Received: 26 September 2020 | Revised: 16 January 2021 | Accepted: 19 January 2021

DOI: 10.1002/cne.25118

REVIEW

JCN RESEARCH IN SYSTEMS NEUROSCIENCE THE JOURNAL OF COMPARATIVE NEUROLOGY WILEY

Astrocytes in rare neurological conditions: Morphological and functional considerations

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Funding information
American Liver Foundation; Stanley J. Glaser Foundation

Abstract

Astrocytes are a population of central nervous system (CNS) cells with distinctive morphological and functional characteristics that differ within specific areas of the brain and are widely distributed throughout the CNS. There are mainly two types of astrocytes, protoplasmic and fibrous, which differ in morphologic appearance and location. Astrocytes are important cells of the CNS that not only provide structural support, but also modulate synaptic activity, regulate neuroinflammatory responses, maintain the blood–brain barrier, and supply energy to neurons. As a result, astrocytic disruption can lead to widespread detrimental effects and can contribute to the pathophysiology of several neurological conditions. The characteristics of astrocytes in more common neuropathologies such as Alzheimer's and Parkinson's disease have significantly been described and continue to be widely studied. However, there still exist numerous rare neurological conditions in which astrocytic involvement is unknown and needs to be explored. Accordingly, this review will summarize functional and morphological changes of astrocytes in various rare neurological conditions based on current knowledge thus far and highlight remaining neuropathologies where astrocytic involvement has yet to be investigated.

KEYWORDS
astrocyte, astrocytosis, central nervous system, function, morphology, neurologic conditions

1 | INTRODUCTION

Astrocytes are well established as the most common type of glial cells, outnumbering neurons over five times in the Central Nervous System (CNS) (Sofroniew & Vinters, 2010). As a heterogenous cell type, they are multifaceted with a myriad of functions relating to CNS homeostasis including modulating synaptic activity, maintaining the blood–brain barrier (BBB) integrity, regulating extracellular ion balance, activating the neuroinflammatory response, and supporting neuronal activity, among others. The astrocyte-neuron dynamic in particular is vital for neuronal homeostasis as astrocytes support neurons by regulating the formation and elimination of synapses, managing extracellular glutamate levels, releasing gliotransmitters, and providing lactate as an energy source for neurons.

Astrocytes have been broadly categorized into four major subtypes, protoplasmic, fibrous, interlaminar, and varicose projection, which are each distinguished based on their morphology and distribution in the CNS (Kettenmann & Verkhratsky, 2008; Miller & Raff, 1984; Oberheim et al., 2009; Sofroniew & Vinters, 2010; Tabata, 2015). Protoplasmic astrocytes are mainly found in the gray matter and have dense and branched processes, while the fibrous astrocytes have thinner processes and are predominantly in the white matter. Interlaminar astrocytes are characterized by their long and vertical processes that originate in layer I of the cerebral cortex and extend into layers III and IV (Vasile et al., 2017). This type of astrocyte is exclusively present in humans and other primate mammals. The functional significance of interlaminar astrocytes is unknown, but few studies suggest that it may be involved with neuronal support (Colombo et al., 2002, 2005). Varicose projection astrocytes are similar to interlaminar astrocytes in that they have long foot processes and are present in higher order primates. Varicose projection

astrocytes are usually found in layers V and VI of the cortex and have prominent varicosities (Oberheim et al., 2009). Their function is also unknown, but it may be likely that they assist in advanced cognitive processing given that they are only found in humans and primates.

In addition to the four major subtypes, research over the last few decades has revealed several other types of astrocytes including reactive astrocytes (A1 and A2), radial astrocytes, and the Bergmann glia of the cerebellum, among others. A1 astrocytes are reactive astrocytes that are predominantly involved in activating a neuro-inflammatory response and have been implicated in various neurodegenerative diseases. A1 astrocytes are different than healthy astrocytes in that they differentially express various receptors, ion transporters, neurotransmitters, and release increased amounts of pro-inflammatory factors and neurotoxic proteins (T. Li et al., 2019). They also induce fewer synapses than healthy astrocytes and are activated by microglia (Liddelow et al., 2017). Furthermore, these astrocytes selectively exhibit an upregulation of Complement 3, CFB, and MX1S (Liddelow et al., 2017). Via the release of complement proteins and other neurotoxins or cytokines, A1 astrocytes can induce apoptosis in oligodendrocytes and neurons as well as facilitate further inflammatory insult.

A2 astrocytes are also a subtype of reactive astrocytes but are induced by ischemic insults. While A1 astrocytes modulate genes that are destructive in nature, A2 reactive astrocytes release neurotrophic factors that promote neuron survival and serve other neuroprotective purposes, such as facilitating synaptogenesis (Arregui et al., 2011; Christopherson et al., 2005; Hayakawa et al., 2014). Although A1 and A2 reactive astrocytes can be distinguished from each other based on their gene expression profile, specific response to various insults, and changes in intracellular signaling cascades, the exact contribution of each of these astrocytes in various neurodegenerative conditions is not well understood.

Several of these aforementioned types of astrocytes are yet to be definitively placed into the historical protoplasmic or fibrous classification; Indeed, some of these types of astrocytes may serve as their own classification in the future.

A shared structure of almost all astrocytes is the intermediate filaments, which are largely constituted of glial fibrillary acidic protein (GFAP), a protein that is widely used as an astrocyte marker. While GFAP is the most commonly used astrocyte marker, other pan-astrocyte markers such as NDRG2, ALDH1L1, and S100β, which are more uniformly expressed in certain parts of the brain, may be more effective (Bushong et al., 2002; Dehghani et al., 2019; Walz & Lang, 1998; Yoon et al., 2017).

In response to CNS insults, astrocytes adopt new functions and characteristics. The most common phenomenon observed is astrocytosis, also known as astrogliosis or reactive astrocytosis, which is a broad term referring to the numerous severity-dependent functional, structural, and morphological changes astrocytes undergo as a result of CNS injury. These changes can induce both neuroprotective and neurotoxic effects such as neuroinflammation and neurodegeneration (Phatnani & Maniatis, 2015; Sofroniew, 2009). Under severe conditions, astrocytes proliferate, express increased GFAP, release pro and anti-inflammatory cytokines, and cluster into polarized bundles around the injured region. Hypertrophied astrocytes and their respective processes can elongate and overlap, forming a glial scar around the injured or inflamed region.

As astrocytes have an incredibly diverse and wide spectrum of functions, astrocytic dysfunction can have drastic biological effects (Figure 1). The characteristics of astrocytes in common neurological conditions such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis has been described and remains a prominent area of study (Phatnani & Maniatis, 2015; Seifert et al., 2006; Siracusa et al., 2019). However, this does not extend to the numerous other rare neurological conditions whose etiologies remain elusive. Accordingly, in this review, we will detail the role of astrocytes in rare neurological conditions through the lens of function and morphology and highlight remaining neuropathologies where astrocytic involvement has yet to be investigated.

2 | RARE NEUROLOGICAL CONDITIONS IN WHICH ASTROCYTIC MANIFESTATION AND FUNCTION HAVE BEEN REPORTED

2.1 | Conditions that show astrocytosis and morphological changes

While there seems to be numerous neuropathologies with neuronal dysfunction, astrocytes have also been implicated in the pathogenesis of various rare neurological conditions, but their morphological and functional changes have not been well established. The astrocyte changes that take place in some of these conditions are detailed below:

Fragile X syndrome (FXS) is a genetic disorder that causes mild to moderate intellectual disability, autism, and delayed speech. FXS is typically caused by replication slippage, resulting in repetition of the CGG triplet repeat over 200 times within the Fragile X mental retardation 1 (FMR1) gene on the X chromosome, which hinders the functional capabilities of the fragile X mental retardation protein (FMRP). This protein is a translational repressor that is expressed in both neurons and astrocytes and is vital for normal synaptic transmission between neurons. Many studies on FXS have been conducted to look at the functional role of astrocytes in various processes including synaptic development, synaptic transmission, and dendritic spine morphology (Ariza et al., 2017; Cheng et al., 2012; Simhal et al., 2019).

