



Dysfunction of Protein Quality Control in Parkinsonism–Dementia Complex of Guam

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Guam parkinsonism–dementia complex (G-PDC) is an enigmatic neurodegenerative disease that is endemic to the Pacific island of Guam. G-PDC patients are clinically characterized by progressive cognitive impairment and parkinsonism. Neuropathologically, G-PDC is characterized by abundant neurofibrillary tangles, which are composed of hyperphosphorylated tau, marked deposition of 43-kDa TAR DNA-binding protein, and neuronal loss. Although both genetic and environmental factors have been implicated, the etiology and pathogenesis of G-PDC remain unknown. Recent neuropathological studies have provided new clues about the pathomechanisms involved in G-PDC. For example, deposition of abnormal components of the protein quality control system in brains of G-PDC patients indicates a role for proteostasis imbalance in the disease. This opens up promising avenues for new research on G-PDC and could have important implications for the study of other neurodegenerative disorders.

Keywords: Guam parkinsonism–dementia complex, mutant ubiquitin, protein quality control, protein aggregation, tau, neurofibrillary tangles, 43-kDa TAR DNA-binding protein, neuropathology

INTRODUCTION

Guam parkinsonism–dementia complex (G-PDC) is a mysterious neurodegenerative disorder that afflicts the indigenous Chamorro people of Guam (Mariana Islands). It was first described in clinicopathological studies by Hirano et al. in 1961 (1, 2). Mental deterioration and extrapyramidal signs (rigidity, tremors, and bradykinesia) characterize G-PDC clinically (3). Neuropathologically, G-PDC is characterized by widespread neurofibrillary tangles (NFTs), consisting of highly phosphorylated tau, marked deposition of 43-kDa TAR DNA-binding protein (TDP-43) and neuronal loss (4).

A remarkably high incidence of amyotrophic lateral sclerosis (ALS) was previously found in the same Western Pacific focus of neurological disease (5–12). Because of co-occurrence and overlapping pathology, displaying features of classical ALS in combination with NFTs, it has been proposed that these cases of ALS and G-PDC are variations of the same disorder, i.e., ALS/PDC of Guam (known in Guam as *lytico-bodig*) (13, 14). However, ALS and G-PDC might be completely separate disease entities: NFTs have been reported to be a frequent background feature in the affected population, and, therefore, occurrence of ALS in Guamanians often results in mixed pathology (15–20).

Although several causes have been suggested for G-PDC, including genetics, infectious agents, mineral deficiencies, and environmental toxins, the etiology and pathogenesis of this disease remain unknown (21–26). Determining the cause(s) of G-PDC and the pathways that lead to neurodegeneration in G-PDC is of great interest, as this could lead to new insights into more common neurodegenerative diseases, such as Alzheimer's disease (AD) and other tauopathies. Similarly, insights derived from studies on other neurodegenerative disorders may be helpful for understanding and revealing unique aspects of G-PDC. Here, we highlight some recent observations that open up new opportunities to investigate disease mechanisms in G-PDC.

NEUROPATHOLOGICAL FEATURES OF G-PDC

The search for the cause of G-PDC has become increasingly challenging due to a notable decline in neurological disease incidence on the island in the last decades (27–31). The rapid Westernization of Guam may have contributed to this decrease. However, neuropathology has been found to be unaltered during this time (although the severity and distribution of pathological lesions may have changed to some extent) (32).

Neuropathologically, G-PDC is characterized by severe neuronal loss and abundant NFTs in different brain regions, including the temporal and frontal cortex, basal ganglia, thalamus, and brainstem (2, 17, 32, 33). NFTs (**Figures 1A,B**) are biochemically and ultrastructurally similar to those found in AD brains (34) and closely resemble those seen in frontotemporal dementia (FTD) tauopathies (35).

Besides frequent tangles, other pathological protein deposits have been identified in neurons of G-PDC brains. These include cytoplasmic TDP-43-containing aggregates (**Figure 1C**) and focal α -synuclein pathology (32, 36–40). This could hint at a role for these particular proteins in specific disease processes in G-PDC. For example, abnormal aggregation of the RNA-binding protein TDP-43 may be linked to defective RNA processing (e.g., pre-mRNA splicing) and several other cellular perturbations, like disrupted nucleocytoplasmic transport, mitochondrial dysfunction, and inhibition of endocytosis (41–46). Amyloid- β (A β) deposits were initially reported to be rare or absent in G-PDC (47) but were later found to be present by several authors (32, 48–51). Intracellular inclusions are often ubiquitinated (32) (**Figure 1D**).

