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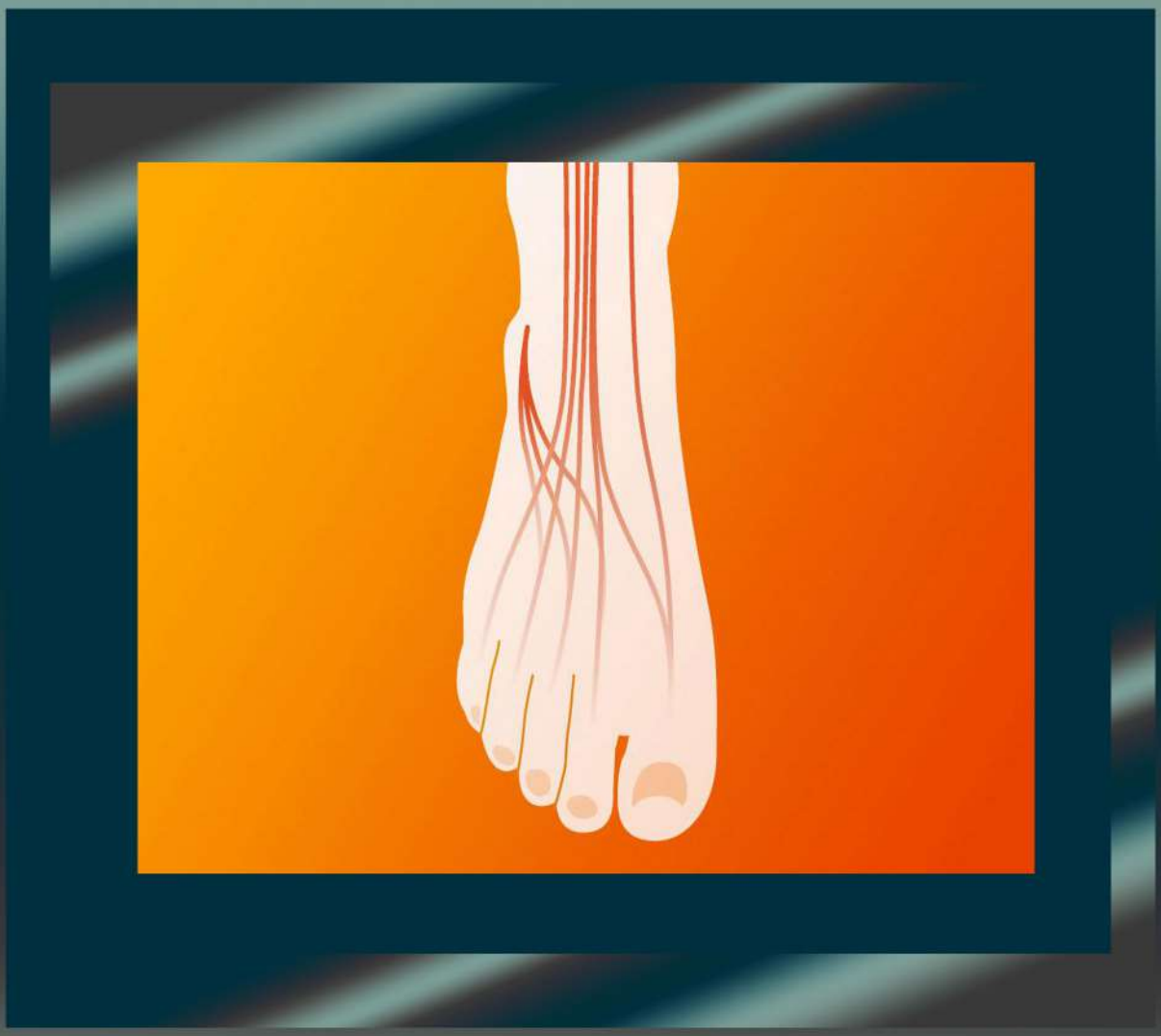

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Case Report

Spontaneous Resolution of Pituitary Cystic Lesion

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ABSTRACT

Differentiating between cystic lesions of pituitary gland may be challenging. Usual differentials are cystic pituitary adenoma (cPA) and Rathke's cleft cyst (RCC). Diagnostic certainty of magnetic resonance imaging (MRI) is limited in the absence of usual suggestive features. Furthermore, RCC can co-exist with approximately 2% of pituitary adenomas. Over time, these cystic lesions may remain static, resolve spontaneously, or result in symptomatology relating to mass effect and/or hormonal disruption. In cases of an asymptomatic lesion being found incidentally, little is known about how it may progress, raising question whether to proceed with surgical management or follow-up. We a present case of a spontaneously resolving pituitary cystic lesion with imaging features more suggestive of cPA than RCC, for which watchful waiting proved a successful treatment strategy. The current case serves as a reminder that small cystic lesions can be followed-up with spontaneous resolution and should be offered active treatment only when clinically required.

