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Neuropsychiatric Symptoms of Urbach-Wiethe Disease

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Abstract Urbach–Wiethe (or lipoid proteinosis) disease (UWD) is a rare autosomal recessive disorder characterized by dermatological, psychiatric, and neurological symptoms. Presentation occurs during childhood, but can be observed from birth. While benign, the disease is progressive and chronic with no known cure. Treatment modalities are palliative for symptoms. The extant literature consists mainly of anecdotal reports and case studies that are limited by small sample sizes and paucity of controlled studies. Incidence and prevalence rates are unknown. There are less than 500 documented cases reported worldwide, and of those, less than 50 cases demonstrate neurological and neuropsychiatric conditions. Worldwide occurrence of the disease is documented, with the largest cohort living in a remote area of South Africa. The affected individuals are mainly Caucasian, born to consanguineous parents, and from Dutch or German heritage. Patients affected have been reported in China, Pakistan and Iran. Current and earlier studies focus primarily on the most visible signs of disease, dystonia and dermatological symptoms, while other studies have reported calcification in the amygdala, hippocampus, parahippocampal gyrus, and the striatum. While central nervous system involvement can lead to a wide range of clinical manifestations such as epilepsy and neuropsychiatric symptoms, there is not a consensus of reported cases with amygdala calcifications accompanied by neurological symptoms. Quantitative research is warranted to further identify the role and relationship between amygdala calcification and neurologic and neuropsychiatric symptoms, while qualitative research will afford insights into the lived experience of individuals and families living with UWD.

Keywords: *Urbach-Wiethe disease, lipid proteinosis, neurological, neuropsychiatric, amygdala*

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1. Introduction

Urbach–Wiethe (or lipoid proteinosis) disease (UWD) is a rare autosomal recessive disorder characterized by dermatological, psychiatric, and neurological symptoms. Studies on the disease have been limited by the small sample size of patients, with very few studies being controlled or having samples of more than 10 subjects [1,2]. Consequently, most literature consists of anecdotal reports or case studies. Studies on UWD, especially the earlier ones, have primarily focused on dystonia and dermatological symptoms such as skin and mucosa abnormalities that are often its most visible symptoms. Other studies have reported calcification in parts of the brain such as the amygdala, hippocampus, para-hippocampal gyrus, and the striatum [3]. The involvement of the disease with parts of the brain that constitute the central nervous system can lead to a wide range of clinical manifestations such as epilepsy and neuropsychiatric symptoms [4]. However, not all studies have found these calcifications to be accompanied by neurological symptoms [5,6]. Therefore due to a paucity of extant literature examining individuals affected with UWD with neurologic and neuropsychiatric comorbidities, a review of the literature was conducted to identify specific gaps and offer recommendations for future research on this population.

2. Overview

The naming of UWD is accredited to Viennese dermatologist and otorhinolaryngologist, Urbach and Wiethe in 1929, after describing in detail, a mucosal condition they termed Lipoidosis cutis et mucosae [7]. In 1939, Urbach revised the name to lipoid proteinosis cutis et mucosa postulating the disorder was connected to the anomalous protein and lipid deposits in diverse tissue samples tested [8]. This systemic autosomal recessive genodermatoses is distinguished by accretion of amorphous hyaline material in the skin, mucosa and viscera caused by loss of function mutations in the gene encoding protein 1 (*ECM1*) on band 1q21 [8]. Furthermore, Hamada et al. [8,9] found that the severity of symptoms in patients with exon 6 mutations were much more severe than those patients with mutations in exon 7. While identification of the specific gene code and strand locus is valuable for further research, the precise systematic correlation between the genetic mutations and the clinical manifestations of the disease remains elusive [9].

The incidence and prevalence data for this chronic disease is not fully known. To date, less than 500 cases

have been reported globally [10]. Additionally, less than 50 cases of documented neuropsychological data exist worldwide [11]. Moreover, a higher prevalence of the disease has been observed in mainly Caucasian individuals with Dutch or German heritage from Europe and South Africa. The largest solitary population of those diagnosed with UWD disease comes from the Northern Cape Province, a remote area in South Africa which Hamada et al. [8] asserts is a potential founder effect. Consequently, higher incidence of the disease occurs in individuals with consanguineous partners [12,13]. Yet, there have been confirmed cases of UWD presenting in patients born to nonsanguineous parents [10,14,15,16]. Additionally, there are also no predilections for sex, age, or race [10].

