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Tremor and Other Hyperkinetic Movements

Reviews

Dentatorubral-pallidoluysian Atrophy: An Update

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Abstract

Background: Dentatorubral-pallidoluysian atrophy (DRPLA) is a rare, autosomal dominantly inherited disorder characterized by myoclonus, epilepsy, ataxia, and dementia. Diagnosis is challenging due to the heterogeneous presentation and symptomatic overlap with other spinocerebellar ataxias. Symptoms vary according to age of onset, with a mean age at onset of 31 years. A CAG repeat expansion in the *ATN1* gene results in neuronal intranuclear inclusions, variable neuronal loss, and astrocytosis in the globus pallidus, dentate and red nuclei. No disease-modifying or curative treatments are currently available

Methods: We performed an online literature search using PubMed for all articles published in an English Language format on the topics of DRPLA or *ATN1* over the last 10 years. Where these articles cited other research as support for findings, or statements, these articles were also reviewed. Contemporary articles from related research fields (e.g., Huntington's Disease) were also included to support statements.

Results: Forty-seven articles were identified, 10 were unobtainable and 10 provided no relevant information. The remaining 27 articles were then used for the review template: seven case reports, seven case series, six model system articles (one review article), four population clinical and genetic studies (one review article), two general review articles, and one human gene expression study. Other cited articles or research from related fields gave a further 42 articles, producing a total of 69 articles cited: 15 case series (including eight family studies), 14 model systems (one review article), 14 population clinical and genetic studies (two review articles), 10 case reports, eight clinical trials/guidelines, four genetic methodology articles, three general review articles, and one human gene expression study.

Discussion: DRPLA remains an intractable, progressive, neurodegenerative disorder without effective treatment. Early recognition of the disorder may improve patient understanding, and access to services and treatments. Large-scale studies are lacking, but are required to characterize the full allelic architecture of the disorder in all populations and the heterogeneous phenotypic spectrum, including neuroimaging findings, possible biomarkers, and responses to treatment.

Keywords: DRPLA, *ATN1*, trinucleotide, polyglutamine, myoclonus, ataxia, epilepsy, dementia

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Introduction

Dentatorubral-pallidoluysian atrophy (DRPLA) (OMIM 125370) is characterized by symptoms such as myoclonus, epilepsy, ataxia, choreoathetosis, and dementia that are variable.[1,2] DRPLA is one of a group of autosomal dominant, hereditary ataxias, and is caused by a CAG trinucleotide repeat expansion (≥48 tandem copies) in the Atrophin-1 (*ATN1*) gene.[3–5] DRPLA was initially recognized in Asian populations, although wider genetic testing has increased diagnosis in other ethnic groups.[6–8] Clinical presentation is frequently heterogeneous and typically varies dependent on age at onset: younger onset individuals often present with seizures, and older individuals more commonly present with ataxia and cognitive impairment. Clinical symptoms are progressive, with life expectancy typically 8–16 years from symptom onset.[1,9] At present, no disease-modifying or curative therapies exist, with current treatment paradigms involving supportive

care provided by multidisciplinary teams.[3,10] As a rare disorder there are a lack of publications: only two general review articles (published in 2010 and 2016)[1,2] and no systematic review articles. This systematic review provides an update of the understanding of the clinical phenotype, underlying disorder molecular and mechanistic pathophysiology, and future therapeutic direction.

Methods

We performed a systematic literature search of the PubMed database using the key words "DRPLA", "dentatorubral-pallidoluysian atrophy", "*ATN1*", and "Atrophin 1" (Table 1). All articles published in English and in peer-reviewed journals, print or online books over the last 10 years were included. We also checked the reference lists of each relevant study that resulted from this search for further appropriate articles. Older articles and research articles from other fields were also cited where appropriate to support findings or statements. Forty-seven articles were identified of which we were able to access 37. Of the 37 articles, 10 were excluded due to lack of relevance to the clinical or molecular pathological aspects of DRPLA, resulting in 27 remaining articles. Supportive articles cited within these 27 core articles were also reviewed and included, together with contemporary research from DRPLA related fields (e.g., Huntington's disease [HD]), giving a total of 69 articles included in this review (Figure 1). The articles are 15 case series (including eight family studies), 14 model systems (one review article), 14 population clinical and genetic studies (two review articles), 10 case reports, eight clinical trials/guidelines, four genetic methodology articles, three general review articles, and one human gene expression study.