Keywords
Pituitary gland; Pituitary cystic lesion; Cystic pituitary adenoma (cPA); Magnetic resonance imaging (MRI).

INTRODUCTION

Pituitary adenomas are an adenohypophyseal neoplasm. One meta-analysis of 13 independent studies suggested a prevalence of greater than one in five. This is based on radiological evidence that included both clinically silent and undiagnosed post-mortem cases.[1,2] Pituitary adenomas may be categorised: by size where the terms micro- or macro-adenoma are applied; by endocrine function being functioning or non-functioning; by radiological appearance being cystic or non-cystic. Of note, Zhang et al hypothesised that solid pituitary adenomas develop into cystic adenomas as a consequence of either ischaemia or haemorrhage.[3] Often, a pituitary lesion is found incidentally when imaging is reviewed for an entirely different indication; these lesions are often termed incidentalomas. An important differential to consider when reviewing pituitary imaging is Rathke's cleft cyst (RCC). RCC results from failure of proper fusion of the pouch between the adenohypophysis and neurohypophysis, leaving a remnant (cleft) of epithelial cells, known as Rathke's cleft, which may later, for unknown reason, form a RCC.

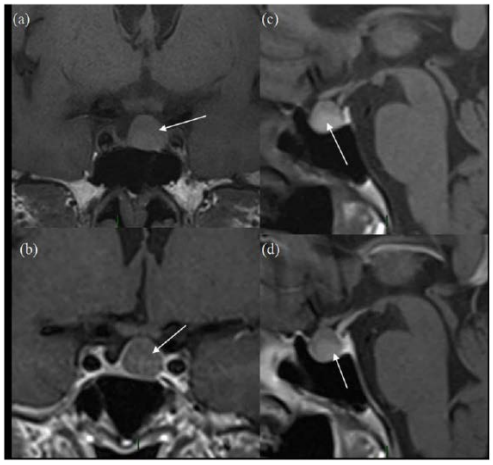
Non-functioning cystic pituitary adenomas (cPAs) and RCCs of large enough size may both produce pressure symptoms including headaches, visual disturbance and hypothalamic-pituitary dysfunction. Though distinguishing features may be present on imaging, the mucinous contents of an RCC are of similar signal intensity to a cPA that has undergone haemorrhage or infarction, which is common in larger cysts, making it difficult to differentiate between the two lesions radiologically. Haemorrhage and infarction are less common in RCC despite its population prevalence being up to 33%.[4-6] Classically, spontaneous resolution of a pituitary cystic lesion is more associated with RCCs than cPAs. However, there are some reports in the literature of pituitary adenomas that spontaneously resolve without associated symptoms of apoplexy.[7-9] It is thought that spontaneous RCC resolution is perhaps more likely to be under-reported than rare.[10-12] Transsphenoidal surgery is a definitive management of pituitary lesions, and is required if the presence of the tumour causes symptoms of mass effect or intolerable hormonal imbalance. Furthermore, surgery may prevent recurrence and allows for histological confirmation of diagnosis. However, the natural history of non-functioning pituitary

incidentalomas is not fully understood. Despite limited data, it is thought that worsening visual fields, new endocrine dysfunction and apoplexy are rare.[13] Though it is useful if classical imaging features are present, it would appear that even in the absence of typical clinical features, asymptomatic small cystic lesions can be conservatively managed as the vast majority of these may remain stable or resolve.

