-term verbal recall. Her digits span scores indicated a problem with attention and concentration. Her short term and immediate recall was appropriate. Her letter-number score on the WAIS was significantly above the norm. This is both an immediate recall and attention measure. The patient indicated significant intermittent problems with short-term memory and in particular attention and concentration. She does perform significantly better with repetition and thus is capable of learning new material with repetition. She indicated significant attention and concentration difficulties.

Frontal lobe and executive functioning: The Trail making B Test indicated multiple errors involving mental agility and planning. Her score of 70 seconds indicated a minimal impairment and confusion involving right hemisphere activity. The Stroop test indicated no impairment of a language nature involving mental agility. This was a left hemisphere task. The similarities score on the WAIS indicated a score above the national average. The matrix reasoning score was slightly above the national average. There was an indication of attention and concentration problem. The Test of Proverbs indicated a mild impairment in abstract reasoning. She indicated a mild impairment of the frontal lobe primarily with attention and concentration, mental agility and abstract reasoning.

Personality: The Beck Scale indicated moderately depressed individual. She felt sad, discouraged and had a sense of failure. She did not enjoy things like she used to and had become annoyed and irritated much more easily. Her decision-making skills had suffered and she got tired much more easily now. She lacked a drive and motivation. She indicated some feelings of dizziness and light-headedness frequently. She was jumpy and had a fear of dying. She felt a weakness and was unable to relax. She was highly nervous. The MMPI indicated a significant psychological disorder in the form of agitation, lagging attention in the midst of crisis. She has unusual beliefs and is alienated and unconventional. She had identity confusion and had difficulty with concentration and thinking. She overemphasized pathology and was cynical. She possessed some unique bodily or somatic delusions and was immobilized by multiple symptoms. She had problems with authority and might have had recurrent work and family problems. She had a history of underachievement and relationship problems. She

probably was insecure, anxious, a worrier and was indecisive. She was an exhibitionist. Her behavior appeared to be functional or psychological in nature rather than attributed to primary organic concerns.

Treatment: Treatment of mycosis in general is a serious challenge to health care personnel and requires the understanding of the basic pathophysiological mechanisms that underlie their drug resistance. In some patients, the symptomatology is more persistent due to patient susceptibility, fungal growth patterns that resist treatment and the occurrence of dormant fungal spores. Although new antimycotic agents are far more promising than the ones used in earlier treatments, relapse rates still remain high. Treatment can include systemic antifungal therapies as well as nonpharmaceutical methods. A number of modern treatment strategies are available and are generally well tolerated and effective. However, the Medical Center for Immune and Toxic Disorders devised a systematic treatment approach that takes into account the sensitivity of drug to fungal organism, adverse-effects profile, dosage schedule, and duration of therapy, concomitant medical conditions, and concurrent medications (Evans, 2001). Nevertheless, complete treatment will depend on several factors, including appropriate spectrum of activity, adverse effects, and potential drug interactions plus patient preferences for specific dosing regimens.

DISCUSSION

Considering the findings in this patient's test analyses, it appeared that three major complex factors might have played a role in her clinical conditions. First, the patient's indoor environment was contaminated with toxigenic molds that were different from those found in her serum. Secondly, there were three toxigenic molds found in the patient's serum to which the synergistic contribution of each toxigenic mold to the patient's psychological condition was difficult to ascertain. Thirdly, the patient had significant traumatic experiences involving her work and marriage, each of which was capable of exerting psychological influence on her well being. The question then is, which of these factors was responsible for the patient's condition? The first factor is ruled out completely, since there was no relationship between the toxigenic mold contamination of the indoor environment, and the toxigenic mold antigens found in the patient's serum. Therefore, the last two factors are most likely responsible for the patient's condition, but the time and sequence of cause-effect is difficult to say without a proper analysis of individual likelihood of exerting psychological effects. Consequently, we looked in depth, at the abnormal antibodies to three

toxigenic mold antigens found in the patient's serum to identify the most likely species that might have exerted the most psychological effects on the patient.

Mycotoxins produced by Alternaria tenuis: *Alternaria tenuis* occurring in isolates from tomato, and polished rice produces tenuazonic acid mycotoxin with two isomeric forms namely: standard tenuazonic acid and isotenuazonic acid. Some species of toxigenic *Alternaria tenuis* produce alternariol (AOH), alternariol methyl ether (AME) (Bjeldanes et al., 1978), and tenuazonic acid mycotoxins, and it was shown that small amounts of tenuazonic acid have pronounced mutagenic activity (Bjeldanes et al., 1978; Scott and Kanhere, 1980).