Case descriptions

Here we provide two examples of clinically typical younger- and older-onset cases

Older-onset case

A 31-year-old Caucasian male presented to the neurology outpatient clinic with a 2-year history of progressive gait disturbance, principally manifesting as unsteadiness and difficulty with balance. More recently he had begun to fall and had started to use a single stick for support when outside the home. In addition to this, his partner had also commented that he was generally more fidgety than normal, with a tendency to move his hands and feet involuntarily when watching the television. He had no past medical history of note and was taking no regular medication. He drank occasionally, was a non-smoker, and had never used recreational drugs. There was a family history of similar symptoms, with both his father and paternal uncle developing atypical movements and memory impairment in their mid-30s, progressing to being wheelchair bound by their early 40s. On examination there was evidence of subtle choreiform movements involving the limbs and perioral region. There was a full range of pursuit eye movements, although saccades were impaired, and there was evidence of both vertical and horizontal nystagmus. Finger–nose, heel–shin, and tandem gait testing revealed clear evidence of cerebellar ataxia. Subsequent investigations included, among other tests, cerebral magnetic resonance imaging (MRI) that demonstrated atrophy of the cerebellum, and to a lesser extent the basal ganglia. Given the family history, genetic testing was undertaken, which initially included the spinocerebellar ataxias (SCA1, 2, 3, 6, 7, and 17) and HD. No mutation was identified with these tests, leading to subsequent testing of the *ATN1* gene.

Younger-onset case

A 12-year-old female presented to her local emergency department with a sustained generalized seizure, having no prior reported seizure history, and was not taking any regular medication at the time. She was currently under long-term review with a local pediatrician because of some evidence of delayed developmental milestones during early childhood, and more recently the development of disruptive behavior in the classroom, as well as progressive difficulties with academic work. Her mother also described infrequent episodes that may have been consistent with visual hallucinations. The patient had no ongoing contact with her father, but her mother was aware of a paternal family history of dementia and progressive gait difficulties. Following post-ictal recovery, the patient was generally found to be withdrawn with a reluctance to engage in the examination. There were occasional brief jerks, consistent with a spontaneous myoclonus, predominantly visible with outstretched arms. The only other clinical finding of note was disrupted horizontal saccades during eye movement examination. Brain MRI demonstrated evidence of a few periventricular white matter hyperintensities, visible bilaterally, but no marked focal atrophy. Subsequent investigation of the family history found that her father had been found to have a CAG repeat expansion (65 repeats) of the *ATN1* gene.

Results

Clinical findings

DRPLA has a median age at onset of 31 years of age and demonstrates no sex bias, affecting males and females equally. Ataxia and cognitive impairment are cardinal features of the disorder; however, age at onset affects clinical presentation.[1,6,9] Typical clinical features of adult-onset disease (⩾20 years of age) include ataxia, cognitive impairment, and choreoathetosis with median age at onset for these presentations of 38–43 years.[1,6,9] Epilepsy and intellectual disability are more common in those with juvenile-onset symptoms, with epilepsy having a median age at onset of 15–19 years, dependent upon the study.[7,9,11] This clinical separation is also observed in juvenile-onset and adult-onset HD, where the juvenile onset form tends to present with rigidity, seizures, and cognitive decline as opposed to the chorea that is the hallmark of the adult form.[12] The length of the CAG repeat expansion in DRPLA within the *ATN1* gene correlates strongly with age at onset ($r^2 = 0.62$, $r = 0.795$, $p<0.001$), with altered clinical phenotype and life expectancy, with longer repeats being linked to earlier onset and more severe disease phenotype.[1,6,9] Mean age at death is 49 years (range 18–80 years), median time from disease onset to death is 15 years, and life expectancy is inversely correlated with CAG repeat length ($r = -0.89$, $p<0.001$).[9] Functional impairment is also inversely correlated with CAG repeat length, such as the age at which an individual becomes wheelchair bound ($r = -0.87$, $p<0.001$) or artificial

Table 1. **Clinical Characteristics of Cohort Studies and Case Series (N⩾2) 2008–2018**

Author	Year	Cohort Description (Male: Female)	Age at Symptom Onset (Range in Years)	CAG Repeat Length (Range)	Clinical Characteristics (No. of Cases with Each Reported Symptom)					
					Ataxia	Choreoathetosis	Extrapyramidal Signs	Cognitive Impairment	Seizures	Psychiatric Symptoms
Sugiyama et al.[14]	2018	10 (4:6)	61–71	52–58	10	1	–	5	1	2
Sone et al.[53]	2015	4 (1:3)	9–23	60–67	4	–	1	3	4	–
Maruyama et al.[11]	2012	9 (6:3)	0.5–12	62–93	5	5	5	–	9	3
Yoon et al.[54]	2012	3 (1:2)	37–42	59–62	3	–	–	1	1	–
Aridon et al.[70]*	2012	10 (8:2)	13–48	58–65	9	2	–	–	6	2
Sunami et al.[46]*	2011	2 (2:0)	19–56	65–70	2	1	–	2	1	2
Hasegawa et al.[9]	2010	183 (82:101)	0–72	56–82	156	78	–	124	98	45
Egawa et al.[56]	2008	17 (9:8)	2–18	64–76	–	–	–	⩾11	17	–
Wardle et al.[7]	2008	17 (11:6)	29–46	51–66	9	6	1	11	9	3

*Single family study.
–, No Reported Cases.