Simhal et al. (2019) recently conducted a study in a mice model of FXS to identify the role of astrocytes in synaptic composition. Via immunofluorescent array tomography, they found that in FMRP knockout (KO) mice, there was a significant reduction in the density and amount of excitatory glutamatergic synapses that were associated with the processes of an astrocyte, suggesting that astrocytes have a diminished functional role in the modulation of excitatory synaptic transmission in FXS, consistent with the findings of other similar studies (Jawaid et al., 2018; Simhal et al., 2019). In addition to changes in excitatory synapse density, astrocytes have been shown in FMRP KO FXS models to have aberrant secretion of various proteins and

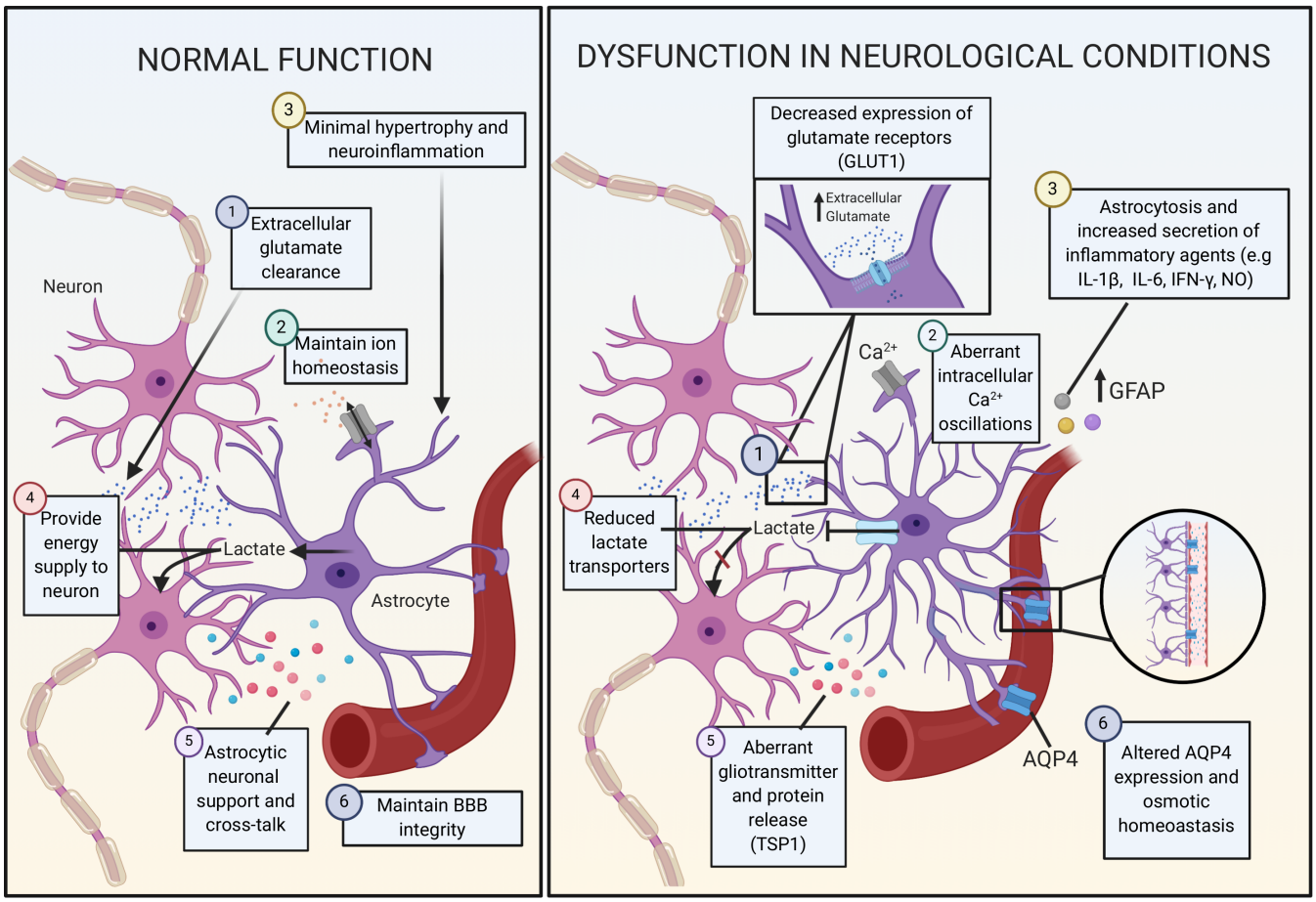

FIGURE 1 Astrocyte function in normal physiology versus neurological conditions: This is a schematic of astrocyte function in both normal (left panel) and diseased states (right panel) based on observed functional differences in all neuropathologies analyzed in this review. For each normal function (numbered 1–6), there is a corresponding matching number that is appropriately color coded on the right panel describing how that respective function has been observed to change in various neuropathologies. Among all neurological conditions reviewed in this paper, the key common functional changes include alterations in (1) extracellular glutamate clearance, (2) ion homeostasis, (3) secretion of inflammatory agents, (4) energy supply to neurons, (5) neuronal support and cross-talk, and (6) blood–brain barrier integrity. AQP4, aquaporin-4; BBB, blood–brain barrier; GFAP, glial fibrillary acidic protein; IFN, interferon; NO, nitric oxide; TSP1, thrombospondin-1 [Color figure can be viewed at wileyonlinelibrary.com]

gliotransmitters, including interleukin-6 (IL-6), hevin, SPARC proteins, GABA, glutamate, and thrombospondin-1 which have all been shown to regulate excitatory synapse development and transmission (Cheng et al., 2016; Krasovska & Doering, 2018; Risher et al., 2014; S. K. Singh et al., 2016; Wallingford et al., 2017; Wang et al., 2016).

Another group studied morphological changes in astrocyte specific FMRP KO mice with wild type (Zibaee et al., 2010) neurons and found that there was an increase in the dendritic spine density and decrease in total neuronal dendritic length in the motor cortex in addition to impaired motor learning (Hodges et al., 2017). However, when they re-induced the astrocyte specific FMRP expression in tandem with KO of FMRP from nonastrocytic cells, the mice still displayed phenotypical characteristics of FXS, suggesting that FMRP expression only from astrocytes is not sufficient to functionally revert the FXS phenotype into the WT phenotype (Hodges et al., 2017). Jacobs and Doering (2010) conducted similar in vitro studies with variations of WT and FMRP KO neurons and astrocytes. Corroborating the morphological findings of Hodges et al. discussed above, they found that the abnormal increased dendritic spine density and branching observed in FMRP KO astrocytes and WT neurons was prevented in the presence of WT astrocytes and FMRP KO neurons (Jacobs & Doering, 2010). These studies together provide evidence that astrocytes indeed play a vital functional role in the abnormal dendritic morphology observed in FXS.

Astrocytosis in FXS has also been shown to occur in mice (F. H. F. Lee et al., 2019; Pacey et al., 2015). Using astrocyte cell cultures from both WT and FMRP KO mice brains, F. H. F. Lee et al. (2019) found that astrocytes underwent significant morphological changes characterized by a large increase in GFAP expression. In addition, they found that actin reorganization was increased in the KO group; specifically, this group had more abnormal actin clusters on the outer parts of the cell in comparison to the WT group and had other abnormal morphology including nonuniform rearrangement of actin and aberrant dendritic spine features (F. H. F. Lee et al., 2019).

As shown above, a large majority of studies detailing astrocyte induced functional or morphological changes in FXS are based on either animal models or human cell lines. While the above few studies indicate some functional changes in neurons relevant to astrocytes, the precise role of astrocytes in this disorder remains to be established.

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder associated with male premutation carriers of FXS. It also occurs as a result of replication slippage but is characterized by a fewer number of CCG repeats (60–200 repeats) compared to FXS. Clinical features of FXTAS include issues related to movement with cerebellar gait ataxia, action tremor, and dystrophic white matter. Several studies and case reports on astrocytic morphological changes in FXTAS have showed the presence of intranuclear ubiquitin inclusions in enlarged protoplasmic and fibrous astrocytes as well as neurons (Chaussenot et al., 2008; Greco et al., 2006; Schluter et al., 2012; Wenzel et al., 2010).

One study on human tissue found a generalized decrease in the amount of the iron-binding proteins transferrin and ceruloplasmin in astrocytes (Ariza et al., 2017). Another study showed that in comparison to WT astrocytes, FXTAS cortical astrocytes exhibited more aberrant spontaneous Ca^{2+} oscillations and reduced expression of glutamate transporters, which negatively affects the ability of astrocytes to modulate synaptic development and transmission (Cao et al., 2013).

Tuberous sclerosis complex (TSC) also known as epiloia is a multisystem genetic disease characterized by the presence of benign tumors in the CNS and peripheral organs (Figure 2(a)). Symptoms include seizures, intellectual disability, developmental delay, skin abnormalities, and lung and kidney disease. Tuberous sclerosis is caused by a mutation in either the TSC1 or TSC2 gene, which code for the proteins hamartin and tuberin, respectively. These proteins act as tumor suppressors by forming the hamartin-tuberin protein complex, which proceeds to regulate a cell cycle regulatory signaling protein called mechanistic target of rapamycin (mTOR). Upon loss of functional hamartin encoded by TSC1, these astrocytes are defective in cell size regulation, presenting with primarily astrocytosis and also abnormal morphology (Uhlmann et al., 2004).