It is interesting to point out that glial cells, i.e., astrocytes and oligodendroglia, also contain pathological inclusions (tau, TDP-43) in G-PDC and that these cells may play a significant role in G-PDC pathogenesis (32, 52). Extracellular NFTs are associated with reactive microglia (53, 54).

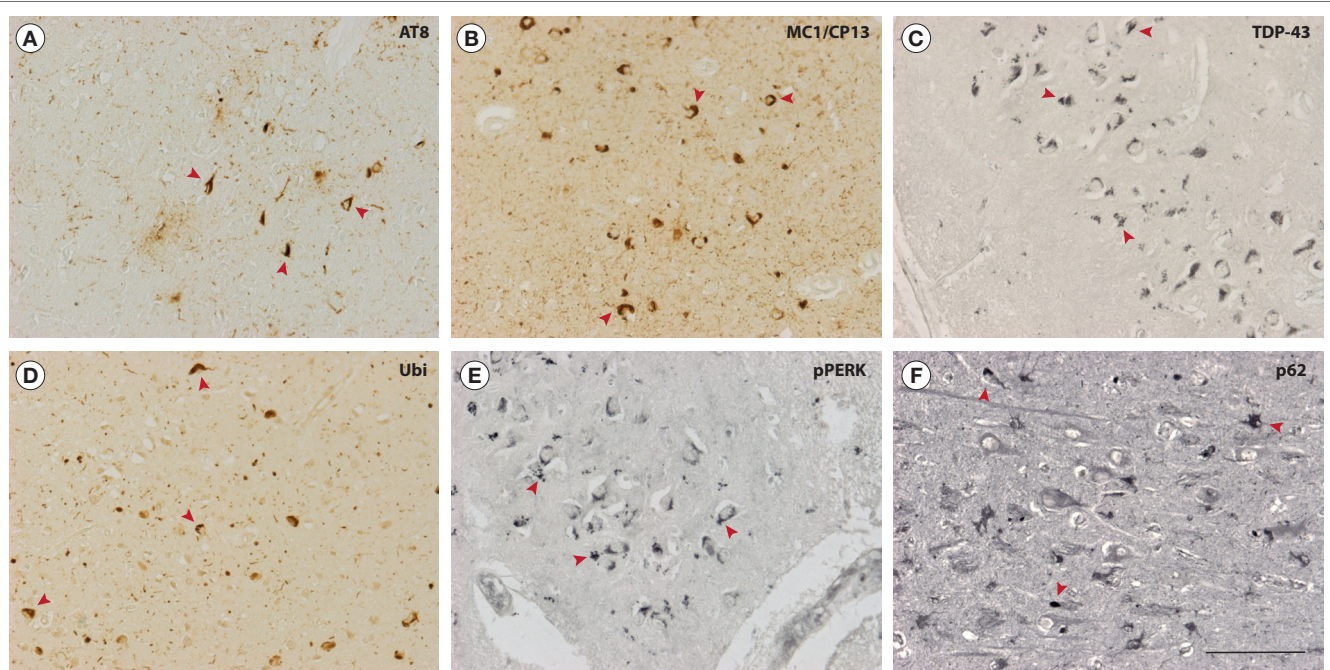


FIGURE 1 | Neuropathological features of Guam parkinsonism–dementia complex (G-PDC). In the brains of G-PDC patients, various pathological protein aggregates can be found, e.g., neurofibrillary tangles (NFTs) (mouse anti-phosphorylated tau, AT8, 1:3,000, Innogenetics; mouse anti-MC1/CP13, 1:200, gift from Dr. P. Davies) (**A,B**) and 43-kDa TAR DNA-binding protein (TDP-43)-positive inclusions (mouse anti-TDP-43, 1:1,000, Abnova) (**C**). Abnormal protein deposits are decorated with ubiquitin (rabbit anti-ubiquitin, Z0458, 1:3,000, DAKO) (**D**). Immunoreactivity for phosphorylated pancreatic ER kinase (pPERK) indicates activation of the unfolded protein response and is associated with granulovacuolar degeneration (rabbit anti-pPERK, sc-32577, 1:400, Santa Cruz Biotechnology) (**E**). Furthermore, the ubiquitin-binding protein p62 is deposited in G-PDC brains (rabbit anti-p62, 1:500, Biomol) (**F**). Accumulation of p62 is a marker for the inhibition of autophagic flux. The photomicrographs in panels (**A–F**) show representative hippocampal sections from G-PDC brains. Arrowheads indicate distinct immunoreactive structures. Scale bar: 100 μ m (Verheijen et al., unpublished data).