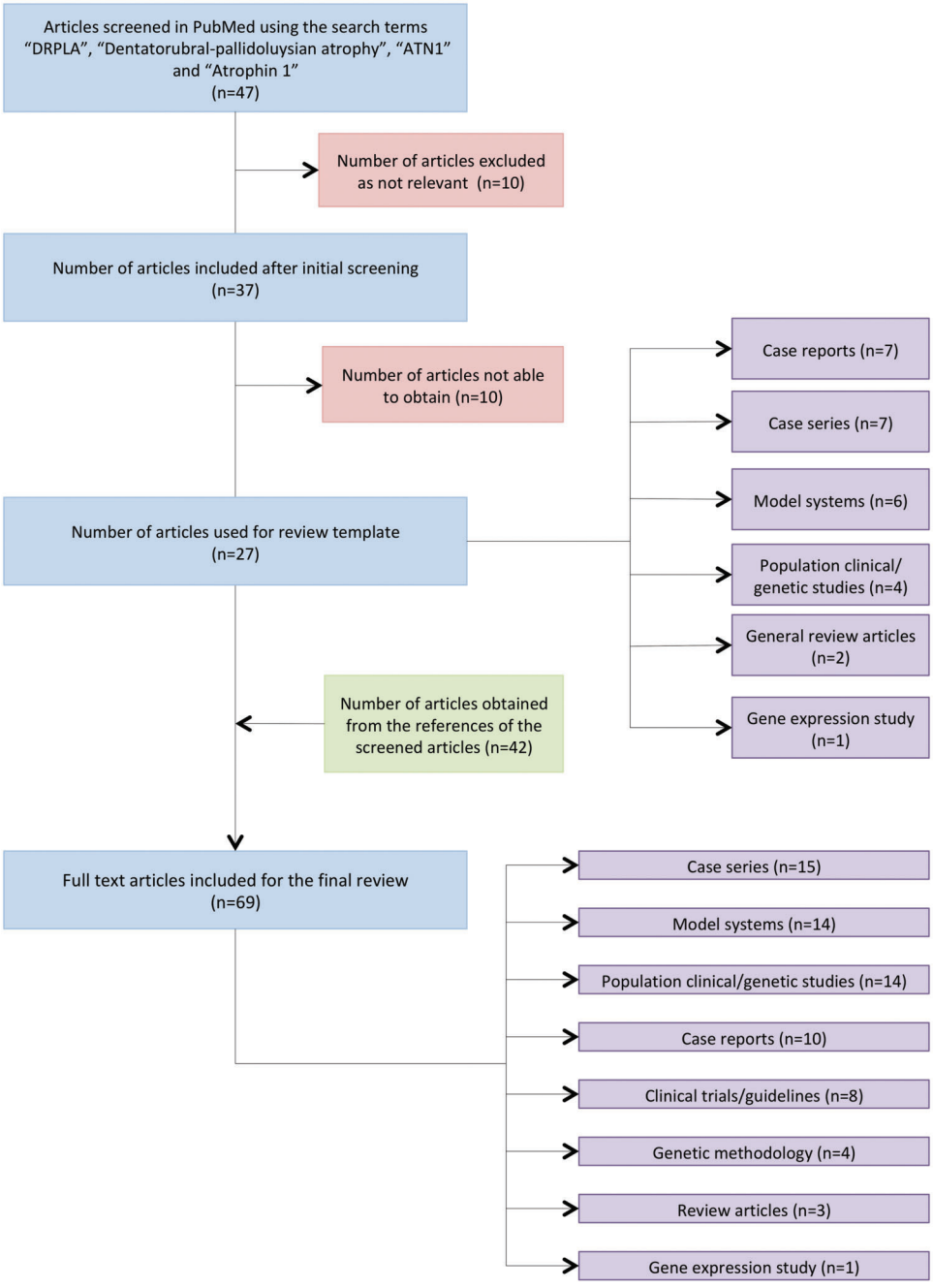

Figure 1. **Flow Diagram Summarizing the Steps Involved in the Literature Search.**

feeding is required ($r = -0.9118$, $p = 0.0013$).[6,9,11] In contrast, there is no direct relationship between CAG repeat length and the rate of disease progression.[9] Pneumonia and less commonly status epilepticus represent the most common causes of death.[9] A summary of common clinical characteristics and their frequencies in patient populations is shown in Table 1.