In regard to morphology, several studies on various human TSC lesions have shown elongated astrocyte processes (A. A. Sosunov et al., 2015), increased amount of astrocytic proliferation, and subependymal giant cell astrocytomas (Figure 2(b); Gipson et al., 2013; Sahin et al., 2016; Uhlmann, Apicelli, et al., 2002; Uhlmann, Wong, et al., 2002; Zou et al., 2017). Analysis of so called microtubers throughout the cortex revealed the presence of cytomegalic cells surrounded by astrocytes with unusually long processes (A. A. Sosunov et al., 2015). The same study also showed that astrocytosis marked by increased GFAP is present around the border of these microtubers in the normal human brain parenchyma. Further analysis into the type of astrocytes within these cortical tubers shows significant heterogeneity. A majority of these astrocytes had long and straight processes comparable to fibrous astrocytes found in white matter (Oberheim et al., 2009; A. A. Sosunov et al., 2015; A. A. Sosunov et al., 2008). Other types of astrocytes found within cortical tubers were large

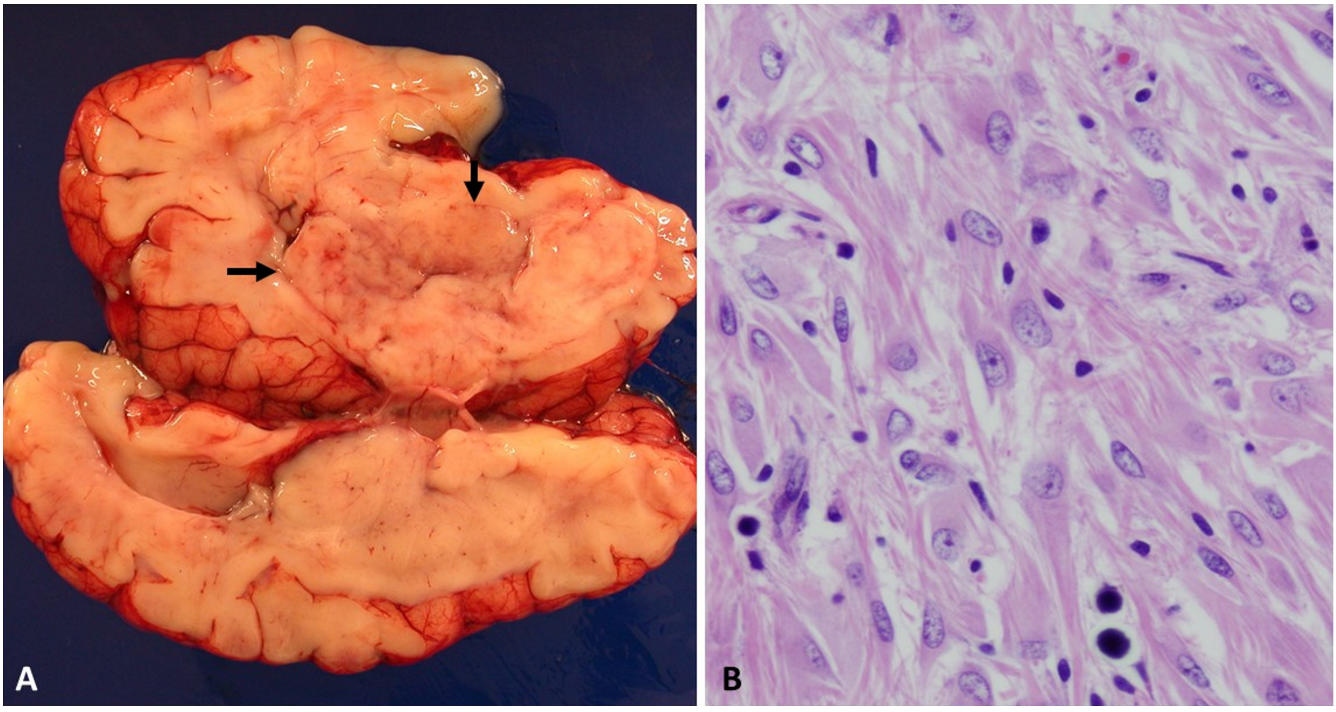

FIGURE 2 Tuberous sclerosis complex: (a) gross image of the brain of a patient with tuberous sclerosis complex. Arrows show a solid well circumscribed mass in the frontal lobe (arrows). (b) Histological examination shows the mass to be composed of fascicles of large elongated cells (subependymal giant cell astrocytoma) [Color figure can be viewed at wileyonlinelibrary.com]

protoplasmic astrocytes in the gray matter with mTOR cascade activation, likely due to loss of function mutations in TSC1 or TSC2 (A. A. Sosunov et al., 2008).

Among these astrocytes, crucial functions relating to glutamate homeostasis are impaired which can lead to a host of downstream detrimental effects including neuronal hyperexcitability and neuronal apoptosis and ultimately epileptic seizures and intellectual disability (Wong et al., 2003; Zeng et al., 2007). As a result, decreased expression of glutamate transporters in astrocytes has been a promising target of potential targeted therapies in TSC induced epilepsy (Zeng et al., 2010). In particular, ceftriaxone, a beta-lactam antibiotic that increases the expression of astrocyte glutamate receptors, has shown efficacy in several preclinical studies (Chu et al., 2007; Lipski et al., 2007; Rothstein et al., 2005; Zeng et al., 2010). Other potential targets for therapy are miR146a and miR147b, which have been shown to reduce severe inflammatory events and astrocytic hypertrophy in human TSC cell cultures (van Scheppingen et al., 2016; van Scheppingen et al., 2018).

Multiple system atrophy (MSA), also known as Shy–Drager syndrome, is a rare neurodegenerative disorder that clinically manifests as tremors, ataxia, and postural instability. MSA is an α-synucleinopathy characterized by abnormal accumulation of fibrillary α-synuclein (αS) in oligodendrocytes. In addition, astrocytes appear to have cytoplasmic inclusions also composed of αS (Wenning & Jellinger, 2005). Astrocytic interaction with neurons and other glial cells has been illustrated in Figure 3. This disease has specific glioneuronal degeneration involving widespread parts of the CNS and peripheral nervous system. Accumulation of phosphorylated αS also occurs in subpial and periventricular astrocytes after long disease duration (Nakamura et al., 2016). These astrocytic inclusions appear to be morphologically distinct from one another as one is granular and the other is filamentous (Krejciova et al., 2019). Astrocytosis in cerebral cortex has been described as well (Radford et al., 2015), and stereological studies found significantly more astrocytes and microglia specifically in the frontal, parietal, and temporal cortex (Jellinger, 2018).

Ménière's disease is a condition of the inner ear characterized by endolymphatic hydrops. Clinical symptoms include loss of hearing and vertigo. Vestibular nerve segments from patients has shown the presence of reactive astrocytes with extensive proliferation of fibrous processes (Spencer et al., 2002). A study in 1981 showed that round areas containing no or very few axons and bundles of proliferated processes of fibrous astrocytes were found in human vestibular nerves following neurectomy (Ylikoski et al., 1981). Other morphological changes include the presence of corpora amylacea (CA) in astrocytic cytoplasm and round or oval shaped, electron-dense bodies with a multilamellar structure, suggesting that CA can be a marker of neurodegeneration (Sbarbati et al., 1996a; Sbarbati et al., 1996b).