CASE REPORT

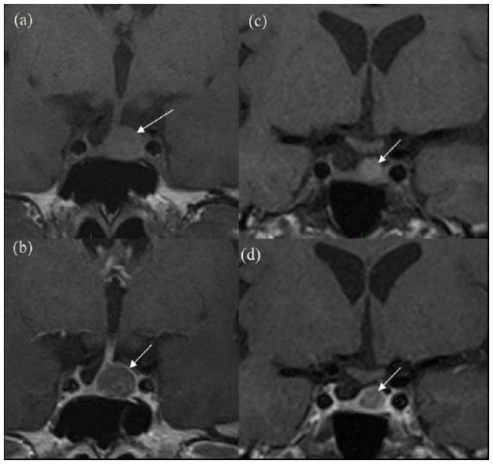
The patient is a 67-year-old lady who presented in 2012 due to hemifacial spasm involving the right lower eyelid, for which she subsequently underwent magnetic resonance imaging (MRI) for assessment of her right facial nerve anatomy. A 1 cm pituitary mass was found incidentally present centrally and slightly on left side of midline, having slightly high T1 signal without contrast enhancement and no optic chiasm compression (Figure 1). Vision was normal. The lesion was thought to be cystic with either haemorrhagic or mucinous contents, with possibilities of a cPA and unusual RCC. Further testing revealed a low serum cortisol that responded appropriately to a short synacthen test by rising to 718 nmol/L at one hour. Follow-up scans performed in 2013 and 2014 showed no change. Subsequent MRI in 2015 and 2016 showed progressive reduction in size of the lesion with persistent slightly high T1 signal without obvious contrast enhancement (Figure 2). Further follow-up scan in 2017 showed further significant reduction in size of the lesion, now seen as a tiny eccentric nodule with high T1 signal on superior aspect of left side of pituitary gland (Figure 3). The overall size of pituitary gland appears quite small in Figure 3, with appearance of "empty sella" and prominent cerebrospinal fluid (CSF) space superiorly. In retrospect, the "normal" pituitary tissue in Figures 1 and 2 is also quite less, suggesting that it has been a pre-existing finding and appears more obvious in Figure 3 due to shrinkage of the cyst.

Figure 1. *Initial MRI Scan*



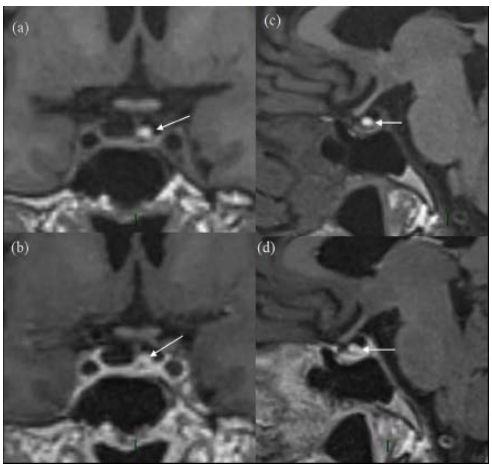
(a) and (b) are pre-contrast and post-contrast coronal images and (c) and (d) are pre- and post-contrast sagittal images. The white arrow represents the pituitary lesion in all sequences, having slightly high T1 signal in (a) and (c) and no enhancement on (b) and (d).

Figure 2. *3-year Follow-up MRI Scans*



(a) pre-contrast and (b) post-contrast coronal images and more posteriorly (c) pre-contrast and d-post-contrast coronal images. White arrows show progressive reduction in size of the lesion in comparison to Figure 1.

Figure 3. *5-year Follow-up MRI Scan*



(a) and (b) are pre-contrast and post-contrast coronal images and (c) and (d) are pre-and post-contrast sagittal images. The white arrow represents the residual pituitary lesion in all sequences with significantly reduced size as compared to Figures 1 and 2, having high T1 signal in (a) and (c) and no enhancement on (b) and (d). The overall size of pituitary gland is quite small, with appearance of "empty sella". In retrospect, the "normal" pituitary tissue in Figures 1 and 2 is also quite less, suggesting that it has been a pre-existing finding.

Serial MRI, described above, was stopped once the pituitary gland had returned to normal size. Serum urea and electrolytes, full blood count, free T4, TSH, random cortisol, IGF1 and prolactin were normal at all times. Her visual acuity and fields did not deteriorate at any time during her 6-year follow-up of her pituitary cyst, although left cataract surgery was performed 1-year after presentation with right pseudophakia 3-months later without complication; a previous diabetes-induced right branch retinal vein occlusion had been treated with macular grid laser. Visual Acuity was 6/12 right and 6/9 left at time of neuro-endocrinology discharge.

Based on the imaging appearances, RCC and cPA were considered the main differentials. Arachnoid cyst (AC) and craniopharyngioma (CP) are sometimes considered differentials although not in this case due to imaging appearances.

Due to absence of hormonal dysfunction, headache like symptoms or pressure effects, conservative management and annual follow-up MRI scans was performed.

The patient had no clinical signs or symptoms during the entire period of clinical monitoring with spontaneous resolution of her (unrelated) hemifacial spasm, that didn't recur. Throughout follow-up, she demonstrated no evidence of pituitary dysfunction and developed no headaches or pressure effects. Serial follow-up MRI scans showed the lesion to be stable between 2012 and 2014 and subsequently showed reduction in size, up to 2017, when the lesion was only seen as a tiny residual lesion (Figure 3). No further routine follow-up scans have been performed. The patient has been discharged and is aware that if any of the relevant symptoms develop, the patient can return for further assessment. She is aware that the red flags for surgical intervention, if her cyst were to recur, would be deterioration of visual acuity and/or visual fields. These are being performed annually.