Importantly, findings related to multiple proteinopathy have been complemented by the detection of molecular markers that link G-PDC to certain protein homeostasis (proteostasis) pathways. We have recently found some evidence for activation of the unfolded protein response (UPR) in G-PDC brain (Verheijen et al., unpublished data). The UPR is an adaptive signaling cascade that is triggered by endoplasmic reticulum (ER) stress and is associated with abnormal protein aggregation and neurodegeneration (55, 56). Phosphorylation of pancreatic ER kinase, an ER transmembrane protein and ER stress sensor, plays an important role in the initiation and regulation of the UPR (Figure 1E). The primary goal of the UPR is to restore proteostasis in the ER via translational block and activation of ER stress responsive genes, but extensive or prolonged ER stress and UPR activation in disease can turn the UPR maladaptive. In addition, the autophagy substrate p62/SQSTM1 accumulates in G-PDC brains (Figure 1F), which could indicate compromised autophagy-mediated degradation (57, 58).

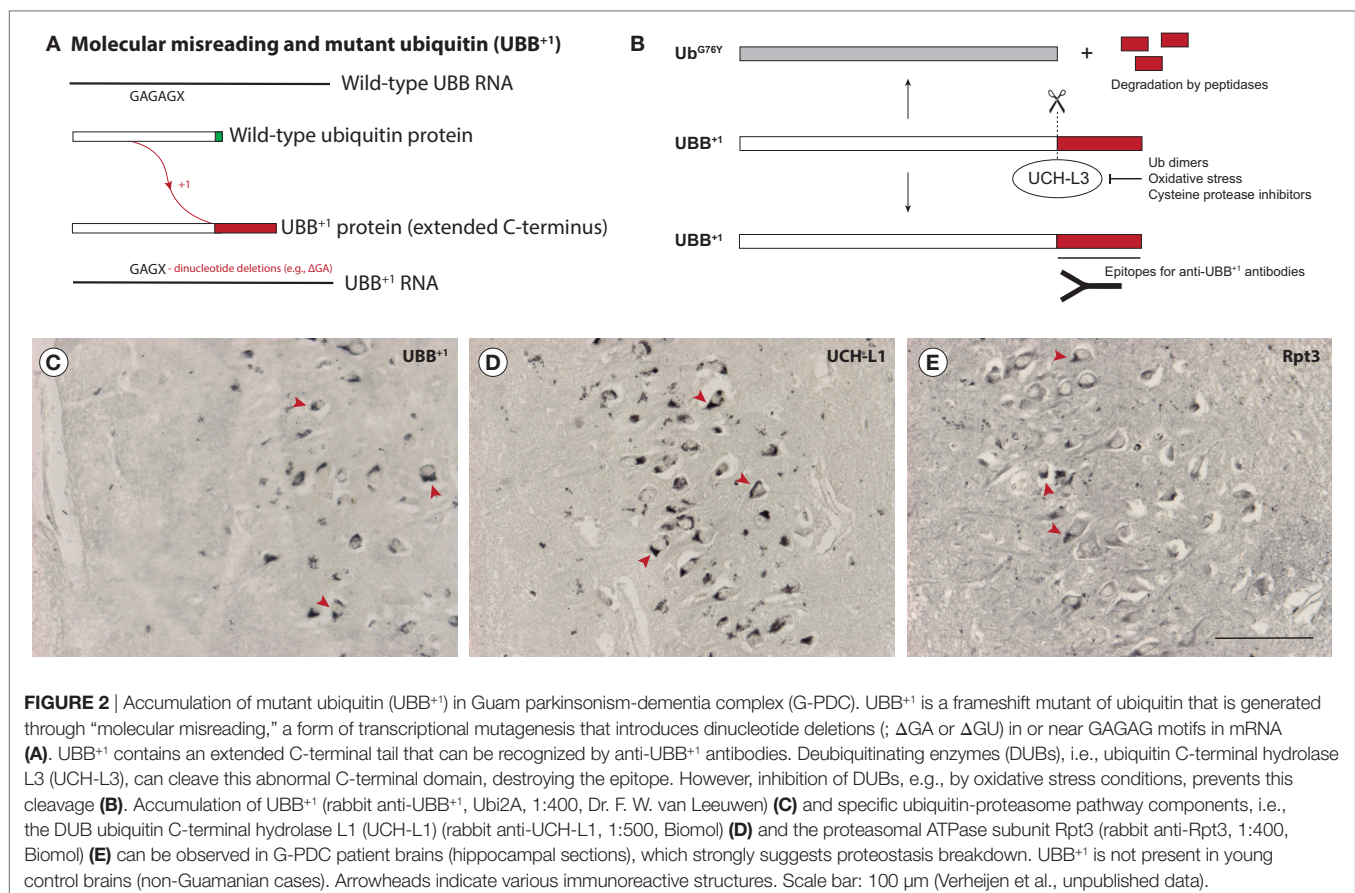
Together, some of these pathological characteristics suggest proteostasis network dysfunction in G-PDC. Disruption of the intracellular protein degradation machinery and proteostasis collapse has been associated with many neurodegenerative diseases, and it will be interesting to see if, and to what extent, protein degradation pathways are affected in G-PDC (59, 60). Failure of protein quality control (PQC) mechanisms to maintain proteostasis may represent a key pathogenic mechanism in G-PDC.