Cerebral arteriosclerosis is a type of atherosclerosis where build-up of plaque in the blood vessels of the brain occurs. A build-up of plaque and hyaline can subsequently lead to complications such as stroke, as the plaque disrupts blood flow within the cerebrovascular arterioles causing ischemia (Figure 4). Diseases associated with cerebral atherosclerosis include hypertensive arteriopathy, Alzheimer's disease with cerebral amyloid angiopathy, cerebral microbleeds, and

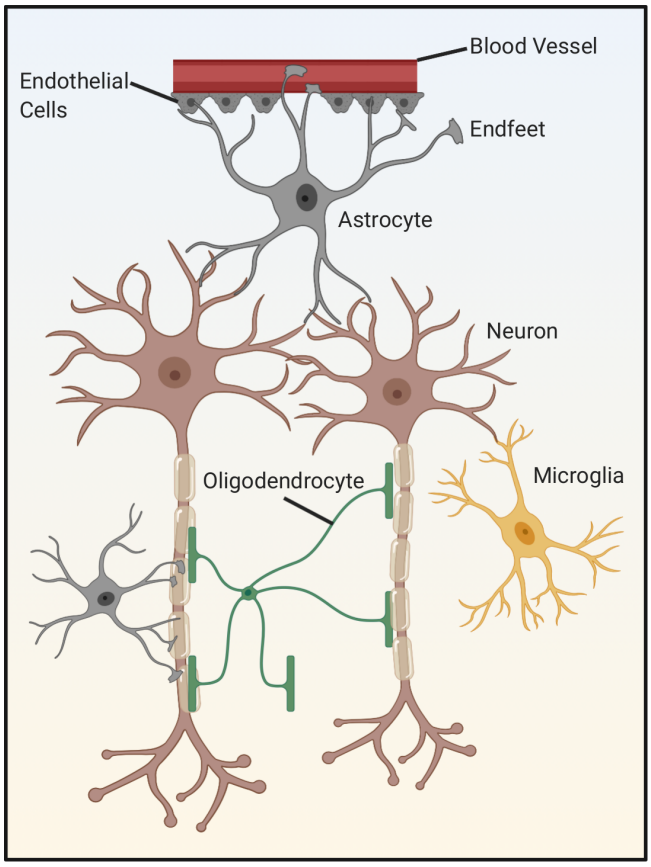

FIGURE 3 Astrocytes in context of other glia and CNS cells: This figure provides an overview of the cytoarchitectural relationship of astrocytes with other cells of the CNS. Astrocytes have processes that come in contact with the neurovasculature, aiding in the blood–brain barrier integrity with the help of endothelial cells (shown in gray). In addition, astrocytic processes come in contact with and modulate synaptic communication between neurons (shown in brown). Oligodendrocytes (in green) serves to myelinate the neuronal axon which is reinforced by astrocytic processes. Microglia (in yellow) are involved with the immune system of the central nervous system and are comparable to astrocytes with regards to morphology and certain functions regarding neuronal support [Color figure can be viewed at wileyonlinelibrary.com]

stroke. Hence, the astrocytic morphology might resemble the one in Alzheimer's disease if there is progress to dementia. Studies have showed that there are reductions in astrocytic GLUT1 and lactate transporters, as well as retraction of astrocyte end-feet and swelling consistent with neurovascular uncoupling, preceded wide-spread β-amyloid plaque pathology (Kim et al., 2020; Merlini et al., 2011). In addition, astrocytosis and subsequent glial scar formation has been shown in mice to functionally protect the brain from inflammation and infarct spread in brain ischemia (L. Li et al., 2008).

Duchenne muscular dystrophy (DMD) is an X-lined genetic neuromuscular disorder associated with significant muscle degeneration, atrophy, and endomysial fibrosis (Figure 5(a)). Chronic inflammation is another manifestation of DMD in which increased inflammatory cytokines alongside astrocytosis are present (Murphy et al., 2015). DMD is

caused by loss of function mutations in the DMD gene encoding for dystrophin, a cytoskeletal protein vital for muscle cell homeostasis, which leads to widespread dystrophin deficiency (Figure 5(b),(c)). CNS involvement and subsequent intellectual disability are not shown in all DMD patients and can vary in severity (Rae & O'Malley, 2016).

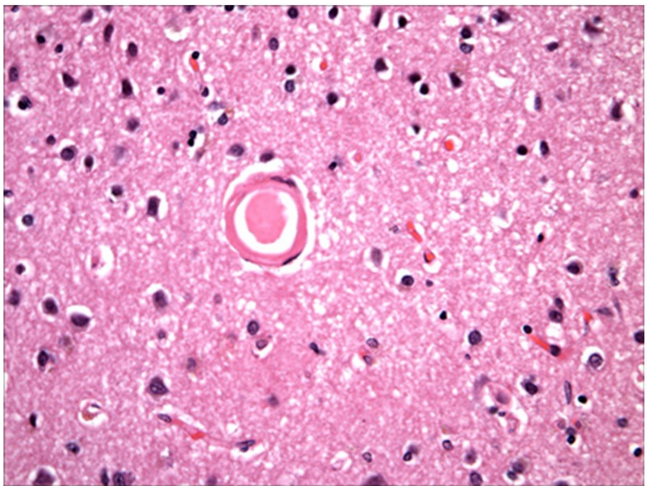

FIGURE 4 Cerebral arteriolosclerosis: A thick "stiff" parenchymal arteriole with hyalinized wall is identified. The differential diagnosis includes amyloid angiopathy but amyloid work up is negative [Color figure can be viewed at wileyonlinelibrary.com]

The biological mechanism underlying cognitive impairment in DMD is an active area of research and may be associated with neuronal hyperexcitability that results from disruption in normal astrocyte function. It has been previously established that dystrophin is ubiquitously expressed in healthy patients throughout the CNS, including in astrocytes (Hendriksen et al., 2016). In the presence of dystrophin deficiency, studies in mice and cultured astrocytes have shown various changes in astrocytic functions relating to neuronal support including defective glutamate clearance, altered Ca^{2+} homeostasis, and abnormal nitric oxide signaling (Murphy et al., 2015; A. M. Patel et al., 2019). As all these functions are vital for synaptogenesis and synaptic plasticity, it is plausible that astrocytic dysfunction is involved in the cognitive phenotypes observed in DMD.

In DMD, astrocytic morphology is also noted to change especially in perivascular astrocytes that help form the BBB. In particular, astrocytic processes and end-feet have been observed to be swollen as a result of decreased aquaporin-4 expression in DMD (Nico et al., 2003; Nico & Ribatti, 2012). But, the mechanism behind how abnormal water flux into the brain via aquaporin-4 connects to the pathophysiology of DMD remains unknown.

Refsum disease is an inherited peroxisomal disorder with neurological deficits characterized by an accumulation of phytanic acid, a branched saturated fatty acid. Phytanic acid is known to have several detrimental effects on astrocytes including oxidative stress, impaired mitochondrial function, and Ca^{2+} dyshomeostasis (Ronicke et al.,

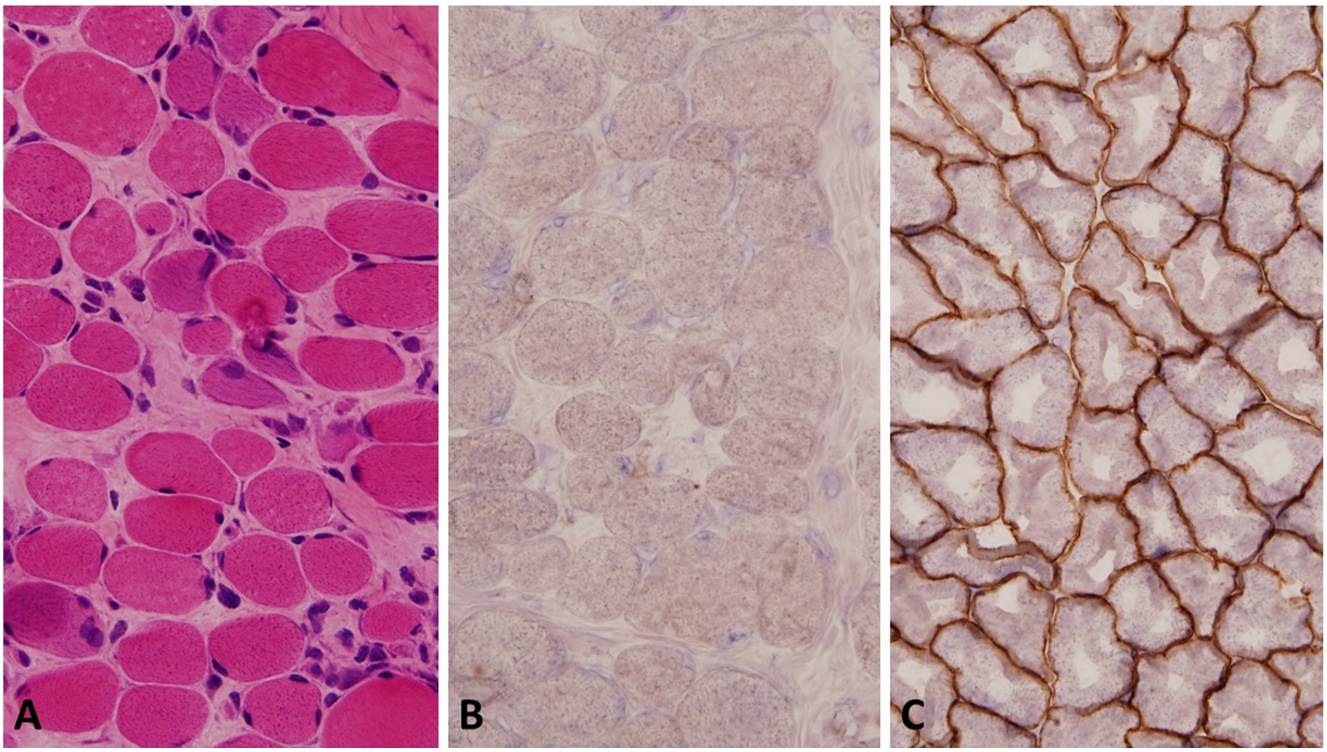

FIGURE 5 Duchenne muscular dystrophy: (a) histologic examination of skeletal muscle shows fibers with variation in size and shape. Note the presence of endomysial fibrosis which is an important feature of dystrophic myopathy. (b) Immunostain for dystrophin shows complete loss of staining. (c) Dystrophin immunostain in a normal patient to use as a control. Note the presence of continuous membranous staining of dystrophin in all fibers [Color figure can be viewed at wileyonlinelibrary.com]