DISCUSSION AND CONCLUSION

Imaging of our asymptomatic patient revealed a small pituitary lesion with usual differentials of cPA and RCC being the focus of this section. RCC tends to be non-enhancing, with rim enhancement often seen in cPA.[14,15] In addition, RCC is typically homogenous and found in the midline between the anterior and posterior pituitary lobes, with minimal infundibular deviation as the cyst proper is thought to have soft constituents.[16] The presence of a nodule is a feature in 75% of RCC and is almost pathognomonic.[17-20] RCC signal intensity is variable depending on the cyst having mucinous, serous or cerebrospinal fluid (CSF) contents.

cPA is more likely to cause pituitary stalk deviation, with other indicative features being the presence of a fluid level, septation and evidence of intracystic signal change.[20] cPA is also more likely to be erosive, with invasion of surrounding sella and extension into the suprasellar space thought to be more characteristic of cPA, or also of CP.[21] Calcification is more suggestive of CP, which is often suprasellar in location. RCC and AC rarely extend into the suprasellar space.[22] AC tends to present later in life than RCC and CP, the latter two of which may occur in childhood and adolescence. Distinguishing between these pathologies is achievable either intra-operatively, if it is possible to visualise that the AC does not communicate with the intracranial subarachnoid space, or by histopathological examination of the cyst lining, which is generally squamous in CP and cuboidal or columnar in RCC.[22] Interestingly, RCC with squamous metaplasia are more likely to recur, and so there is a suggestion in the literature that RCC and CP are more similar than currently thought.[21-23] Other considerations are dermoid cyst, epidermoid cyst and empty sella. In the current case, the lesion was within the pituitary gland and although the lesion appeared rather central on the initial scans, the last scan showed the lesion to be quite eccentric and probably exophytic, thereby suggesting that cPA is the most likely diagnosis; the lesion also showed no classical features of RCC and CP. The high T1 signal can be assumed to be due to underlying haemorrhage, although it can be argued that some RCCs can show mucinous contents and can show high T1 signal, mimicking blood products; therefore it is difficult to completely exclude an RCC in an unusual location with mucinous contents.

There is no confirmed mechanism attributable to cPA resolution, but there is some suggestion towards that of RCC, which may be applicable to both lesions. Specifically, there exist two hypotheses in the literature regarding spontaneous RCC resolution. The first is that an imbalance between cyst reabsorption and secretion leads to fluctuation in volume of cyst cavity contents, which was first suggested in the context of case reports describing fluctuant visual field defects and MRI imaging demonstrating a change in cyst size but not signal intensity.[24] The second is that the cyst capsule ruptures, with or without haemorrhage, thereby facilitating reabsorption. It is rare that RCC present as a mimic of apoplexy, but there is evidence that haemorrhage into the cyst with an associated severe headache does lead to shrinkage.[25,26] It is thought that the presence of xanthogranulomatous infiltration, which is a well-recognised histopathological feature of RCC, is indicative of cyst rupture and that a severe, sudden-onset headache as seen in pituitary apoplexy is not necessarily a clinical feature.[26] Further case reports ascribe the resolution of cPA to apoplexy.[27,28] In the current case, the asymptomatic presentation and clinical course with serial imaging demonstrating high T1 signal would suggest that haemorrhagic rupture in the absence of apoplexy-associated headache can occur followed by spontaneous resolution.

The current case is a reminder that a small asymptomatic cystic pituitary lesion, even in absence of typical diagnostic features, potentially with haemorrhage or proteinaceous contents, can remain stable or spontaneously resolve and can be managed conservatively if there is no risk to vision, and the patient can be counselled on this basis.