MUTANT UBIQUITIN AND IMPAIRED PROTEOLYSIS IN G-PDC

Multiple neuropathological observations imply impaired PQC in G-PDC. In a recent study, abnormal components of the ubiquitin-proteasome pathway (UPP), i.e., frameshift mutants of ubiquitin-B (UBB⁺¹), have been found to accumulate in G-PDC brains (61).

The UPP is a major mechanism for the clearance of (abnormal) proteins in cells and impairment of the UPP has been reported to occur during neurodegeneration (62–65). UBB⁺¹ is a dose-dependent inhibitor of the UPP that is thought to be generated through “molecular misreading,” a poorly understood process that introduces mutations (e.g., ΔGA or ΔGU dinucleotide deletions) not present in DNA into mRNA, resulting in the generation of aberrant proteins (66–68) (Figure 2A). The mutant protein lacks a C-terminal glycine residue (G76, which is replaced by a 20-amino acid extension in UBB⁺¹) that is necessary to ubiquitinate other proteins, but can still be ubiquitinated itself. The abnormal C-terminal domain of UBB⁺¹ can be recognized by UBB⁺¹ antibodies (69) (Figures 2B,C).

UBB⁺¹ accumulates in several neurodegenerative diseases other than G-PDC, including tauopathies (e.g., AD) and polyglutamine (polyQ) diseases (e.g., Huntington’s disease) and has been shown to be detrimental to neurons (66, 70–73). The mechanisms by which UBB⁺¹ exerts its effects on the UPP and



neuronal function are not known exactly, but it has been demonstrated that UBB⁺¹ is an inhibitor of deubiquitinating enzymes (DUBs) (74), and that it can affect mitochondrial function (75). UBB⁺¹ expression in primary neurons causes neuritic beading of mitochondria in association with neuronal degeneration, presumably due to impaired axonal transport (76). Transgenic expression of UBB⁺¹ in mice results in contextual memory deficits and central breathing dysfunction, which are consistent with neurodegenerative disease (77, 78). Also, UBB⁺¹ was shown to increase mutant protein load in a mouse model for familial encephalopathy with neuroserpin inclusion bodies (FENIB), by impairing ER-associated degradation (79). UBB⁺¹ might act as a modifier of the aggregation and cytotoxicity of other aggregation-prone proteins, such as prion protein and disease-associated huntingtin (80).