Clinical diagnosis is frequently challenging, with case reports illustrating confounding factors such as family history of another neurodegenerative disease[13] or non-specific age-associated neuroimaging findings.[14] In childhood, features of delayed developmental milestones and seizures have a broad differential diagnosis, while in adolescence and early adulthood psychiatric symptoms such as irritability, depression, and psychosis may be the presenting features.[15–19] Late-onset DRPLA presented as isolated cerebellar ataxia in 50% individuals and ataxia with or without dementia in 70% individuals in a recent elderly-onset (>60) case series.[14] Differential diagnosis is

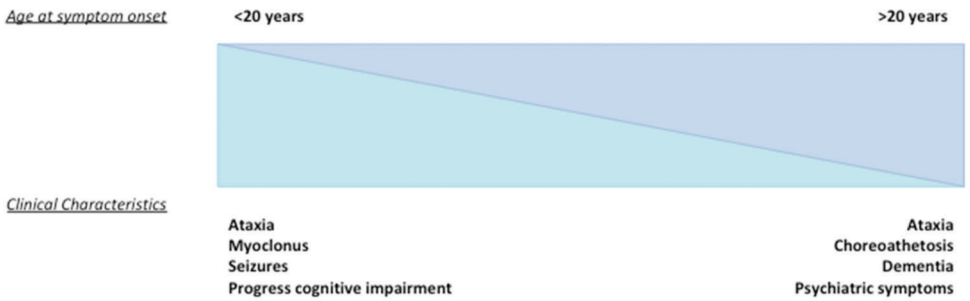

Figure 2. **Schematic Representation of the Differences in Clinical Symptomatology with Variation in Age at Onset.** This is a schematic representation of the variation in more clinical phenotypic presentation between those with juvenile symptom onset (<20 years), and those with adult-onset disease

therefore broad, making diagnosis of DRPLA difficult in the absence of a known family history of the disease. In addition, neuroimaging findings can be non-specific,[14] with clinical mimics including HD and the genetically determined SCAs (e.g., SCA1, 2, 3, and 7).[13,20]

Longer CAG repeat lengths of ⩾65 are often found in patients with a progressive myoclonus epilepsy (PME) phenotype of DRPLA consisting of generalized seizures, myoclonus, and progressive intellectual disability, and these individuals typically present before the age of 20 (juvenile-onset DRPLA).[6,9,11] In a recent case series with partially complete phenotypic data for nine individuals with repeat lengths ⩾62 and onset before 13 years of age, nine had epilepsy, eight had intellectual disability, and six exhibited myoclonus.[11] Patients with the adult-onset (age ⩾ 20) or non-PME phenotype invariably harbor shorter repeat lengths of <65 repeats and present with ataxia, choreoathetosis, dementia, and psychiatric features, with seizures being a rare presenting complaint as shown in reviews of DRPLA cases of non-Asian[6] and supported by significant differences between the above clinical features between <65 and ⩾65 repeat allele carriers of Asian ancestry[9] (Figure 2). In addition to genetic testing to confirm diagnosis, a contemporary study found that the age at which hypoalbuminemia occurred in DRPLA patients inversely correlated with CAG length in eight of nine individuals ($p<0.01$), indicating a potentially useful biomarker for future clinical trials.[21]

Epidemiology

DRPLA is most commonly recognized in populations of Japanese ancestry, with an incidence of 2–7 per million.[7,8,22,23] DRPLA is thought to occur at lower rates in non-Asian populations, although these estimates are based on the evaluation of cohorts diagnosed with SCA and may therefore represent an underestimation of DRPLA prevalence.[7] Worldwide the prevalence of SCAs is 2.7 per 100,000,[24] and within these cohorts the highest frequency of DRPLA is seen among Japanese groups (7–20%), with lower rates in other Asian populations (Singapore, 6%; Korea, 3%).[25] In European populations, DRPLA has a frequency of 2–4% in Portuguese SCA families,[8] 0.25–1% in other SCA samples of European descent,[23,26,27], and 0.14–3.1% in Latin-American SCA cohorts.[25,28] However, these estimates may be higher in some populations, potentially because of a higher proportion of "high-normal" repeat lengths or sampling variation.[7] Longer repeat lengths appear more commonly in populations of Japanese origin than in Caucasians.[29] There are no reported differences in disease characteristics between populations such as the incidence of adult-onset and juvenile-onset cases, although cohort sizes in some populations remain small.[6]

Genetics

The atrophin-1 gene (*ATN1*), located on chromosome 12p13.31, encodes a transcriptional co-repressor widely expressed in the central nervous system and elsewhere in the body.[30] *ATN1* mutations are inherited in autosomal dominant fashion, with the CAG repeat responsible for DRPLA present in exon 5, and is typically present at ≤35 repeats. Repeat length alleles of >20 are uncommon and considered mutable normal alleles, with one allele >20 repeats in a sample of 177 Caucasian families with mixed SCAs.[1,11,29] Such alleles may be at higher risk for future intergenerational expansion.[8,23,26] CAG repeat lengths differ between populations, such as a >40 repeat length allele frequency of 20% in families with SCA of Japanese ancestry versus 0% in Caucasian families ($p<0.0001$).[29] Repeat lengths ⩾48 demonstrate a fully penetrant clinical phenotype, while alleles of 35–47 repeat length are incompletely penetrant and have been associated with a milder DRPLA clinical phenotype in a small number of cases.[1,6,11,31] There is one report of an asymptomatic individual aged 81 with a repeat length of 51.[31]