2009; Schonfeld & Reiser, 2016). In addition, phytanic acid accumulation appears to lead to astrocytosis and even premature astrocytic apoptosis (Borges et al., 2015; Reiser et al., 2006). Autopsy studies have also revealed insight as inclusions with bilamellar ribbon-like structures have been noted in astrocytes (Cervos-Navarro, 1990). Further studies are needed to determine if all these astrocytic toxicities induced by phytanic acid are contributive factors to the disease or if they are coinciding effects.

Lysosomal storage diseases are a group of approximately 50 rare autosomal recessive metabolic disorders that result from defects in lysosomal function due to a deficiency of an enzyme required for the metabolism of sphingolipids, glycolipids, proteins, or mucopolysaccharides.

Niemann–Pick disease involves a group of inherited metabolic disorders characterized by the accumulation of sphingomyelin in the lysosomes of cells. Clinically, it can manifest as cognitive difficulties, seizures, or slurred speech. A mice model of Niemann–Pick disease revealed that astrocytic involvements include astrocytosis and increased neuroinflammatory cytokine expression, both of which may contribute to neuronal degeneration (Baudry et al., 2003).

In Niemann–Pick disease type A, sphingomyelin and its metabolite sphingosylphosphocholine (SPC) accumulate in the brain. SPC, when accumulated, can induce toxicity in the brain leading to various neurological symptoms. The buildup of SPC has been shown to impact astrocytic function by increasing Ca^{2+} signaling and glutamate release, which leads to astrocytic proliferation and ultimately neuroinflammation followed by neurodegeneration (Chiulli et al., 2007).

Similar to FXS, abnormal Ca^{2+} oscillations in cortical astrocytes have been shown in mice with mutations in the Nieman–Pick type C 1 (NPC1) gene (Saez et al., 2013). In addition, these cortical astrocytes in mice were observed to have reduced gap junctions between other astrocytes, which is often associated with neuroinflammation in the various Niemann–Pick diseases (Saez et al., 2013). Corroborating these findings, restoring astrocyte-specific NPC1 in the presence of KO neurons increased survival and delayed neuronal degradation, suggesting that astrocytes do indeed have a functional role in Niemann-Pick disease (Borbon et al., 2012; S. C. Patel et al., 1999; M. Zhang et al., 2008).

Krabbe disease (KD), or globoid cell leukodystrophy, is an autosomal recessive lysosomal storage disorder caused by a deficiency of the enzyme galactosylceramidase encoded by the GALC gene, resulting in toxic accumulation of galactolipids and psyochine. Clinical symptoms include seizures, vomiting, and delay in motor development, among others. KD leads to astrocytosis, demyelination of white matter, and immune response activation (Jesionek-Kupnicka et al., 1997; Mohri et al., 2006; Snook et al., 2014). It has been shown that at an early stage, microglia form distinct nodules surrounded by hypertrophied astrocytes and that later on these reactive astrocytes are no longer centered around the microglial nodules, indicating that microglia are activated prior to astrocytes in KD (Potter & Petryniak, 2016). Eventually, it appears that reactive astrocytes ultimately propagate diffusely and no longer occur near microglial nodules (Potter & Petryniak, 2016; Snook et al., 2014).

Mucopolysaccharidoses (MPS) are a group of eight lysosomal storage disorders and are all caused by the accumulation of undegraded glycosaminoglycans. Deficiency or KO of any of the 11 enzymes required to degrade these sugar chains can induce the diseased phenotype. MPS type I is characterized by the build-up of the thioflavin-S protein, which induces astrocytosis as shown by an increased number of immunoreactive GFAP positive astrocytes (Viana et al., 2020). In a murine model of MPS type I, Wilkinson et al. (2012) show that both fibrous and protoplasmic of astrocytes were much greater in number throughout each whole section of the brain in comparison to WT mice. Similarly, MPS type III is characterized by the accumulation of a different molecule called heparan sulfate, but astrocytes in this type are also reported to produce several pro-inflammatory cytokines, ultimately leading to neuroinflammation (Dwyer et al., 2017; Holley et al., 2018; Puy et al., 2018).

Metachromatic leukodystrophy is a lysosomal storage disease characterized by a deficiency in arylsulphatase A, which causes a buildup of sulfatides and subsequent white matter degeneration. A murine model of metachromatic leukodystrophy showed that this buildup of sulfatide is often associated with concurrent astrocytosis in the gray matter (Molander-Melin et al., 2004). A recent study by Frati et al. (2018) used induced pluripotent stem cells (iPSC) to observe morphological changes in developing neurons and glial cells in metachromatic leukodystrophy. They noticed that GFAP expressing astrocytes presented with abnormal morphology, specifically the absence of the expected long and thin processes branching from the soma toward neighboring neurons (Frati et al., 2018). Other studies have added to these findings, showing evidence of astrocytosis and other aberrant morphological changes including decreased cell body size, cytoplasmic inclusions, lamellar structures, and a herringbone pattern (Assadi et al., 2013; Ponath et al., 2017).

Sandhoff disease/Sandhoff–Jatzkewitz disease, variant 0 of GM2-Gangliosidosis, is an inherited neurodegenerative lysosomal disorder caused by the inherited deficiency to create functional beta-hexosaminidases A and B encoded by the HEXB gene. Mutations in HEXB have been reported in mice to lead to astrocytosis (Ogawa et al., 2017), to activate the astrocytic secretion of inflammatory cytokines (Loth et al., 2016; E. J. White et al., 2017), and to increase astrocytic expression of adenosine A(2A) receptor (Ogawa et al., 2018). All of these findings point to astrocyte involvement in Sandhoff disease via activation and propagation of a significant immune-mediated neuroinflammatory response.

Fabry disease can affect many parts of the body including the kidneys, heart, and skin. The loss of function mutation that causes Fabry disease prevents the function of alpha-galactosidase A, which subsequently causes a build-up of a type of fat called globotriaosylceramide (Gb3, GL-3, or CD77) in the body. The role of astrocytes in Fabry disease has yet to be fully elucidated. One study on human tissue has reported the formation of CD77 immunoreactive inclusions within the soma and perivascular end-feet of astrocytes in the olfactory trait (Del Tredici et al., 2020). Future work on Fabry disease is needed to add on to these findings and to detail any morphological changes in astrocytes.

Tay–Sachs disease is an inherited metabolic disorder caused by a deficiency of beta-hexosaminidase and subsequent accumulation of GM2 ganglioside within cells, which can lead to toxicity and neurodegeneration. Neuroinflammation appears to be a key factor in the observed toxicities as seen by increased astrocytic activation and inflammatory cytokine secretion (Myerowitz et al., 2002). Studies also showed the presence of large lipofuscin-like cytoplasmic inclusions in astrocytes (de Baecque et al., 1975). Similar to other metabolic disorders, these inclusions have not been shown to directly contribute to the pathogenesis of Tay–Sachs disease. As a result, astrocytosis and the release of inflammatory cytokines seem to be the primary functional contribution of astrocytes to this disease (Figure 6).

Progressive multifocal leukoencephalopathy (PML) is a demyelinating condition caused by reactivation and subsequent brain infection of the polyomavirus, also known as the JC virus. It predominately affects people with compromised or weakened immune systems as well as those on regiment immunosuppressants. Multifocal demyelination, reactive gliosis, and the presence of bizarre, infected oligodendrocytes are all histopathological features of PML (Figure 7(a)–(d); Berger et al., 2013). While the virus appears to be primarily located in oligodendrocytes rather than astrocytes or neurons, bizarre astrocytes with lobulated nuclei have also been described in PML (Berger et al., 2013; Mesquita et al., 1996).

