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EMOTIONAL DISTURBANCES IN URBACH-WIETHE DISEASE WITHOUT VISIBLE AMYGDALA DAMAGE

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Abstract

A 19-year-old man with Urbach-Wiethe disease (UWD) – a rare genetically-based syndrome which usually is accompanied by various dermatological changes and bilateral calcification of the amygdalae – was investigated neuropsychologically and neuroradiologically. As consequence of amygdalar damage, typical functions mediated by this structure are disturbed. These are alterations in emotional behavior – both with respect to positive and negative emotions – changes in sensory perception, primarily olfaction and taste, and impairments in certain memory domains. Especially the emotional flavoring of autobiographical memories is impaired, both with respect to anterograde and retrograde memories. As the neurological changes in the amygdalae occur gradually over time, it is of major importance to investigate (a) whether there is major amygdalar damage already at age 19, and (b) whether in case of no major measurable amygdalar damage, UWD-related behavioral changes are nevertheless apparent.
Case: The patient had genetically-proven UWD and had been investigated by us at age 9 and at age 19. He visited high school, but was every day accompanied by an assistant, who helped him to keep track of his duties and to co-ordinate his school work. His mother said that he is quite uncoordinated. Both a computer tomography and magnetic resonance imaging failed to show evidence of brain damage, which is an unusable finding in comparison to other, and even younger patients with UWD. On the other hand, the neuropsychological tests revealed a number of deviances from normality. These were seen with respect to his attention and concentration abilities, with respect to emotional behavior and personality dimensions, and with respect to certain aspects of memory. As predictable from his mother's judgment, he was found to have concentration problems. On the emotional level, he had problems in judging facial emotional expressions. And with respect to personality, he scored high on dimensions of depression, compulsion, and anxiety.
These findings indicate that behavioral changes precede measurable brain organic changes and that UWD has a major impact on the well-being, even when the usual bilateral amygdalar calcification is not yet apparent.

Keywords: *Affect, static brain imaging, effort, calcification, personality dimensions.*

1. Introduction

Urbach-Wiethe disease (UWD; also named *Lipoid proteinosis* or *Hyalinosis cutis et mucosae*) was first described by the Austrian scientists Erich Urbach and Camillo Wiethe (Urbach & Wiethe, 1929) and constitutes an autosomal recessive disorder which is characterized by a number of changes of body and brain. Among them are a thickened skin, scarring on the skin, beading of papules around the eyelids, a hoarse voice, and changes in the position of the teeth, compared to normal. In the great majority of patients who up to now were investigated with brain imaging, symmetrical calcifications in the medial temporal lobes, especially the amygdala and the periamygdaloid region were found (e.g., Siebert et al., 2003; Koen et al., 2016).

It is known from studies in animals as well as from work with human patients that damage to the amygdala – especially, if it is bilateral – leads to various behavioral changes, above all changes in emotional behavior (Feinstein et al., 2011; Markowitsch & Staniloiu, 2011) and in emotionally-colored memories (Cahill et al., 1995; Phelps, 2004). The interpretation of odors (Siebert et al., 2003) as well as that of facial expressions is centrally mediated by the amygdala (Demos et al., 2008; Jones et al., 2009). The amygdala controls positive as well as negative emotions (Janak & Tye, 2015), as well as hedonic and

reward-related evaluation processes (Tiedemann et al., 2020) and the perception of social support (Sato et al., 2020).

In the following we will describe the case of an adolescent with genetically proven UWD, who – up to now – lacks significant brain calcification, but already shows a number of behavioral symptoms which are indicative of a progressive cognitive-emotional deterioration.

2. Case description

The 19-year-old is a high school student who since the first years of his life required special care (also up to the present in school). He has under-weight and looks more like a 14-year-old. He has the tendency to not attend to his duties and is easily distracted. Furthermore, he is more introverted and socially deviant from his school companions. He states that he has not much interest in others. When asked about a future with a significant other, he stated that he has no interest in having a friend or a partner.

He agreed to participate in neuropsychological testing and was also eager to have his brain scanned. We obtained informed consent from him for publishing his results.