DRPLA, in common with other microsatellite repeat disorders, shows genetic anticipation whereby disease symptoms occur earlier and more severely generation on generation. Previous studies have provided estimates of CAG repeat length (median and range) dependent on age at onset of symptoms: <21 years (68 repeats; range 63–79), 21–40 years (64 repeats; range 61–69), >40 years (63 repeats; range 48–67). This phenomenon is thought to be driven by CAG repeat expansion in the gametes, particularly in spermatogenesis, as anticipation is more pronounced on paternal inheritance. A small number of DRPLA cases occur in the absence of any family history of the disease, suggestive of a *de novo* repeat expansion from the normal or intermediate range into the disease-causing range. The factors driving these cases are unknown.

Expanded polyglutamine (poly-Q) repeats are characteristic of other autosomal-dominant neurodegenerative disorders such as HD and six

of the SCA disorders, which also demonstrate features of *de novo* expansion and genetic anticipation.[30,32–34] CAG repeats can expand or contract during gametogenesis; therefore, a non-pathogenic sized CAG repeat may expand and become a *de novo* pathogenic allele in an offspring.[6,7] Alternatively, a disease causing a CAG repeat may expand in subsequent generations leading to an earlier-onset and more severe disease: the phenomenon of anticipation,[6,7,35] which is greatest during paternal transmission.[4–6] Both phenomena may have a role, with a founder Asian haplotype either expanding to other population groups, or the CAG expansion within these groups arising due to the *de novo* phenomenon.[6,7,23]

Models

Although CAG repeat expansion disorders are all driven by similar expanded repeats in the DNA that result in central neurodegeneration, these repeats are in genes encoding different, unrelated proteins and so it is unsurprising that they induce variable clinical syndromes associated with different neuropathologies.[30] Invertebrate models of neurodegeneration in DRPLA include the fruit-fly *Drosophila melanogaster,* where the introduction of a human disease allele causes age-dependent neuronal loss, potentially due to defects in lysosomal autophagy, and accumulation of the poly-Q repeat protein.[30] Homozygous *Atn1* knockout mice are viable, without obvious phenotype.[36] There are several transgenic mouse models of DRPLA, one of the first involved introducing a single mutant copy of human *ATN1* with a 65 CAG repeat-length human mutant allele.[37] These mice showed tremor, ataxia, and seizures with premature death; however, although there was widespread distribution of the mutant protein with neuronal intranuclear inclusions (NIIs) there was no clear neuronal loss or macropathology.[37]

A distinct murine model, involved introduction of a 76 CAG repeat human disease allele into background wild-type lineage (Q76). However, in spite of widespread neuronal intranuclear accumulation (NIA) of mutant protein, initially in an anatomical pattern similar to DRPLA, these mice exhibited no clear neurological phenotype and did not form NIIs.[38,39] They did however develop a cognitive phenotype with deficits in spatial learning and memory.[40] The same background murine lineage was used to produce a model with a much longer repeat length, 129 CAG repeats (Q129), with a repeat of this length demonstrating features more akin to that seen in humans, including myoclonus, ataxia, epilepsy, and weight loss that progressed rapidly to death within 16-weeks.[38,39] NIIs appeared, although some time after symptom onset, and although brain weight and cortical thickness of the Q129 mice was reduced there was no indication of astrocytosis or neuronal loss.[38,39] Further models with varying repeat lengths have been generated from this lineage and show that CAG repeat length correlates with disease severity, as in DRPLA.[40] These mouse models suggest that NIA forms an important pathological marker in DRPLA and occurs before symptom onset, that pathology is widespread within the nervous system, although DRPLA anatomical areas are affected preferentially, and that neuronal atrophy and dysfunction are the hallmarks of the disease.[38,39]

In vivo conditional knockdown of an atrophin-1 interacting gene, *Lsd1*, in mice has indicated a role for Atrophin-1 in regulating neuronal progenitor proliferation, a process that can be influenced by the LSD1 inhibitor tranylcypromine. *In vitro* cellular models have shown a neuronal accumulation of mutated cleaved products and that longer repeat length polyglutamine tracts are degraded more slowly than normal repeat lengths.[41,42]

Amelioration or reversal of pathology has not been shown in DRPLA models yet; however, there have been promising findings from HD.[43] The growing field of allele specific gene-silencing technologies include allele-specific oligonucleotides (ASOs) and less-specific methods of RNA interference, such as small-hairpin RNA (shRNA). The latter has been shown to reduce levels of mutant huntingtin *in vitro* and *in vivo* in a transgenic mouse model of HD, with improvement of motor function.[44,45] CRISPR/Cas technology, which allows *in vitro* or *in vivo* genome editing, has also been shown to reduce levels of both mutant and wild-type huntingtin in a transgenic mouse model of HD with improvement of motor function.[43]