2.2 | Conditions that show nonspecific changes of astrocytes

Some of the neurological conditions simply present with a gliosis that involves the proliferation or hypertrophy of several different types of glial cells, including astrocytes, microglia, and oligodendrocytes. Some of these conditions include chronic inflammatory demyelinating polyneuropathy/chronic relapsing polyneuropathy, Distal spinal muscular atrophy type functional neurological disorder (FND), Idiopathic intracranial hypertension, leukoencephalopathy with vanishing white matter, megalencephalic leukoencephalopathy with subcortical cysts, Pelizaeus–Merzbacher disease, mitochondrial myopathies, narcolepsy, olivopontocerebellar atrophy, Zellweger syndrome, paraneoplastic syndrome, Spina bifida, Spinocerebellar ataxia, iron deposition disorders like superficial hemosiderosis and Karak syndrome, Unverricht–Lundborg disease, Chronic fatigue syndrome, and Schizencephaly and transverse myelitis, neuronal ceroid lipofuscinosis, Opsoclonus Myoclonus syndrome, neurofibromatosis, trigeminal neuralgia, and Fahr's syndrome. Several of the more prominent of these rare neurological conditions are detailed below:

Complex regional pain syndrome (CRPS), also known as Reflex Sympathetic Dystrophy, is a chronic disorder of the limbs often caused by trauma or injury. CRPS manifests as extreme pain, decreased range of movement, swelling of joints, and changes to the skin and bones. As astrocytes form systems with themselves and are involved in modulating synaptic transmission including nociception, ample studies have shown that activation of spinal glial cells (astrocyte and microglia), as marked by increased GFAP expression, occurs as a result of increased cytokine levels or other inflammatory agents in CRPS (Linnman et al., 2013; G. Tian et al., 2017). As a result, compounds such as polydeoxyribonucleotide and FTY720 which produce anti-inflammatory effects have shown preclinical efficacy in reducing astrocyte activation and hypertrophy by reducing intercellular cytokine levels (B. J. Lee et al., 2020; S. H. Lee et al., 2020). A more translational study by Helyes et al. (2019) introduced autoantibodies from humans with CRPS into mice and then observed reduced astrocytic activation upon blockage of proinflammatory cytokine interleukin-1. To date, no

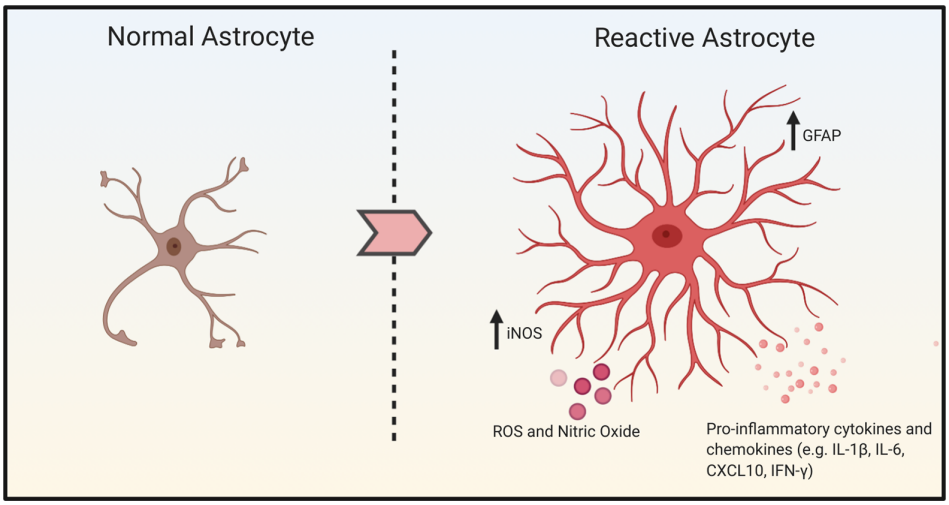

FIGURE 6 Notable changes in reactive astrocytes compared to Normal astrocytes: The figure portrays distinct characteristics of reactive astrocytes compared to normal astrocytes. An emphasis is placed on secreted factors that contribute to downstream neurotoxicity, degeneration, and inflammation. Morphological differences are also shown by the different branching and density of processes as well as overall cell size. Changes in expression of key markers of astrocytosis including GFAP are shown via an accompanying arrow. Descriptions of secreted factors are provided below the respective molecules. GFAP, glial fibrillary acidic protein; IFN, interferon; iNOS, inducible nitric oxide synthase; ROS, reactive oxygen species [Color figure can be viewed at wileyonlinelibrary.com]

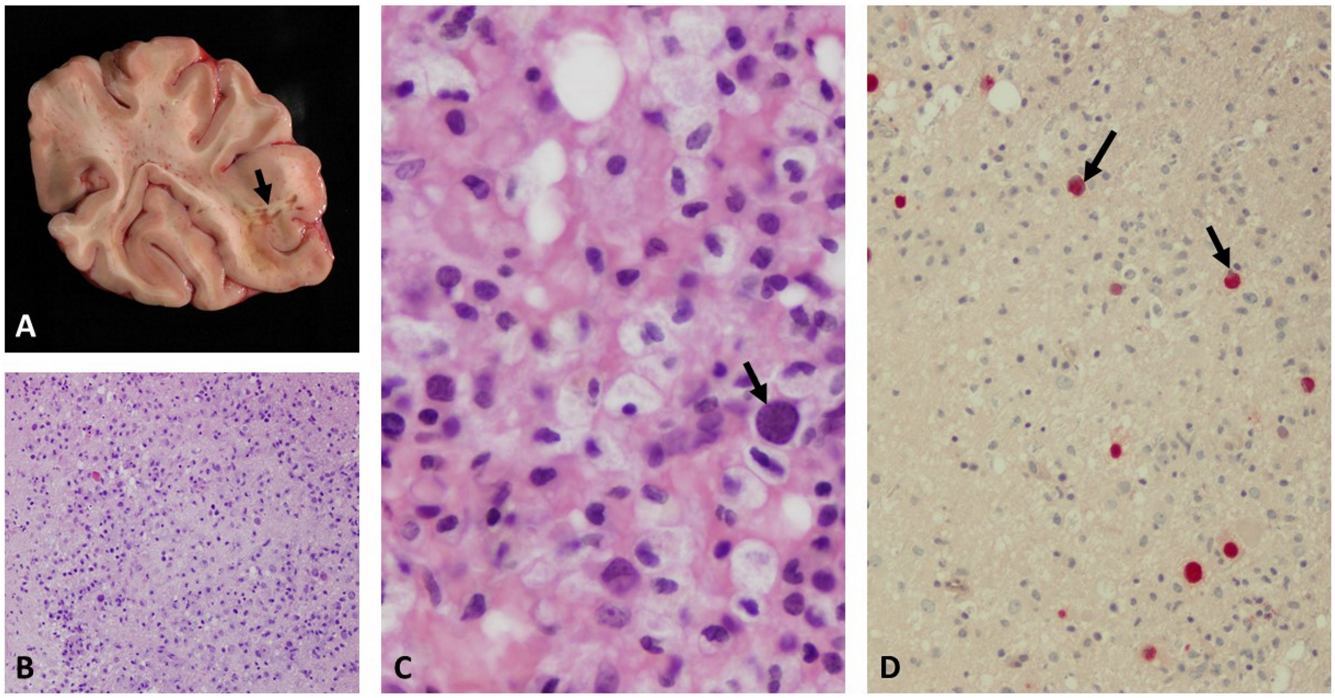

FIGURE 7 Progressive multifocal leukoencephalopathy: (a) gross examination of the brain shows a focus in the white matter (arrow) with punctate demyelination. (b) Myelin stain shows complete loss of myelin in this focus along with prominent reactive gliosis. (c) Histologic examination shows atypical oligodendrocytes (arrow). (d) Immunostain for polyoma virus confirms the presence of the virus within the oligodendrocytes (arrows) [Color figure can be viewed at wileyonlinelibrary.com]

morphological changes have been observed in patients or animal models of CRPS.