CONSENT

The authors have received written informed consent from the patient.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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Editorial

Neurofibromatosis 1 Somatic Mutation Triggering Cellular Apoptosis to Prevent *Neurofibromatosis 1* Progression

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Persons with ordinary, prototypical *Neurofibromatosis 1* (*NF1*) are born with a germinal/zygotic mutation at the *NF1* locus on the long arm of chromosome 17 (17q) present in all of their cells. An *NF1* germinal mutation is the "first hit," accounting for haploinsufficiency at the *NF1* locus. The *NF1* somatic mutation is the "second hit," accounting for diploinsufficiency (deranged or lost function of both alleles) at the *NF1* locus. The *NF1* somatic mutation occurs in a variety of somatic (i.e., non-germinal) cells, including, and especially the schwann cells (SC). I suggest that *NF1* haploinsufficiency provides the conditions for the SC (and other cells) to develop *NF1* diploinsufficiency rather than *NF1* diploinsufficiency developing independently of the conditions in which it originates. In either case, imagine a viral analogue with an apoptosis trigger held in abeyance unless an *NF1* somatic mutation occurs in the presence of an *NF1* germinal mutation or whole gene deletion. That is, instead of altering the feature, for example, decreasing neurofibroma size and symptoms with MEK inhibitors, I herein suggest an approach to preventing certain *NF1* features, keying off the fact that almost *NF1* features involve somatic mutation of the cell's *NF1* wild type (WT) allele.

The *NF1* phenotype, that is, the *NF1* syndrome, has many elements, not all with the same "causal relationship" to *NF1* genotype. *NF1* features are elements closest in causal proximity to the genomic disturbance, for example, neurofibromas or vertebral dysplasia.[1] *NF1* consequences, derived from *NF1* features, include atypical neurofibromas and spinal scoliosis.[1] *NF1* complications, derived from *NF1* consequences, include neurofibrosarcoma and spinal cord compression.[1] Respecting the publication of F.L. Rice and colleagues,[2] there is also the matter of the precursor of the *NF1* feature. Their article emphasizes the importance of *NF1* syndrome elements that are precursors to the syndrome's characteristic features. Specifically, they describe a precursor to the *NF1* cutaneous neurofibroma (cNF). One important question the article raises is the presence or timing of the *NF1* somatic mutation with regard to the development of the *NF1* feature. Does the *NF1* somatic mutation derive the precursor or does the *NF1* somatic mutation account for the conversion of the precursor to the feature? I expect that often it is the latter. Respecting this general type of reasoning, perhaps the *NF1* syndrome progression could be reversed or stopped early on through genetic manipulation before elements of the disorder compromised the person. For example, we could modify the zygote's *NF1* mutation, amplify expression of wildtype allele or use the occurrence of an *NF1* somatic mutation as a trigger to remove the affected cell through induced apoptosis.

Many factors other than the *NF1* locus or the latter's protein product, Neurofibromin (Nfn), might or can influence Cnf development, such as mast cells,[3] collagen deposition[4] and skin adnexae.[5] Rice, et al[2] makes a clear case for cell-cell cooperativity in *NF1* syndrome skin potentially contributing to the development of *NF1* diploinsufficiency. Terminal sensory axons in the skin are not always associated with other skin components (sweat glands, sebaceous glands, sweat ducts, vascular bundles, etc.). But, when they are, SCs may be dislodged from the involved nerve and proliferate according to new schedules. Such cell divisions afford new opportunities for the occurrence of SC *NF1* somatic mutations, ultimately affording both *NF1* haploinsufficient SC and *NF1* diploinsufficient SC accumulations, in turn providing a cellular and intercellular conglomeration that either anticipates or represents an early-stage cNF. The overall point is that something about *NF1* haploinsufficient cellular cooperativity affords the opportunity for, or actually triggers, *NF1* somatic mutations.[6,7]

As one peruses the natural history of the *NF1* syndrome at the cellular level, recurrent *NF1* diploinsufficiency, that is, recurrent *NF1* somatic mutation, occurs very frequently

in multiple types of tissue, including that of the central nervous system, the peripheral nervous system, the skin, the skeleton, stem cells, endocrine glands, the vascular system, the pulmonary parenchyma, etc. In a seventh-decade *NF1* adult, thousands of somatic mutations may have occurred. Exactly why this happens has escaped clarification, but these somatic mutations can be usurped or obviated nonetheless, as suggested herein.

Recently, a significant portion of medical genetics clinical research has shifted from focusing on a disorder's natural history to genetic modification, which, for example, might convert a genetic mutation "back" to the normal (i.e., wildtype allele). Respecting this general type of reasoning, it seems that the *NF1* syndromefeatures (*sensu strictu*) could be prevented early on through genetic manipulation. Gene editinghas garnered the most interest, using deoxyribonucleic acid (DNA)-editing substances such as CRISPR/Cas9.[8] The restorative molecule is introduced into each of the organism's cell nuclei, the DNA region of interest identified and that region modified from the mutant structure to a wildtype allele.[9,10] However, although CRISPR/Cas9 cell-by-cell gene editing has substantial potential benefits, it is fraught with technical, political and ethical problems.