Neuropathology

Post-mortem neuropathological findings in DRPLA include an overall smaller neuraxis, with neuronal loss and astrocytosis in the dentatorubral and pallidoluysian systems, with intrafamilial variability of neuroimaging findings being reported.[46] The lateral segment of the globus pallidus is the area most greatly affected by neuronal loss, with the dentate nucleus and subthalamic nucleus affected to a lesser extent.[2] In the red nucleus, astrocytosis is more prominent than neuronal loss, and in all affected areas neurons can appear swollen or shrunken.[2] A single case report described severe cerebral white matter damage without axonal loss and mild atherosclerotic changes, although white matter findings have not been widely reproduced elsewhere.[47] There are no published comparison studies of neuropathological findings between adult-onset and juvenile-onset DRPLA; however, a family study of a father and son that showed overall similar neuropathological findings for other cases of DRPLA exhibited marked frontal lobe and pontine atrophy in the juvenile-onset case that was postulated to contribute to the severe cognitive deterioration and epilepsy observed.[46]

DRPLA is one of a number of CAG repeat disorders that exhibit NIIs, with some debate as to whether these represent a key pathogenic feature, or are unrelated to the primary pathological process, potentially representing a failed neuroprotective process.[48] Immunohistochemistry of DRPLA post-mortem brains using an antibody aimed at identifying polyglutamine stretches shows wide variation in the deposition of mutant protein, from diffuse intraneuronal accumulation (NIA) to densely packed areas of mutant protein within the nucleus of affected neurons (NII).[38,49] NIIs are spherical, non-membrane bound structures that are eosinophilic, contain a mixture of granular and filamentous structures, are ubiquitinated, and contain the mutant ATN1 protein.[49] Nuclear pathology and nuclear intranuclear inclusions are widespread in the CNS, although some regions, such as the

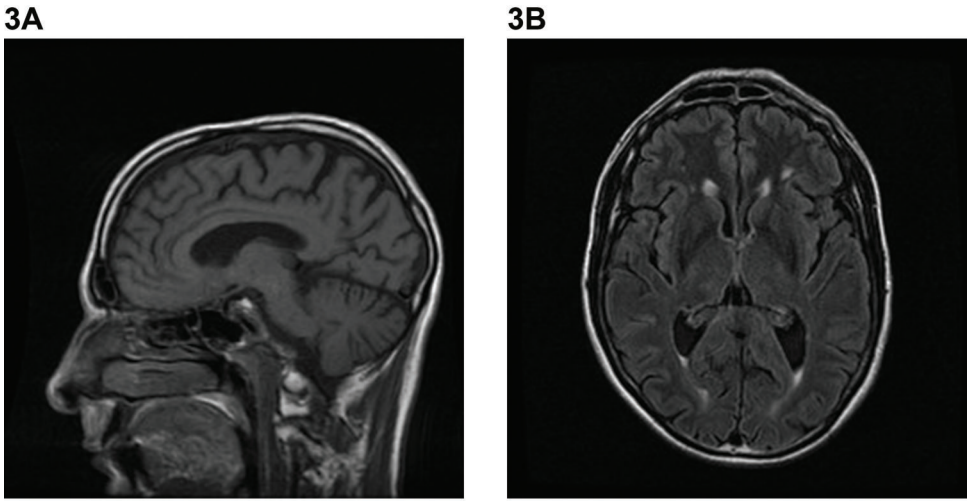

Figure 3. **Example of Magnetic Resonance Imaging Findings in Dentatorubral-pallidoluysian Atrophy.** (A) Sagittal T1-weighted image demonstrating global cerebral atrophy, with more marked cerebellar atrophy. (B) Axial T1-weighted image demonstrating bilateral periventricular white-matter lesions.

hippocampus, appear to be spared, with some debate as to whether these inclusions are protective or pathological to the neuron.[49,50]

Neuroimaging

Brain MRI findings are variable and many case reports report only mild or non-specific changes in the early-stage of disease.[10,18,19,51–53] There are only two small studies of DRPLA cohorts (n = 10, >60 years of age; n = 3, aged 39–46 years) and these have identified characteristic findings in later disease, including brainstem and cerebellar atrophy and high-intensity T2/fluid-attenuated inversion recovery weighted signal in the cerebral white matter, thalamus, and brainstem.[14,54] Other imaging studies have used varying sequence protocols on individual cases[10,17,20,47,52] or small pedigrees,[16,46] with inconsistent findings ranging from small vessel disease to more typical cerebellar and brainstem atrophy, and cerebellar and supratentorial white matter changes with leuokoencephalopathy, in later disease. An individual case report highlighted the potential utility of susceptibility weighted imaging in DRPLA, with the possibility of iron or other cation deposition in susceptible areas. However, further and larger studies are required to determine whether this modality provides diagnostic value.[52] Figure 3 shows the common MRI features of DRPLA.