Although benign, the disease trajectory is both insidious and progressive with no known cure. Yet caution is required when treating affected patients, for the potential does exist for disease to cause morbidity from airway obstruction (laryngeal involvement), dysphonia, dysphagia, gastrointestinal hemorrhage (bowel involvement), and secondary glaucoma with ocular association [14]. Treatment is palliative and therapeutic trials using oral steroids, oral dimethyl sulfate (DMSO), intralesional heparin, D- penicillamine and acetretin to alleviate symptoms have not produced enough evidence to support sustained treatment benefits [17,18,19].

In a pilot study by Zhang et al. [20] a 12-year-old Chinese male child with sclerotic oral mucosa and anaphylaxis, was treated with an oral mucosal injection of compound betamethasone along with an oral application of hydrocortisone. Outcome of the treatment in the study demonstrated a dramatic decrease in the client's symptoms. The child exhibited a C220G mutation of ECM1 gene, which Zhang et al. suggests is a founder effect for the allele in the Chinese population with this disorder. While the results of the pilot are promising, a strong limitation of the study is the non-generalizability and replicability of the study to all populations with UWD due to the specificity of the observed gene mutation.

The disorder typically presents in early childhood, though abnormalities may exist in the affected individual as early as birth [13]. Initial clinical manifestations documented by anecdotal reports and case studies include hoarseness of voice, swelling of the lips and tongue, dysphonia, and dysphagia [15]. After the onset of otolaryngological symptoms, inflammatory skin lesions form which resemble varicella, impetigo and acne, with trait residence occurring on eyelid margins, dorsum of hands, scalp, trunk and lower extremities [13]. The lesions are characteristically yellowish-white in color and beading of lesions at the eyelid margins is a hallmark characteristic of the disease [16].

Radiological hallmark of the disease is denoted by comma shaped calcifications in the temporal lobes of the amygdala, which has been demonstrated in patients with extended duration of disease [14]. While mucocutaneous involvement is documented in the literature (thickening of the tongue and frenulum, dental anomalies, lesions, scarring, alopecia, and dystrophy of the nails) extracutaneous manifestations have also been reported. Epilepsy and neuropsychiatric abnormalities with associative calcification of the hippocampi and temporal lobes have been observed in this particular cohort, although the number of anecdotal reports and case studies found to date in the literature is sparse [8,17].

3. Neuropsychiatric Comorbidities

3.1. Amygdala

The amygdala is a miniscule cohort of functionally heterogeneous nuclei located deep within the limbic system [21]. With its high connectivity to other areas of the brain, the amygdala is the central command center for both emotional and sensory integrative functions [22]. The amygdala plays a pivotal role in the assessment and response to threat [23], the processing of affective stimuli and long term memory [1], facilitates the evaluation of motivationally relevant sensory events [24], processes facial emotions [25] as well as fear [26].

UWD in patients has been found to manifest itself in a diverse spectrum of neurological and psychiatric symptoms. The documented conditions include epilepsy, paranoia, aggressive behavior, personality disorders, intellectual disabilities, and depression. Most of these symptoms are speculated to be a direct result of the amygdala made dysfunctional by calcification.

3.1.1. Headache

Headaches unaccompanied by other neurological symptoms have not been widely associated with UWD. However, one case report was documented in the literature delineating an incidental diagnosis of UWD in 52-year-old male who presented with a headache lasting for 6 months, and referred for computerized tomography (CT) [10]. Family history was unremarkable and parental consanguinity was denied. The client was negative for all physical hallmark symptoms of UWD and was oriented to person, place, and time. Blood chemistry was within normal limits. However, he did present with very faint and disparate yellow patches on his left forearm. CT findings validated symmetric comma shaped hyperdensities in the medial aspect of the temporal lobe, which is consistent with UWD. Additionally, calcification in the right posterior parietal region was discovered, which had never been reported in earlier studies [10].

3.1.2. Epilepsy

Epileptic seizures have been reported in about 25% of patients with UWD due to abnormal electric activity among neurons that are not found to be directly correlated to calcification in the brain [27]. Boudouresque et al. [28] described epileptic seizures in a patient that began with epigastric sensations and ended with feelings of calm and well-being. Appenzeller et al. [4], through neuroimaging, speculated that the disease when in an advanced stage can lead to epileptic seizures. Claeys et al. [29] reported a Belgian patient who was diagnosed with UWD solely because of the occurrence of epileptic seizures and migraine, with no visible dermatological symptoms. Similarly, Omrani et al. [30] reported a female patient with no other visible manifestations of UWD other than complex partial seizures.