Dystonia is a neurological movement disorder syndrome characterized by a twisting, repetitive movements, tremors, and abnormal postures. Lubag is a specific type of dystonia that is an X-linked recessive dystonia-parkinsonism primarily affecting the Filipino population. In this disease, a unique mosaic pattern of astrocytosis has been observed in the caudate and lateral putamen (Waters et al., 1993). Another case report of a patient with generalized dystonia from the age of 10 showed a similar mosaic pattern of striatal pathology as well as the presence of gliosis in parts of the striatum (Gibb et al., 1992). Other studies have found the presence of reactive astrocytes (Zhao et al., 2008) and unusual astrocytes with dense processes but have not found clustering of astrocytes in the striatum as described above (Gearing et al., 2002). Further studies in addition to case reports are required to fully elucidate any morphological changes among astrocytes and to determine whether astrocytosis alone contributes to the physiology or if gliosis of other glial cells produces the same effects.

Creutzfeldt-Jakob disease (CJD) is a rare human prion disease that often manifests as acute dementia. Sporadic CJD is the most common type and occurs spontaneously without cause. Genetic CJD is another type and is characterized by inherited mutations in the PRNP gene, which leads to misfolding and multimeric assembly of an infectious prion (PrP). Astrocytosis as well as increased numbers of microglia and inflammatory cytokines have been noted in many types of CJD (Andres Benito et al., 2018; Kohama et al., 2020; Llorens et al., 2014). In sporadic CJD, however, there appear to be conflicting findings on the roles of astrocytes in the propagation of prion infection. On the one hand, astrocytes are involved in the uptake and degradation of abnormal PrP aggregates in the gray matter of patients (Choi et al., 2014). But, on the other hand, astrocytes have also been shown to support and facilitate prion replication as well as prion transmission to neurons (Krejciova et al., 2017; Victoria et al., 2016). Further studies are needed to fully delineate functional contributions of astrocytes to the pathogenesis of sporadic CJD.

Although CJD lesions are primarily in gray matter, white matter involvement has also been described. In pan encephalopathic type CJD, inducible nitric oxide synthase (iNOS) is over induced within astrocytes of the degenerating cerebral white matter (Kohama et al., 2020). Interestingly, these astrocytes also have polyribosome-like granules in the cytoplasm alongside increased superoxide dismutase 1, which is responsible for the degradation of toxic oxygen molecules. This suggests a novel mechanism in which astrocytes protect themselves from the cytotoxic effects of nitric oxide in CJD. In addition to these polyribosome-like complexes, other bizarre morphologies have been observed in CJD patients, including emperipolesis where reactive astrocytes engulf nearby oligodendrocytes (Liberski et al., 1997; Shintaku & Yutani, 2004).

Periventricular leukomalacia (PVL) is an ischemic condition caused by diffuse injury to the white matter surrounding the ventricles (Figure 8(a)). This condition primarily affects premature infants and complications can include intraventricular hemorrhage (Figure 8(b)). The etiology of PVL is unknown but hypoxia-ischemia, infection, and inflammation may be contributing factors. Increased presence of pro-

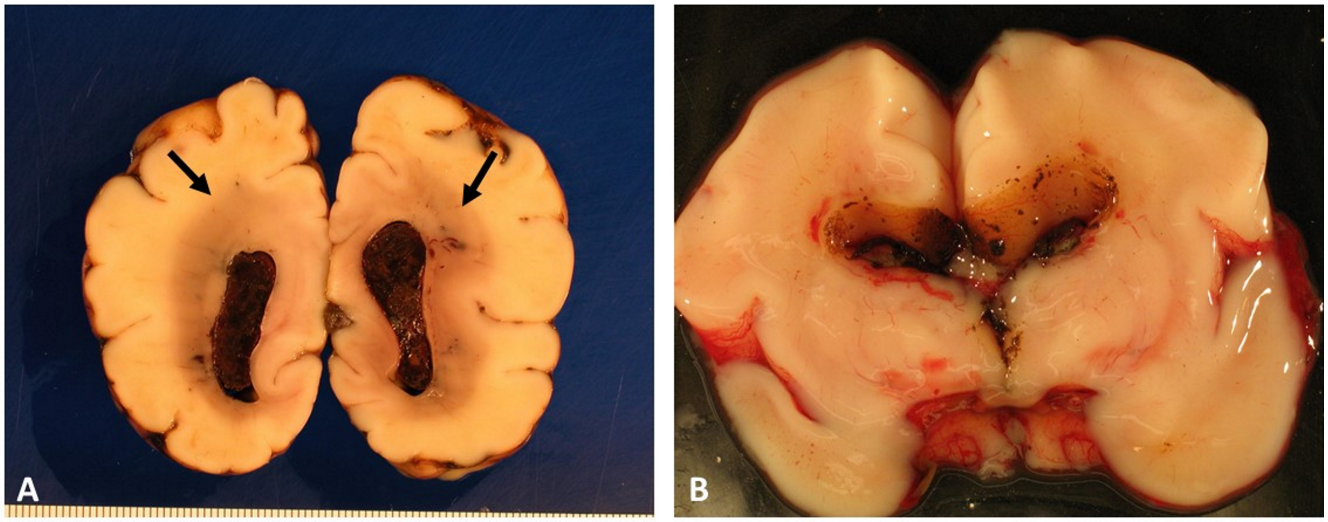

FIGURE 8 Periventricular leukomalacia (PVL): (a) cross section of cerebral hemispheres showing a dark gray periventricular zone (arrow). This represents ischemic/hypoxic changes around the lateral ventricles. (b) another manifestation of PVL is the presence of punctate hemorrhage in the subependymal region. The rupture of these vessels results in intraventricular hemorrhage [Color figure can be viewed at wileyonlinelibrary.com]

inflammatory cytokines and oxidative stress as a result from heightened lipid peroxidation appears to primarily affect premyelinating oligodendrocytes which predominate these regions of the brain in the early weeks of development (Haynes et al., 2003; Volpe et al., 2011). Astrocytic involvement in PVL is largely unknown but diffuse gliosis has been observed in astrocytes alongside microglial activation. In addition to oxidative stress, reactive nitrogen species as a result of increased iNOS has been hypothesized to also contribute to the observed focal necrosis; Haynes et al. (2009) found an increase in iNOS immune-positive reactive astrocytes near the white matter lesion. Other studies have looked into the dysregulation of astrocytic glutamate transporters as a potential contributor to the pathogenesis of PVL, but further investigation is warranted (Desilva et al., 2008; Jantzie et al., 2010).

2.3 | Neuropathologies with distinct changes in astrocytic morphology and function other than astrocytosis

It has been shown up thus far that gliosis is the most common phenomenon observed in neurological conditions. However, some conditions have more specific changes and it is worth noting these specific morphological and functional changes in astrocytes as studied in the following conditions:

Cockayne syndrome/Neill-Dingwall syndrome is an inherited fatal autosomal recessive neurodegenerative disorder caused by mutations in ERCC8 and ERCC6, which are required for proper DNA damage repair. Clinical symptoms include growth failure, premature aging, and microcephaly. Neuropathology results in several case reports show the presence of reactive astrocytosis and atypia of the Bergmann glioma (Karikkineth et al., 2017; Koob et al., 2010; Miyahara et al., 2015; Rapin et al., 2006). Observed unique morphologic characteristics include bizarre enlarged multinucleated astrocytes with profuse cytoplasm (Koob et al., 2010; Miyahara et al., 2015; Rapin et al., 2006; Weidenheim et al., 2009). In addition, abnormal aggregates of DNA binding protein TAR in astrocytes have been reported in another patient (Sakurai et al., 2013). As current findings are based solely on case reports, further preclinical studies are needed to further delineate why astrocytes have such abnormal characteristics in Cockayne syndrome.

Dawson disease/subacute sclerosing panencephalitis is caused by a fatal re-emergence of the measles virus that affects the CNS of primarily children and young adults. The measles virus may remain dormant for long periods and then reappear 6–15 years later, causing brain inflammation and the death of nerve cells. Although the measles virus strain was not detected within astrocytes (Jehmlich et al., 2013), morphological changes in astrocytic nuclei include abundant nuclear bodies and granulofilamentous inclusions as found by histopathological examination (Hoppen et al., 2003; Lewandowska et al., 2001).

Polymicrogyria (PMG) is a cortical malformation involving multiple small gyri that create excessive folding of the brain leading to an abnormally thick cortex. PMG is commonly associated with abnormalities of neuronal migration including heterotopia (Barkovich, 2010; Guerrini & Parrini, 2010). The importance of the radial glial cells (radial precursor cells) for neuronal migration and cortical formation is well established (Rakic, 2007). The integrity of the connection between radial precursor end-feet and the brain surface is essential for their survival. If damaged, it leads to apoptosis and a reduction in cortical size (Radakovits et al., 2009). In human PMG, there are abnormal large blood vessels and many hypertrophic astrocytes seen (Miki et al., 2015; Squier & Jansen, 2014). Case reports have also shown eosinophilic granular cytoplasmic inclusions in the astrocytes of the cerebral cortex (Barnett et al., 2011; Minamitani et al., 1994).