Dissecting the precise role of UBB⁺¹ in neurodegeneration is complicated by its dual role as both substrate and inhibitor of the UPP: at low concentrations, UBB⁺¹ is degraded via the ubiquitin-fusion degradation pathway, but at high concentrations it is a potent inhibitor of the UPP (81–85). In addition, UBB⁺¹ can induce cytoprotective programs, like chaperone expression (86), which may compensate for diminished UPP function. Overexpression of UBB⁺¹ in AD transgenic mice resulted in an unexpected decrease in A β plaque load (87), which could suggest that accumulation of UBB⁺¹ is actually part of a cellular protective response. It is tempting to speculate that UBB⁺¹ can interfere with non-degradation-based PQC processes like misfolding-associated protein secretion (MAPS) as well, because MAPS enables PQC when conventional proteasomal degradation is impaired (88). Recent progress in identifying and understanding the roles of different ubiquitin chain topologies potentially adds another layer of complexity to the study of UBB⁺¹, because different ubiquitin chain linkages on UBB⁺¹ could change its properties (89–91). The E3 ubiquitin ligases and DUBs that regulate UBB⁺¹ ubiquitination in neurons also remain to be identified (73).

In G-PDC, UBB⁺¹ deposits are not exclusively located in neurons, but are also present in glial cells (61). Such glial deposits have previously been observed in progressive supranuclear palsy (71), a disease that shares some similarities with G-PDC (23, 92, 93). The role of the UPP in glia with regard to neurodegenerative disease has been somewhat neglected (94), and it would be interesting to find out how UBB⁺¹ impacts neuroglia. In cultured astrocytes, UBB⁺¹ expression seems to confer protective effects via various mechanisms, ranging from regulation of pro-inflammatory signaling to altering mitochondrial dynamics (95, 96). Thus, UBB⁺¹ and UPP inhibition may elicit cell type-specific responses in the context of disease.

In addition to UBB⁺¹, several other proteins related to the UPP were found to be present in G-PDC aggregates, i.e., the DUB ubiquitin C-terminal hydrolase L1 (UCH-L1) (Figure 2D) and the proteasomal ATPase subunit Rpt3 (Figure 2E) (61). Accumulation of these UPP components has been associated with neuropathology in earlier studies (97, 98). Mutations in UCH-L1 lead to motor dysfunction in patients (99, 100) and mice lacking functional UCH-L1 show neurodegeneration (101). Strikingly, motor neuron-specific knockout of Rpt3 results in an ALS-like phenotype in mice (102).

Based on these findings, we conclude that the UPP is disturbed in G-PDC. The definite roles of UBB⁺¹, different UPP components, and PQC mechanisms in G-PDC remain to be determined.

PROTEOSTASIS IMBALANCE AND NEURODEGENERATION IN G-PDC

Accumulation of (abnormal) PQC components in G-PDC brains could be an important clue as to why disease-associated proteins aggregate and neurons degenerate in G-PDC. Impaired PQC and several neurodegenerative diseases have been causally linked through genetic analyses of familial cases [e.g., in familial Parkinson's disease (PD) (103)], demonstrating that PQC dysfunction can be a disease-initiating factor. Moreover, pharmacological inhibition of PQC via injection of proteasome inhibitors causes parkinsonian features in rats (104). Age-related decline in PQC function might (in part) explain the loss of proteome integrity associated with age-related neurodegenerative disorders, including G-PDC (105, 106).

Detailed examination of the PQC system and UBB⁺¹ in the context of the multiproteinopathy that characterizes G-PDC, in different experimental models (e.g., *in vitro* neuronal cell culture and experimental animal models), will likely increase our knowledge of the timing (early vs. late) and relative importance of different disease processes. We take the view that mechanistic studies in such experimental model systems, and validating new findings against the reality of human tissues (neuropathology), will be a powerful approach for making discoveries. It is well recognized that abnormal PQC is implicated in AD, ALS(-FTD), PD, and other neurodegenerative disorders. Because this is a quite recent finding for G-PDC, insights derived from studies on other neurodegenerative diseases will be valuable to help understanding G-PDC, including its unique characteristics.