Increasing WT *NF1* gene expression, especially cogent when the initial (germinal or zygotic) genetic change involves a whole gene deletion, involves increasing the WT allele's protein production to more than is usual or ordinary for the WT allele. However, one wonders about increasing the "activity" of Nfn in all cells, since the *NF1* gene locus might normally be silent or quiescent in certain cell types. In cells in which it is not ordinary, *NF1* gene expression might have serious negative repercussions. For the *NF1* gene (locus), it is not clear that both alleles are equally expressed. Nor is it clear whether the monoallelic protein product functions on its own as a monomer or pairs as a dimer; and, if it is a dimer, whether the two parts derive from the same or different alleles.

Immediate removal of *NF1* diploinsufficient cells is probably the safest genetic treatment approach for interfering with progression of the disorder by imposing a penalty for a particular development within the cell. What I have in mind here is a molecule constructed like, and emulating, a virus homologue or paralogue. This molecular construct would occupy the nucleus in each of the *NF1* person's cells and has two critical abilities: 1) monitoring the long arm of Chromosome 17 to sense that the *NF1* wildtype allele is present; 2) triggering initiation of apoptosis in the event of loss of the *NF1* wildtype allele. In this way, any cell that converts from *NF1* haploinsufficiency to *NF1* diploinsufficiency will be shed immediately from the person through apoptosis. If the *NF1* wildtype allele realizes an intragenic mutation or whole gene deletion, the monitoring system activates cell-specific apoptosis. None of the *NF1* person's cells would be able to survive the change from *NF1* haploinsufficiency to *NF1* diploinsufficiency.

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Short Communication

Current Emerging Therapy for Amyloidosis Neuropathy

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ABSTRACT

Peripheral neuropathy is a type of neurological disorder in which patients with complex inherited neurological defects present significant phenotype in the peripheral nervous system. Hereditary amyloidogenic transthyretin (hATTR) neuropathy is typical polyneuropathy caused by single-nucleotide variants in the gene encoding transthyretin (TTR) and leads to transthyretin misfolding and systemic deposition of amyloid. One of the clinical hallmarks of hATTR neuropathy is polyneuropathy of the destruction of the somatic and autonomic peripheral nervous system, leading to loss of autonomy. Progressive amyloid accumulation also causes multi-organ dysfunction and death. There are many therapeutics that have been proposed and developed in these years. These therapies aim to reduce or eliminate hATTR from the plasma, stabilize the hATTR to prevent deposition, and dissolute the amyloid misfolding matrix. Recently, gene therapy strategy is being deployed to treat recessive genetic disorders by eliminating the expression of the mutated genes. Thus, gene-silencing approaches have been used to manage this amyloidosis neuropathy in the broad stages and produce some degree of improvement of this disease. Food and Drug Administration (FDA) approved Inotersen (an antisense oligonucleotide (ASO)) and patisiran (a small interfering ribonucleic acid (siRNA) for the treatment of hATTR polyneuropathy to suppress hATTR expression. Inotersen, a 2'-O-methoxyethylmodified ASO, which acts by reducing the production of transthyretin, and has been demonstrated to improve the quality of life in early hereditary transthyretin amyloidosis polyneuropathy. I here focus on the RNA-targeted therapy with particular emphasis on the molecular mechanisms by which antisense oligonucleotide can be designed to modulate transthyretin RNA function for being a novel therapy for hereditary amyloidosis neuropathy.

Keywords
Peripheral neuropathy; Amyloidosis; Antisense oligonucleotide (ASO).

PEREPHERAL NEUROPATHY

Peripheral neuropathy is a typical phenotype based on the problems that happened at the root of the damaged nerve. Over 50% of peripheral neuropathy are inherited neurological disorders caused by several numbers of causative genes, and it usually comes with different levels of phenotype. Among the peripheral neuropathy, polyneuropathy accounts for the massive amount of cases. It occurs when there are multiple nerves throughout your body present malfunction. It has been known that several reasons may cause polyneuropathy, including exposure to specific toxic or poor nutrition, or due to a side effect from diseases. The most common symptoms of polyneuropathy are tingling, numbness, loss of sensation, and a burning sensation in the extremities. One of the most severe polyneuropathies called guillain-barre syndrome (GBS), a rare disease that strikes suddenly when the immune system attacks nerves. Symptoms tend to appear quickly and worsen rapidly, sometimes leading to paralysis.[1] Currently, around 20-30% of Americans suffering from peripheral neuropathy. Although the influence is broadly cross all ages, the older adults are at increased risk. According to the statistic of peripheral neuropathy, there are 30% of patients with diabetic peripheral neuropathy (DPN),[2] 30% of patients with chemotherapy-induced peripheral neuropathy (CIPN),[3] and around 35% of patients with the human immunodeficiency virus-induced peripheral neuropathy.[4]