3.1.3. Paranoia

Symptoms of paranoia in patients with the disease have phenomenological similarities to schizophrenia. Emsley and Paster [12] reported paranoia in two patients who also had long-term memory impairment and bilateral medial

temporal lobe calcification. The causes of paranoia were conjectured to be either psychosocial, where the patients were reacting to their disfigurements and impairments, or alternatively, directly linked to temporal lobe lesions. The amygdala has been found to play an active role in modulating aggressive behavior [31] and multiple studies have reported rage attacks in patients that have been attributed to bilateral amygdaloid calcifications [32]. Lupo et al. [33] reported a patient who felt anxiety, fear, and experienced rage attacks that were immediately followed by amnesia. Kleinert et al. [34] also reported a patient with paranoiac hallucinatory psychosis and rage attacks along with involuntary muscle activity and epileptic seizures. However, autopsy in this study found no calcifications in the brain and the disease was diagnosed as UWD primarily on the basis of dermatological symptoms.

3.1.4. Affective Perception

The dysfunction of the amygdala due to UWD is also associated with deficits in affective perception. Patients with the disease as well as evidence of bilateral amygdala damage caused by calcification have been reported to decrease ability in recognizing negative emotional experiences [1,35]. Some studies have also linked bilateral amygdala damage specifically to impaired recognition of facial expressions of fear [36,37]. Siebert et al. [1], while confirming damage in the bilateral amygdala of 10 patients with UWD, also showed that there were significant differences in their ability to judge emotions in facial expressions. However, in contrast to previous studies [36,37], it found that patients differed only slightly in rating fearful faces but showed significantly less intense judgments of surprise and disgust when compared to normal subjects.

Adolphs and Tranel [38], in an effort to elucidate the controversiality of the amygdala's role in processing happiness and sadness, conducted a study using participants with bilateral and unilateral amygdala damage matched with a control group. The study's results showed that unilaterally damaged participants rated comparably to the controls. Those participants with bilateral damage demonstrated specific impairment rating sad faces. Conversely, normal performance was seen with the same group when rating happy faces. Interestingly enough, those participants with right unilateral amygdala damage demonstrated a greater impaired performance than those with left unilateral damage. Thornton et al. [2] in a study of 27 patients from South Africa, found participants performing poorly in recognizing both positive and negative emotions of faces. There are parallels to autism [39] and patients show failure in making use of information from the eyes [40,41] primarily due to their inability to fixate normally on the eyes.

3.1.5. Intellectual Disabilities

Studies have also found mixed evidence on the impact of the disease on intellectual disabilities – ranging from moderate mental retardation to no significant differences when compared to normal participants. Emsley and Paster [12] reported borderline mental retardation in one of two patients recorded in their study along with intact visual-motor abilities and severely impaired associative memory. Böhme and Wahlgren [42] also speculated that evidence of mental retardation in one of their patients could be attributed to the disease. Sainani et al. [16] reported evidence of mild mental retardation in a 9-year-old male child diagnosed with the disease. Computed tomography (CT) indicated mesial temporal lobe calcification, which was highly redolent of a positive diagnosis. Bahadir et al. [42] found evidence of both childhood depression and mild mental retardation in a 14-year-old patient. Similarly, Salih, et al. [43] in a study of Saudi families, reported two siblings who were moderately mentally retarded with intelligence quotients of 60 but otherwise found no evidence of other non-dermatological symptoms such as seizures or emotional problems. However, other studies have found no significant differences in intelligence when compared to normal subjects [1,32,34,35].

3.1.6. Memory

Studies have shown that UWD significantly affects non-verbal visual memory. Markowitsch et al. [44] found that patients had impairments with respect to emotional memory for words and pictures. Cahill et al. [45] showed that memory does not get enhanced with emotions in patients with UWD, a finding replicated by Adolph et al. [46]. Similarly, Hurlemann et al. [47] found both retrograde and anterograde modulatory effects of emotional items are absent in patients suffering from the disease. Patients also exhibited selective memory impairments of autobiographic episodes though they did remember autobiographic facts.