2.1. Brain scanning

He received magnetic resonance imaging of his brain shortly after his 18th birthday. Unfortunately, the results were not very clear due to artefacts. Therefore, one month later he received an additional cranial computer tomography. None of the two scans demonstrated any visible calcifications in his temporal lobes.

2.2. Neuropsychological testing

Tests were administered for the following functions:

- Standardized tests for lateralization and intelligence/general cognitive status
- Standardized tests for the evaluation of attention, concentration, and processing speed
- Standardized test for the evaluation of constructional functions and planning
- Standardized tests for the evaluation of verbal and non-verbal explicit anterograde long-term memory
- Tests for the assessment of executive functions, problem solving, and cognitive flexibility
- Symptom-validity-tests
- Tests for the assessment of emotional functions
- Questionnaires on personality dimensions and eating

3. Results

Due to space limitations, results are only summarized. The patient was clearly above average in his verbal intellectual abilities (estimated IQ of 124); in screening tests of his intellect, he was normal as well. In attention and concentration abilities, the patient was average in two tests and subaverage in one. In problem-solving, mental processing speed and proneness to interference he was normal as well.

In memory tests without a direct speed component (e.g., having to react within 3 seconds) he was normal to even above average. This held especially for the revised version of the German Wechsler-Memory-Scale (Härting et al., 2000). In two test of memory malingering (Rey-15-Item Test; Test of Memory Malingering; Lezak et al., 2012; Tombough, 1996) he performed without errors, so that there was no tendency for malingering at all.

Tombaugh, T. N. (1996). *Test of Memory Malingering (TOMM)*. New York: Multi Health Systems.

With respect to emotional functions, he scored subaverage. This was found in the “Reading the Mind in the Eyes Test” (Baron-Cohen et al., 2001), where he made nine errors in the 24 items (37.5% error rate) and in the more complex subtests of the Florida Affect Battery (Bowers et al., 1991; Breitenstein et al., 1996). In this test battery, he made three errors (15%) in discriminating affects (subtest 2), four errors (20%) in naming the correct emotion out of five alternatives (subtest 3), and six errors (30%) in matching facial affects. In a test on remembering neutral and emotional pictures (Cramon et al., 1993), he showed the reverse effect to normal by being worse than the normal control group in re-identifying emotional pictures, but better than the control group in re-identifying neutral pictures. Though the differences were not significant, they show a trend, especially as the control group received the pictures a second time after a delay of 30 min, while UW received them immediately after the first trial was over.

In questionnaires, the patient performed in part conspicuously. In the German version of the Interpersonal Reactivity Index (Saarbrücker Persönlichkeitsfragebogen; Paulus, 2012) he received nearly maximal scores for fantasy and empathy (19 out of 20 points) and also a high score on perspective taking (17/20). With respect to feeling distress, he scored slightly above average (13/20). In the Symptom-Check-List (SCL-90-R; Franke, 2002), scores revealed that the patient is uncertain about social contacts and that he scored high on the dimensions of depression, compulsion, and anxiety.

The Freiburg-Personality-Inventory (Fahrenberg et al., 2001) provides a detailed picture of the patient's personality. Here, he received scores in the more extreme range: A maximum was in negative 'social orientation', which the authors of the Inventory equalize to be being very dissatisfied, dejected, and having a negative attitude to life (stanine 9). He viewed himself as non-aggressive (stanine 2), as controlled and as socially responsible, helpful, and as caring about others (stanine 9). However, he also thought that others take advantage of him (stanine 8) and that he can control himself with respect to his emotionality (stanine 8).

The scale of 'openness' only had a stanine score 2, which the test authors interpret as either being strongly oriented towards social conformity or as tending to make a good impression. So, he either is seen as having a lack of self-criticism or as idealizing himself. The most likely interpretation is that he seems to deny socially undesirable behaviors. It also appeared that he frequently feels stressed, nervous, and overwhelmed; and as being emotionally labile, anxious, and with many problems.

The results in the scales 'achievement orientation' and 'extraversion' (each stanine 3) suggest a not very extensive achievement orientation and an "introverted, reserved, pondering and serious" character.