FAMILIAL AMYLOID POLYNEUROPATHY

Among different factors induced peripheral neuropathy, familial amyloid polyneuropathy (FAP) is a peculiar form of peripheral neuropathy, induced by a genetic mutation. FAP usually leads

to progressive lower extremity weakness and loss of pain sensation.[5,6] It is an autosomal dominant disorder characterized by the deposition of amyloid in the peripheral nerve system. Amyloidosis occurs due to the misfolded extracellular protein generating amyloid fibrils that are deposited into different tissues. The deposition of *transthyretin (TTR)* amyloid fibrils in tissue is known as amyloidosis transthyretin (ATTR).[7] The cause of hATTR is due to a mutation that occurred in the TTR gene. The main feature is polyneuropathy (hATTR-PN) or cardiomyopathy (hATTR-CM). There are over 150 reported mutations of the *TTR* gene.[7] The most common variation is Val30Met, where valine is replaced by methionine at position 30 (148G to A). The Val30Met variation is endemic in Portugal, Sweden, and Japan.[8] Although polyneuropathy is a common presentation, initial symptoms range from chronic inflammatory demyelinating polyneuropathy (CIPD), cardiomyopathy, carpal tunnel syndrome, lumbar canal stenosis, chronic digestive disease, and idiopathic polyneuropathy.[7] The global prevalence of hATTR amyloidosis was estimated round 10,000, with estimates ranging from 5,000 to 40,000 affected individuals. This estimation was based on the prevalence in seven core countries. However, the number might be an underestimate due to the phenotypic variability of hATTR.[7]

Hereditary transthyretin amyloidosis (hATTR) is a devastating polyneuropathy due to amyloid accumulation in the peripheral nervous system. Initial therapy for hATTR-PN is symptomatic. The pain from the polyneuropathy is often severe and debilitating. Treatment of hATTR includes removing the source of mutant TTR using small molecules, Diflunisal[9] and Tafamidis,[10] reducing the amount of ATTR deposition using doxycycline[11] and tauroursodeoxycholic acid (TUDCA),[12,13] or genetic therapy with *TTR* oligonucleotides to reduce the production of both mutated and Wild-type (WT) TTR.[14] Both tafamidis and diflunisal are selective TTR stabilizers has been approved for the treatment of FAP patients with early-onset polyneuropathy to delay neurological impairment.[9,10] Doxycycline has shown its effect *in vivo* in ATTR Val30Mat transgenic mice.[11] TUDCA, a natural compound, is a potent antioxidant agent since it reduces cytotoxicity in neurodegenerative diseases. Also, TUDCA treatment significant decreased the amount of TTR toxic aggregates.[12]

EMERGING THERAPY OF AMYLOIDOSIS NEUROPATHY

In 2018, two ribonucleic acid (RNA)-based therapeutic showed positive results in the clinical trial III and lead to Food and Drug Administration (FDA) approval route. The first drug is Patisiran, an RNA interference drug developed and marketed by Alnylam. The other drug is Inotersen, a 2'-O-methoxyethyl-modified antisense oligonucleotide, which acts by reducing the production of transthyretin, developed by Ionis Pharmaceuticals.[15,16]

Ribonucleic acid therapy is one of the updated technology for the therapeutic of hATTR-PN. RNA interference (RNAi) or small interfering RNA (siRNA) targets the messenger RNA (mRNA) for further cleavage or inhibition of mRNA expression. RNAi is mediated by binding mRNA in the cytoplasm and leads to a degradation of mRNA by Dicer siRNA mechanism. Patisiran® (ALN-TTR02; Alnylam, Cambridge, MA, USA) is a siRNA encapsulated in a lipid nanoparticle delivered to intracellular compartments of hepatocytes using an intravenous infusion.[16] It binds to the 3'-UTR of mutant and WT TTR mRNA. FDA approved Patisiran in 2018.[16] In the phase III trial of Patisiran, there were 225 patients that were randomly assigned to receive Patisiran or placebo. In the Patisiran treated group, transthyretin level was rapidly reduced in the serum and sustained over 18-months. At the end-point, 56% of the patients who received Patisiran had an improvement compared to 4% improvement of the patients who received a placebo. However, 97% of the patients in each trial group reported adverse events.[16] Revusiran (Alnylam, Cambridge, MA, USA) is another siRNA compound that conjugated with N-acetylgalactosamine and given subcutaneously (SC) for hATTR-CM. However, the clinical trial was halted due to an imbalance of mortality in the treatment compared to controls.[17]