Working memory is an essential cognitive process. Without working memory, meaningful thoughts and cogent ratiocinations are unfeasible. Therefore, in effort to assess working memory in UWD clients with amygdala calcification and basolateral involvement (BLA), Morgan et al. [11] performed a study to provide distinctive contributory evidence demonstrating the facets of brain-behavior in this area. Their seminal work utilized both structural magnetic resonance imaging (sMRI) and functional magnetic resonance imaging (fMRI) to assess amygdala function in 3 women with UWD. The participants in the study all had normally functioning amygdala with a rare and selective bilateral calcification in their basolateral complex (BLA). Their findings revealed that all three of their study participants demonstrated evidence of paradoxical functioning enablement of working memory performance. Moreover, Morgan et al. expressed that for the first time, their study exhibited the most lucid substantiation of the role that BLA plays in mediating the antagonism between salience and executive systems for attentional stores.

3.1.7. Depression and Suicide

Many studies report depression amongst patients, with Claeys et al. [48] reporting a patient with suicidal tendencies. Wiest et al. [49] reported an UWD patient with depression and panic attacks that ceased on anti-depressive treatment. The study however contradicted previous studies that attributed panic attacks solely to the amygdala, and showed that other central nervous system sites were also responsible. Decisions under risk and ambiguity have also been found to be compromised in patients with UWD [50].

With the sample size of patients suffering from UWD both small and heterogeneous with respect to race, gender, age, and socio-economic status, studies show considerable

variations with respect to observed symptoms. However, most studies now confirm that damage to the amygdala and other parts of the central nervous system by the disease manifests itself in psychological and neurological symptoms.

4. Discussion

The purpose of this review was to examine the neuropsychiatric symptoms associated with UWD. To date, the total number of reported cases is sparse, and the number of individual cases reported is even less. Additionally, the majority of literature surveyed included anecdotal reports and case studies. While the majority of available literature concentrated on dermatological symptoms and dystonia, other studies directed their attention to the reported calcification in the amygdala, hippocampus, para-hippocampal gyrus and striatum [3].

It has been demonstrated that individuals diagnosed with UWD display a diverse portraiture of neurological, neuropsychological, and psychiatric symptoms including epilepsy, paranoia, aggressive behavior, personality disorders, intellectual disabilities and depression. *Amygdala* calcification and subsequent dysfunction, as a result of the disease, has been conjectured to be the mitigating cause. With *amygdala* calcification occurring in only 50% of the known UWD population, there is not a consensus among the current literature that supports finding these calcifications to be accompanied by neurological symptoms [5,6].

Moreover, while sMRI has been utilized to discover the presence of calcification in the amygdala and fMRI has been used adjunctively to demonstrate *amygdala* activity with respect to observed neurological and neuropsychiatric conditions [23,51], fMRI is unable to depict baseline attention in order to identify the specific structures responsible for certain functions [38]. Therefore, lesion studies have been employed in some cases, to potentially elucidate phenomena that the fMRI cannot visualize [11], in order to better understand the role and relationship between dysfunctional *amygdala* activity and the neuropsychiatric conditions observed in UWD.

While there was only one documented report of incidental diagnosis made late in life in the current body of literature [10], it has been concluded that some of the manifestations of the disease are variable, thereby potentiating possible misdiagnosis [16]. Furthermore, any combination of multiple organ system involvement (gastrointestinal, dermatological, neurological, ophthalmic and dental) would necessitate the coordination of and collaboration with diverse medical specialists in rendering supportive management to this cohort [10]. Therefore, the rarity of this chronic disease compels awareness of this condition across applicable healthcare disciplines. Additionally, with the wide scale accessibility of CT, and MRI worldwide, this disease can now be identified earlier than when it was first identified in 1929 by Urbach and Wiethe [7]. Since this disorder presents in early childhood, and changes in the amygdala due to calcification occur during late childhood into adolescence, it is critical to monitor those affected in order to assess for any potential deviations in neurological or neuropsychiatric status.