The cellular mechanisms that control proteostasis are not limited to protein degradation by the UPP, but also involve protein synthesis, folding, trafficking, and other (extracellular) clearance routes (107). PQC critically depends on additional cellular machinery, such as molecular chaperones (108, 109), and is often associated with specific cellular compartments/organelles (e.g., ER, mitochondria). Crosstalk within the proteostasis network and interactions between disease-related proteins and various disease mechanisms (e.g., DNA damage, defective RNA processing, ER and mitochondrial dysfunction, nitrate and oxidative stress, cytoskeletal defects, Golgi fragmentation, abnormal stress granule formation, prion-like mechanisms, neuroinflammation, synaptic malfunction, disrupted membrane trafficking, and excitotoxicity) can determine whether a neuron will degrade (toxic protein aggregates) or degenerate. It should be mentioned that protein aggregation itself, even though it reflects failure of PQC to get rid of potentially harmful proteins, need not be pathogenic and in some cases may even be protective (110).

Ultimately, new mechanistic insights may result in the identification of therapeutic targets that prevent or slow down neurodegeneration. If G-PDC and other neurological disorders converge on the dysregulation of proteostasis as a common underlying mechanism of pathogenesis, exploring PQC pathways to restore proteostasis could be a promising strategy

to find therapies for multiple neurodegenerative diseases. Current advances include the use of UPP activation to remove and stop propagation of pathogenic protein species (111–113). Other targets, such as chaperones and autophagy, are also being explored (58, 109, 114). However, different proteins, in different protein states, can be cleared via separate pathways. Ideally, a proteostasis “reset,” rebalancing the entire proteostasis network in proteotoxically stressed neurons, would be desirable, because this could counteract many defects at the same time. It is unknown whether such a reset switch exists in human neurons, but some cells appear to exhibit a remarkable capacity to reestablish proteostasis (e.g., via lysosome acidification and metabolic shift in *C. elegans* germ lineage, “exopher” formation in *C. elegans* neurons and during differentiation of mouse embryonic stem cells) (115–117). Combinatorial therapies are likely to be required to generate robust treatments that effectively restore homeostasis in human somatic cells in such a way. The diverse pathology of G-PDC provides an excellent paradigm for interrogating interactions between multiple pathogenic proteins, the proteostasis network and different mechanisms of neurodegeneration.

FUTURE DIRECTIONS

Novel neuropathological findings in G-PDC stress the importance of utilizing pathway-specific markers to unravel disease mechanisms. While determining the (possibly multifactorial) cause of G-PDC, perhaps through new genetic and/or exposure (i.e., the totality of all environmental exposures) studies in the geographical isolate, remains a major outstanding problem, more studies into the pathomechanisms underlying neurodegeneration in G-PDC are warranted. Applying insights derived from studies on other neurological diseases that share molecular neuropathology, including work on postmortem human brains and various experimental model systems, will help to identify critical disease mechanisms. Investigating the interplay between G-PDC-associated pathological proteins and specific cellular/molecular pathways (e.g., PQC pathways), using relevant experimental models (e.g., patient induced pluripotent stem cell-derived neurons), will be an exciting and challenging task for the future. Such studies have also been initiated on the Kii peninsula of Japan, another hyperendemic focus of ALS/PDC (118–120) (Verheijen et al., under investigation). The resulting insights could improve our understanding of other neurodegenerative diseases and might result in the identification of new

biomarkers or therapeutic targets. It will be important for future studies to replicate findings in other populations with increased prevalence of ALS/PDC (121, 122).

SOME OPEN QUESTIONS

- Is impairment of the PQC system an important pathogenic mechanism in G-PDC?
- Does UBB⁺¹ modify the cytotoxicity of aggregation-prone proteins, like tau and TDP-43?
- What is the role of glia in G-PDC? What are the effects of UBB⁺¹ on glial cells?
- Are UBB⁺¹ and PQC proteins also deposited in diseases that are similar to G-PDC, e.g., Kii ALS/PDC?
- What are the roles of the UPR and other adaptive stress response pathways in G-PDC?
- Is accumulation of UBB⁺¹ and PQC dysfunction an early or late event in G-PDC? Is it a cause or consequence (or both) of disease?
- How can new insights into pathogenic mechanisms of G-PDC be used to advance the understanding and treatment of other neurodegenerative diseases? E.g., can UBB⁺¹ and particular PQC components be used as therapeutic targets in neurodegenerative disorders?

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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