The two applied measures on possible eating disturbances showed a minor risk for the presence of an eating disorder.

The results of all the questionnaires should be interpreted with caution and may in part not reflect true opinions of the patient. This is, because of his low stanine score (2) in the Freiburg-Personality-Inventory on 'openness'.

4. Conclusions

A young adult with confirmed Urbach-Wiethe disease was studied with the principal question, whether already at his age of 19-years calcifications in the amygdalae are found with the consequence of possible deteriorations in cognitive and emotional functions. Scanning the brain of the patient with magnetic resonance imaging and computer tomography surprising revealed no visible brain damage. We furthermore subjected him to intense neuropsychological testing which demonstrated largely undisturbed and in part even above average functions on the intellectual side, but several deviations on personality dimensions.

4.1. Brain

Up to now, we studied 14 patients, aged 17 to 63 years, with Urbach-Wiethe disease (Babinsky et al., 1993; Markowitsch et al., 1994; Siebert et al., 2003; Brand et al., 2007; Markowitsch & Staniloiu, 2011); all of them showed calcifications in the amygdalae. Other groups reported amygdala calcifications in their Urbach-Wiethe disease patients as well (Tranel & Hyman, 1990; Hurlemann et al., 2007; Koen et al., 2016). The apparently youngest patient, reported to have proven significant bilateral brain damage in the region of the amygdala was 17 years old (Brand et al., 2007).

In a paper on ten cases with Urbach-Wiethe disease we stated "that the principal brain degeneration in patients with UW [Urbach-Wiethe] disease lies within the amygdaloid region and seems to develop over time" (Siebert et al., 2003, p. 2634). The present case seems to confirm this thesis, but leads to further questions, as the other youngest patients from our previous publications (Siebert et al., 2003; Brand et al., 2007) had amygdaloid calcifications. Both of previous patients were female and had little school education. It might be that there are gender-specific effects which determine start, speed and extent of calcifications. Furthermore, specific variants of the gene mutation may determine the intensity and time-related appearance of the calcifications.

4.2. Neuropsychology

Our patient knew from young age on that he was "special" in comparison to his peers. It seems obvious that the description of the disease had an impact on his psychic bell-being. Though he was intellectual unimpaired, he had a number of deviations from the average: These appeared in a below average performance in speed-related attentional tasks, which was confirmed by his mother, who stated that he needed throughout his school years guidance by an assistant, is generally somewhat slow in mental following, and seems to be unable to keep order in his room at home. Furthermore, the patient had

problems with emotional processing and in his personality dimensions (questionnaires). In emotional functioning there were negative deviations from normality in all major tests. In the "Reading the Mind in the Eyes Test" he was clearly subaverage (only 9 out of 24 correct identifications [in spite of a 25% chance to vote correctly by chance]). In the Florida Affect Battery he was subaverage in the three more complex subtests. For the comparison of the emotional and neutral photographs, he also showed a trend towards problems with emotion processing by being worse than normal individuals with respect to the emotional, but better than normal individuals with respect to the neutral photographs.

From the results of the questionnaires, it became evident that he was insecure in social contacts and had tendencies towards depression, obsessiveness, and anxiousness (SCL-90-R). In scales on empathy and social orientation he scored high. Eating disturbance could not be verified by the questionnaires used. However, all these scores have to be evaluated with caution due to a stanine score of 2 in the FPI-R scale on openness; they may not reflect his true opinions. This especially, as he certainly is of above average intelligence.

4.3. Implications on Urbach-Wiethe disease in young individuals

The results of both the neuroimaging and the neuropsychological analyses revealed that our young adult patient (still) does not show evidence for neuroanatomical changes in his brain and can be considered to be a so-called high-functioning individual from a behavioral-cognitive perspective. Koen et al. (2016) wrote that "[c]alcification of the amygdala tissue is most often slowly progressive and benign" (p. 505). Our patient confirms this view. The calcification of the amygdala may indeed start only in the third decade of life and its effects on behavior – particularly on emotional functions – may be retarded by cognitive strategies or alternative routes circumventing the amygdala (Siebert et al., 2003, p. 2635).

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