While the number of quantitative studies found in the body of literature is meager, only one study was found that employed a qualitative design. Tranel et al. [26] examined emotion in a 26-year-old female with focal bilateral amygdala damage. Consequently, he sought to illuminate whether the individual had a normal phenomenological experience of emotion, specifically negative emotion. The results showed that the client demonstrated a defect in the recognition of negative emotions in external stimuli. Yet she also showed an analogous defect in the experiential facets of her life. Tranel et al. concluded that in the phenomenology of the client's life, a modicum of her innermost negative emotions were in absentia, such that it was analogous to the defect noted in her ability to perceive similar emotions via external stimuli. However, the young woman's capability to demonstrate a series of suitable socially and emotionally comportment was intact. The most interesting and compelling part of this study was that both psychologists, who were blind to the woman's past medical history, denied finding any pathology after they interviewed her, finding her to be "resilient" and demonstrating "heroism" (p. 225). Only when the interviews were completed and the psychologists were made privy to the woman's medical background, did they change their neurological evaluation. While no psychopathy was evident, they concluded the client had an emotional life that was partially truncated. Therefore, Tranel et al. concluded that it was likely the woman suffered amygdala damage early on in her course of the UWD, and that if an individual has a compromised ability to recognize emotions during adolescent development, an abridged catalogue of emotional experiences may result. Subsequently, it was concluded that further research is warranted in order to determine if a robust causal relationship exists between emotional experience and the amygdala. Therefore, the findings in the study by Tranel et al. affirm the requisite for additional qualitative research to further study this phenomenon among clients with UWD. Additionally, Tranel et al. asserted that the developmental life stages of childhood and adolescence is the time when emotion recognition becomes replete and as seen in their study, *amygdala* dysfunction truncated the repertoire of emotional experiences of the study participant. Thus, longitudinal studies of this population are also warranted in order to monitor the client and be able to evaluate specific changes due to the neuropsychiatric conditions present with this disease.

5. Conclusion

UWD is a rare autosomal recessive disorder of the skin and mucous membranes that is depicted by the hallmark otolaryngological symptom of a hoarse voice, later followed by dermatologic lesions that are yellowish-white in color [7]. Incidence and prevalence rates are unknown, and there is no predilection for age, gender or sex [10]. Additionally, parental consanguinity is most often associated with offspring inheritance of the disease [12,13], although there were several documented cases in the literature of clients with UWD with nonconsanguineous parentage with no other significant family history [10,14,15]. While the total number of those affected

worldwide is less than 500 cases reported anecdotally or via case study [10], the largest cluster population exists in a remote area in South Africa. The disease has been observed in mainly Caucasian individuals with Dutch or German heritage and has also been documented in other regions of the world [8].

Histopathological presentation of lesions is a result of copious deposits of hyaline in both the dermal and subdermal layers of the skin and mucosa. The symptoms of the disease may be present as early as birth, but can occur at any stage in early childhood [13]. While hoarseness of voice is the tell-tale symptom early on, affected individuals may also experience swelling of the tongue and lips, dysphagia, and dysphonia [15]. This benign disease is both progressive and insidious, yet there is no known cure. Consequently, caution is required to assess for potential causes for morbidity, such as airway obstruction, dysphagia, gastrointestinal hemorrhage and secondary glaucoma [14].

To date, palliative treatments are the only means of disease management available for clients, to aide in the relief of symptoms. No conclusive data exists that validates substantial effects of the current treatment modalities in curing the disease [17,18,19]. Only one pilot study by Zhang et al. [20] reported a specific treatment regimen shown to ameliorate symptoms in a 12 year old Chinese boy with a C220G mutation that Zhang et al. reports is a founder effect in the Chinese population.

The disease occurs as a result of a mutation of extracellular matrix protein 1 gene (*EMC1)* situated on the 1q21 strand [9]. There are documented variants in the original gene mutation that has been shown to be a result of a founder effect [20]. The symptoms of affected persons who have exon 6 mutations were documented to be much more severe than the symptoms seen in clients' symptoms with mutations in exon 7 [8,9].

Radiologic confirmation of the disease is denoted by either bean or comma shaped calcifications within the temporal lobes of the amygdala [14]. As such, neuropsychiatric abnormalities and epilepsy with associative calcification of the temporal lobes and hippocampi have been detected [8,17]. Amygdylar damage is apparent in 50% of the reported cases of UWD, and less than 50 cases of neuropsychological data exists worldwide [11]. Since the amygdala is the chief command center for both sensory and integrative functions, and UWD presents with amygdalar damage in half of the reported population, deficits in both areas were noted.

In summary, with a dearth of literature existing for not only reported cases of UWD, but also reported cases of UWD and neuropsychological data, there is a requisite for additional quantitative research to add to the current body of literature to better understand the neuropsychological relational properties observed in affected individuals. Additionally, longitudinal studies would provide a clearer clinical picture of the individual's disease trajectory across the developmental lifespan, since the disease commences in early childhood. Last, consideration of the lived experience of those individuals and their families living with UWD would illuminate phenomena that have yet to be uncovered in this particular cohort. The results of further research in these areas would assist transdisciplinary health care providers with the ability to render more specific clinically, psychosocially and culturally competent care for these clients and their families across the developmental life span.

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