The use of imaging to distinguish DRPLA from other clinically similar disorders is challenging. In late-onset disease, in particular, isolated atrophy of the brainstem and cerebellum increases the likelihood of more common diagnoses being made (e.g. alcohol-induced cerebellar degeneration), and imaging may show no supportive features in an elderly population.[14] The SCAs and the cerebellar variant of progressive supranuclear palsy (PSP-C) often have similar imaging features to those with DRPLA; however, a single study (n=15) identified increased signal in the brainstem and thalamus as a useful marker for identifying DRPLA.[55] Few functional imaging studies have been undertaken, with no common disease-specific findings to date. However, striatal glucose hypometabolism was observed in two individuals with juvenile-onset DRPLA, which may warrant further investigation in a larger cohort.[53]

Neurophysiology

There are few reported electrophysiological studies performed on patients with DRPLA, with only one retrospective cohort study of 12 juvenile-onset individuals with video-electroencephalography (EEG)[56] and the remainder being individual case studies.[10,20,56] The seizure types observed in individuals with DRPLA vary widely and are not specific for the disorder. For example, a retrospective cohort study in juvenile-onset DRPLA found that half (six out of 12) exhibited generalized seizures and/or focal seizures, with slightly fewer atypical absence seizures (five out of 12), and myoclonic seizures (four out of 12), and one individual exhibited an atonic event.[56] Reported EEG evidence so far indicates that myoclonus is likely to be cortical.[10,56] Seizure semiology also typically evolves with early features of short-lived generalized seizures, with subsequent focal seizures and focal seizures with secondary generalization.[10,56] EEG abnormalities have also been detected in the inter-ictal period, with evidence of frontal intermittent high-amplitude delta activity.[13]

Diagnosis

No established clinical diagnostic criteria have been established for DRPLA, with the genetic diagnosis typically made during the investigation of symptomatic individuals.[1,51] Diagnostic genetic testing should be considered in any individual with an autosomal dominant pattern of family history involving cognitive impairment, dementia, or movement disorder.[7] Consensus guidance on testing within adult-onset ataxia for DRPLA focuses on clinical findings, Asian ancestry, and family history as being important factors to consider.[3] Family history can identify neurological presentations with overlapping clinical features, such as atypical Parkinsonism with cerebellar ataxia, Parkinsonism dementia, and cerebellar atrophy. [10,57]

Diagnosis may be most difficult in an late-onset adult DRPLA where other differential diagnoses are more common, and the clinical presentation may be less typical;[14] when isolated ataxia is the sole clinical finding, more common causes of ataxia are likely to be considered (e.g. a background of alcohol excess), potentially resulting in DRPLA not being considered during the diagnostic work-up.[1] Genetic testing is typically via polymerase chain reaction amplification across the *ATN1* CAG repeat region followed by gel or capillary electrophoresis, which identifies 100% of pathogenic expansions of ⩾48 CAG repeats.[1] Although next-generation sequencing technologies are promising they have not been widely used or validated for the *ATN1* repeat expansion and diagnosis of DRPLA, and repetitive genomic elements remain problematic to assay via short-read next generation sequencing technologies.[58–60]

Management

The clinical management of those diagnosed with DRPLA is predominantly supportive within the context of a multidisciplinary team. Genetic counseling is ideally undertaken early to ensure families are aware of the autosomal dominant nature of the disease, to discuss predictive testing and potential means of family planning.[1] EEG investigation is indicated in the context of the clinical suspicion of seizures, and neuropsychological assessment for evidence of dementia or psychiatric disturbance, particularly when deciding on psychological support or psychotropic medication.[1]

There are no clinical trials assessing the efficacy of different anti-epileptic medications in treating seizures in DRPLA. Myoclonic seizures can be managed with carbamazepine or phenytoin, unlike with other forms of myoclonic epilepsy, while sodium valproate, perampanel, and zonisamide have been used in the treatment of generalized seizures.[10,51,56] Case reports describe the use of various combinations of anticonvulsants in specific circumstances, but it is unclear whether these regimens are more broadly useful. For example, a 17-year-old male diagnosed with juvenile-onset DRPLA exhibiting segmental myoclonus, gait ataxia, and several daily atonic falls improved with the addition of levetiracetam to sodium valproate, zonisamide, and taltirelin (2,500 mg, 1,000 mg, 200 mg, and 10 mg per day, respectively),[10] and a bedbound, non-verbal 9 year old with frequent myoclonic and seizures and generalized tonic–clonic seizures showed gradually improved ambulation and communication (but no change in seizure frequency) with the addition of perampanel to lamotrigine, sodium valproate, clobazam, and phenobarbital (0.4 mg, 100 mg, 600 mg, 20 mg, and 90 mg per day respectively).[51]

Choreoathetoid and dystonic movements have been managed with tetrabenazine, risperidone, bromazepam, and gabapentin (no doses given).[47] Consensus European guidelines advise that riluzole (100 mg/day) is likely effective in reducing ataxia symptoms for adult ataxias regardless of etiology, with a mean decrease of 7 points (>5 points was deemed clinically relevant) on the International Cooperative Ataxia Rating Scale after 8 weeks (Class II evidence).[3,61,62] There is weaker evidence for the use of amantadine 300 mg/day for ataxia.[3,63] Education, physiotherapy, occupational therapy, and environmental adaptation may also be needed at different disease stages. Specialist palliative care input is recommended throughout the disease course, with evidence suggesting particular importance later in disease course.[1,3] A summary of case reports and clinical trials detailing response to treatments in DRPLA and cerebellar ataxia is shown in Table 2.