Another updated technology for the therapeutic effect of hATTR-PN is ASO therapy. ASO therapy was developed in the late 1970s. Due to the massive negative polarity, ASOs were challenging to cross the cell membranes. Another challenging part of ASOs is immune responses trigger. These challenges were addressed recently by chemical modification on the ribose backbone with phosphorothioate (PS), which facilitated cell update and beneficial for pharmacokinetics (PKs) broadly *via* binding to the cell surface and intraocular proteins.[18] Additional 2'-O-methoxyethyl (2'-MOE) modifications also improve PKs and the binding affinity to plasma protein, which would allow the stability of antisense oligonucleotides (ASOs) against nucleases. Besides, 2'-MOE modification also increases the potency by improving the binding affinity of complementary hybridization. Moreover, the MOE modification enhances the safety profile *via* eliminating the nonspecific binding inducing toxicities.[19] The protein expression can be altered using two different mechanisms. The first mechanism is enzymatic RNA degradation using ribonuclease H (RNase H), which is an endonuclease in the nucleus. RNase H can recognize the RNA/deoxyribonucleic acid (DNA) heteroduplex and catalyzes the cleavage of RNA. That would reduce the expression of mutant and wild-type protein. Also, RNase H can prevent RNA from attaching to the ribosome to block protein transcription. The second mechanism is targeting on RNA splicing. ASO can bind to the pre-mature RNA to alter the RNA splicing without triggering RNA degradation. This exon-skipping mechanism can inhibit translation to reduce the production of the toxic protein, enhance the translation to restore the deficient protein, or obstruct interactions to modify the functional effect of the protein.[20]

Inotersen™ (Ionis, Carlsbad, CA, USA) is the most potent ASO target to TTR 3'-UTR mRNA that identified as a hepatic TTR inhibitor. Inotersen consists of 20 bases full-PS chimeric ASO with five 2'-MOE-modified ribonucleotides at each terminus, and a central region of ten 2'-deoxynucleotide residues (a 5-10-5 gapmer structure).[21] It binds to the mRNA with complementary base pairing mimicking the DNA/RNA complex and then recruits RNaseH1-mediated degradation of TTR mRNA to prevent mutant TTR production. Thus, the formation of TTR amyloid fibril deposits will be reduced and slows disease progression effectively.

hATTR is a devastating disorder with death, and it often occurs in patients around the age of 30. The inability of the previous small molecule to prevent hATTR progression led to the discovery of RNA and ASO therapeutic. Especially, Inotersen™, an ASO can be given once a week. Inotersen becomes available for hATTR to prevent disease progression and improve quality of life for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults in 2018. The study investigated 172 patients (112 patients were in the Inotersen group, and 60 patients were in the placebo group). Patients received three subcutaneous injections to achieve steady-state drug levels, followed by a once-weekly dose for the next 64-weeks. At the end-point, pre-specified sensitivity analyses showed a robust and beneficial Inotersen treatment effect. Further study showed 36% of the patients in the Inotersen group had an improvement in the mNIS+7, and 50% of the patients had an increase in the Norfolk quality of life questionnaire–diabetic neuropathy (QOL-DN) score. However, there were five deaths in the Inotersen group. The most severe adverse events in the Inotersen group were glomerulonephritis (3%) and thrombocytopenia (3%).[15] Although Inotersen showed a significant improvement, it doesn't cross the blood-brain barrier to the reach the central nervous system. Thus, it would not be effective in hATTR patients with predominant retinal or leptomeningeal symptoms. The delivery of the ASO in patients may be performed intravitreally and intrathecally to address these issues.[20,22]

CONCLUSION

Currently, there have been a couple of treatment options for hATTR patients. Primarily, RNA therapy (patisiran) and ASO therapy (Inotersen™) represent a significant advance in the field of amyloidosis. The unique mechanisms of action of inotersen™ and patisiran® overcome many limitations of other treatments. Both are efficacious in hATTR patients with early- and late-onset stages. Besides, both improve and slow the neuropathy progression. Although RNA therapy and ASO therapy are emerging treatments for peripheral neuropathy and other neurological disorders, formulation, dosing, and safety monitoring are different than conventional medicines. Thus, additional research is still necessary to understand the detail mechanism and effectiveness of these pioneer therapies when patients with hATTR receive these emerging therapies. As these pioneering and emerging therapies expand, the prospect for patients is becoming more promising, offering hope for a debilitating and life-threatening disease.

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