Pullularia pullulans lack mutagenic and or carcinogenic potential, therefore, lack significant toxicological activity (Velcosvsky and Graubner, 1981; Tarabasz-Szymanska and Galas, 1993; Kimoto et al., 1997), even though, acute exogenous allergic alveolitis with the typical symptoms of unproductive cough, dyspnoea on exertion, fever, weight loss, headache, and limb pains was observed in a 24-year-old bank employee. Also, pullulans have been implicated in leucocytosis, hypoxemia, and marked restrictive ventilatory defects (Velcosvsky and Graubner, 1981). Kimoto et al. (1997) found no indications of an adverse effect of pullulans on hematology and clinical chemistry values of treated animals and there was no indication of pullulan-related toxicity in terminal organ and body weights.

Epicoccum nigrum synthesizes extracellular fungal polysaccharide, called epiglucan (Schmidt et al., 2001). The *Epicoccum nigrum* extracts used in allergy disorders exhibit batch-to-batch variations in protein composition and allergenic potency (Bisht et al., 2000). Ambivalently, *Epicoccum nigrum* (EN) was obtained consistently from four patients who were having allergic fungal sinusitis (AFS), indicating that *E. nigrum* can colonize nasal sinuses and cause AFS (Schmidt et al., 2001), and that EN is a significant allergen in urban communities (Dixit et al., 1992; Schmidt et al., 2001). However, *Epicoccum nigrum* has antibiotic properties (e.g., epicorazine A), hence, was found to exhibit an activity against *Staphylococcus aureus* (Baute et al., 1978; Deffieux et al., 1978; Deffieux et al., 1978).

Which toxigenic mold was responsible for the patient's health condition? The question here is, which toxigenic mold antigen was responsible for the patient's condition? It is rather difficult to say with greater confidence without further experimental evaluation of the physiological and toxicological effects of these antigens. However, from the

background literature that was stated thus far, it appeared that each of these antigens must have contributed in different measures, to the patient's conditions. Considering the structural and functional groups in the metabolites of the three toxigenic molds, one would suggest that *Alternaria tenuis* probably has the most damaging effects since it exhibits mutagenicity and carcinogenicity. *Pullularia pullulans*, on the other hand, no such effects besides allergenicity, which was the patient's main health problem. *Epicoccum nigrum* produces metabolites that are more of antibiotics than mycotoxins. Therefore, it is more likely that *Alternaria tenuis* may have major contributory psychological effects than the other two toxigenic molds.

Relationship between patient's physical experience and toxigenic molds: It is true that the human brain has the ability to maintain its normal function even when the mind is placed under a severe physical pain. However, if the brain is anatomically damaged, such an endowment is compromised and the individual becomes susceptible to psychological changes. It is possible therefore that the time sequence of events that led to the patient's psychological conditions probably began with the chronic toxigenic mold antigens in the serum that in turn, led to the changes in the brain structure consequent upon which the mind and behavior were affected.

Conclusion: In several cases reported in the literature, it was often obvious to observe an association between indoor environmental toxigenic mold exposures with the patients' relevant seromycological positives. However, this "axiom" is not always true because, as we have found in this case, the identity of the abnormal levels of toxigenic molds observed in the indoor environment were different from those observed immunologically in the patient's blood. Clinical neuropsychological impairments associated with chronic exposures to those toxigenic molds (*Alternaria tenuis*, *Pullularia pullulans*, and *Epicoccum nigrum*) have been reported. The overall findings seemed support the views that certain toxigenic molds are particularly a risk factor for adverse human health, including neuropsychological disorders. In addition, abnormal antibodies to toxigenic molds in the serum of the patients may reflect the adverse health conditions synergistically, however, only one abnormal antibody to toxigenic mold antigen could have the most adverse toxicity leading to neuropsychological effects. It is concluded therefore, that although, it is acknowledged that the contamination of the indoor environment by toxigenic molds directly related to adverse the health effects on the occupants, however, there could be a

situation where such relationship does not exist. Here, we have reported such a situation.

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