Future directions

DRPLA forms one of a wider spectrum of CAG repeat expansion diseases, including HD, some SCAs, and spinal and bulbar muscular atrophy.[32] DRPLA shares similarities with HD including that the clinical and genetic differences between juvenile-onset and adult-onset DRPLA remain intriguing and unexplained, although extrapolation from HD literature points towards a combined loss-of-function and increasingly toxic gain-of-function against the remaining normal allele with increasing repeat length.[12] HD is the most widely studied CAG repeat expansion disorder and developments in gene silencing via RNA interference (RNAi) include an antisense oligonucleotide to huntingtin that alleviates disease in a mouse model.[64] *In vitro* and *in vivo* studies have shown allele-specific RNA interference of multiple alleles is possible within the central nervous system.[65]

Intrathecal administration of an antisense oligonucleotide directed towards huntingtin is in phase 2 clinical trials for HD, demonstrating a dose-dependent reduction in the overall levels of the mutant protein in cerebrospinal fluid, although the full results of this initial phase of work are yet to be published.[66] Similar approaches might be adopted to treat DRPLA. Previous success with intrathecal ASO therapy in neurodegenerative disease has been seen with spinal muscular atrophy, with higher levels of synthesis of the wild-type allele, and improved clinical motor function in phase 3 trials, resulting in an expanded access program for appropriate patients.[67,68] Gene-replacement therapy via an adenovirus vector has also shown promise in this disorder.[69] Given the rarity of DRPLA it is more likely that therapeutic advancements will arise through the understanding of other neurodegenerative and CAG repeat expansion disorders. At present, optimized clinical management includes a timely diagnosis and access to the multidisciplinary team, as well as the resources needed for ongoing care.

Discussion

Clinical diagnosis of DRPLA in the absence of known family history of the disease remains challenging within the context of neurodegenerative movement disorders, is currently intractable to medical treatment and causes significant disability for those diagnosed with the disorder. Cohort studies to date are underpowered to draw comprehensive conclusions of the true allelic spectrum that causes clinical symptoms, characteristic neuroimaging findings, and responses to current treatments. Larger scale, collaborative international studies are required, and would provide an opportunity for further understanding of this rare disorder, making use of next-generation genetic sequencing technologies, standardized neuroimaging pipelines, and fostering an environment for future clinical trials. As described above, there are promising developments in the discovery of disease-modifying therapies

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Table 2. **Reported Treatment Outcomes in the Management of DRPLA and Other Forms of Degenerative Ataxia**

Author	Year	No. of individuals managed	Treatment	Outcome
Shiraishi et al.[51]	2017	DRPLA (1)	Perampanel 0.4 mg/day (added to lamotrigine, sodium valproate, clobazam and phenobarbital)	Myoclonic seizures and weekly generalized seizures resolved
Romano et al.[62]	2015	SCA (19), FA (9)	Riluzole 100 mg/day	Improved SARA score after 12 months of treatment
Kobayashi et al.[10]	2012	DRPLA (1)	Levetiracetam 2,500 mg/day (added to sodium valproate, zonisamide and taltirelin)	Reduced frequency of segmental myoclonus and cessation of falls
Ristori et al.[61]*	2010	Chronic cerebellar ataxia (19)	Riluzole 100 mg/day	Mean decrease of 7/100 points on the ICARS following 8 weeks of treatment
Botez et al.[63]†	1996	Degenerative cerebellar ataxia (30)	Amantadine maximum 300 mg/day	Improvement of visual and auditory reaction times and movement times at 3–5 months
Egawa et al.[56]	2008	DRPLA (8)	Carbamazepine discontinuation	No change in seizure frequency or myoclonus
Egawa et al.[56]	2008	DRPLA (5)	Phenytoin discontinuation	Phenytoin re-started in one patient owing to increased seizure frequency

Abbreviations: DRPLA, Dentatorubral-pallidoluysian Atrophy; FA, Friedrich's Ataxia; ICARS, International Cooperative Ataxia Rating Scale; SARA, Scale for the Assessment and Rating of Ataxia; SCA, Spinocerebellar Ataxia.
*Cited in van de Warrenburg et al, 2014.[3]
†Cited in Veneziano and Frontali, 2016.[1]

for other neurodegenerative disorders, which may be able to be translated to DRPLA in the future.

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