Rabies is caused by the rabies virus (RABV) and is transmitted through infected animals. The rabies infection has been around for hundreds of years yet remains an endemic, likely in part because lab attenuated viruses tend to functionally differ from WT RABV (B. Tian et al., 2017). As primary microglia and astrocytes undergo active viral replication (Ray et al., 1997), they may be directly contributing to the pathogenesis of Rabies infections independent of infected neurons. A study of rabies-infected human brain cells showed astrocytes were also present in inflamed CNS tissue but showed no evidence of apoptosis (Fernandes et al., 2011). These infected astrocytes exhibited RABV-positive cytoplasmic inclusions and RABV antigens (Fernandes et al., 2011; Jogai et al., 2000).

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited monogenic small vessel disease, which hinders blood flow within cerebral vessels in the brain. Vascular aggregation of a protein called Notch3 has also been identified as a known marker of CADASIL. Limited research has been done to date on the role of astrocytes in this condition. In CADASIL Notch 3 mutant mice, Ghosh et al. (2015) observed increased detachment of astrocytic end-feet from cerebral micro vessels in mice. Another study showed that GFAP was downregulated in the cortex (Brennan-Krohn et al., 2010), suggesting a loss of astrocytes or impaired astrocyte function in CADASIL but further studies are needed to confirm these findings.

Lafora disease/Lafora progressive myoclonic epilepsy is an inherited genetic condition characterized by the accumulation of glycogen-like inclusions called Lafora bodies in the CNS. Clinical manifestations include recurrent epileptic seizures and rapid cognitive deterioration. Glycogen storage and metabolism in the brain is largely reserved for astrocytes (Duran & Guinovart, 2015). In Lafora disease, excess aggregation of glycogen inclusions occurs within both astrocytes and neurons, but these Lafora bodies appear to be located primarily in the processes rather than the soma of astrocytes and are distinct from those found in neurons (Auge et al., 2018; Oe et al., 2016; Rubio-Villena et al., 2018; Valles-Ortega et al., 2011).

Changes in astrocytic function are also believed to contribute to the pathobiology of Lafora disease. In particular, astrocytic glutamate clearance and transport seem to be compromised in Lafora disease. Several studies have shown that astrocytic glutamate transporter GLUT1 is impaired, leading to a higher extracellular glutamate concentration which can contribute to epileptogenesis (Munoz-Ballester et al., 2016; Munoz-Ballester et al., 2019).

All in all, these results and findings suggest that impaired astrocytic glutamate clearance as well as the presence of glycogen inclusions in astrocytes may play a crucial role in the pathophysiology of Lafora disease.

Hydrocephalus is caused by the accumulation of cerebrospinal fluid within the ventricles of the brain, often leading to increased intraventricular pressure and cerebral edema. The onset of hydrocephalus is often attributed to dysfunction and denudation of the neuroependyma that tiles the ventricular walls (Abouhamed et al., 2009; Dominguez-Pinos et al., 2005). In response, astrocytes appear to then proliferate (Paez et al., 2007) to form a new layer on top of the denudating epithelium (Paez et al., 2007). Interestingly, a study in mice found that these astrocytes in the newly formed layer acquire several new functional and morphological changes (Roales-Bujan et al., 2012). Morphologically, they appear to develop intercellular digitations and increased microvilli projected into the ventricle. Functionally, they adopt new functions mimicking those of epithelial cells including increased connexin-43 gap junctions and aquaporin-4 water transporters. Together, this suggests that in hydrocephalus, the proliferating astrocytes adopt epithelium-like morphology and function to compensate for denudating ventricular ependyma. However, further clinical studies are needed to validate if this phenomenon found in mice pertains to humans as well.

While the product of astrocytic proliferation outlined above was beneficial, for the most part, astrocytosis and general gliosis involved in hydrocephalus have been shown in vivo to contribute to chronic neuroinflammation (Paez et al., 2007) via astrocytic secretion of IL-1β (Olopade et al., 2019).

Friedreich's ataxia is an inherited neurodegenerative movement disorder with clinical symptoms of ataxic gait and loss of proprioception. It is caused by a large trinucleotide repeat expansion in the FXN gene, which codes for frataxin, a protein with downstream effects on mitochondrial ATP production. Frataxin deficiency in Friedreich's ataxia can lead to oxidative damage and subsequent neurodegeneration. As gait and coordination-related symptoms are hallmarks of the disorder, the neurons and glia in the cerebellum may be particularly disrupted (Kanner et al., 2018) as a result of frataxin deficiency. Recent studies in mice and humans indeed found increased reactive oxygen species in the mitochondria of frataxin deficient developing cerebellar astrocytes (Franco et al., 2017) and activation of the p53 pathway, leading to premature astrocytic apoptosis (Loria & Diaz-Nido, 2015). Enhanced cell death and aberrant morphology were also noted in WT neurons in a frataxin deficient medium, suggesting that neuronal-glial interactions are impaired (Kanner et al., 2018) in Friedreich's ataxia. A related disorder, ataxia telangiectasia, which is also caused by mutations in a single gene, has similar astrocytic features to that observed in Friedrich's ataxia, including premature apoptosis and astrocytosis (Meshulam et al., 2012; Shimoda et al., 2017). In the case of ataxia telangiectasia, abnormal changes in the ATM gene causes distinct clinical features including dilated blood vessels in the conjunctiva (Figure 9(a)) and ectatic blood vessels in the choroid (Figure 9(b)).

2.4 | Neuropathologies with underlying functional astrocytic changes regarding inflammation, transporter expression, synaptic regulation, and genetic phenomena

In certain neuropathologies, instead of morphological changes, the predominant involvement of astrocytes centers around molecular and functional changes including aberrant receptor/transporter activity, activation of a cytokine-induced inflammatory response, abnormal genetic events, or ultrastructural changes. Some of these

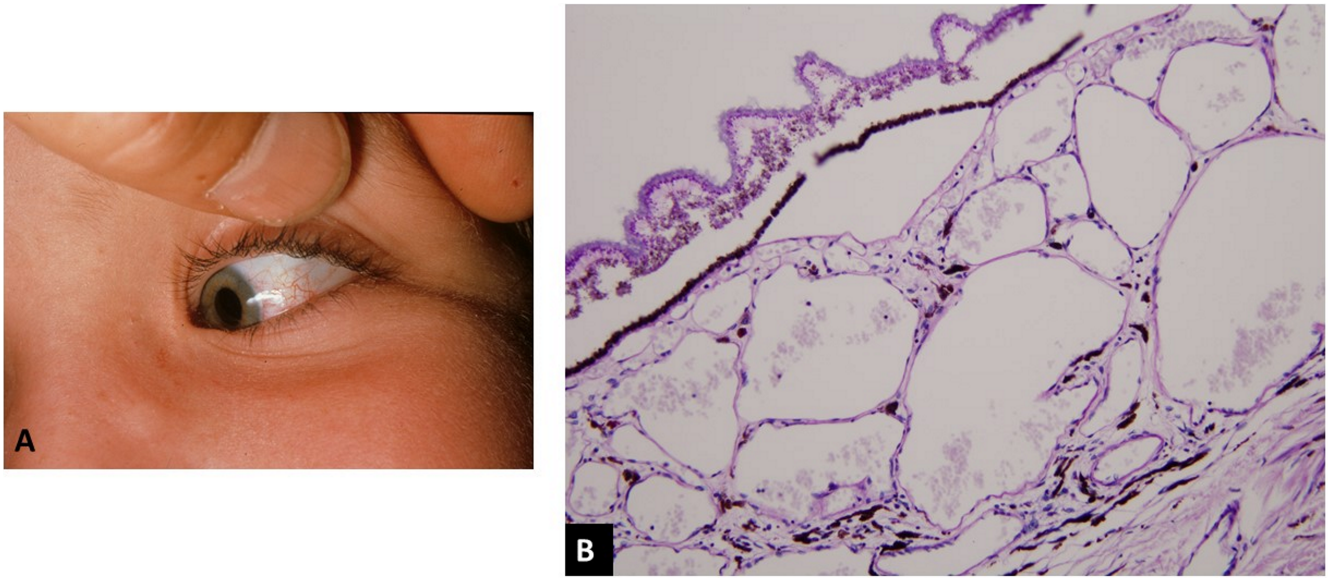

FIGURE 9 Ataxia telangiectasia: (a) numerous dilated blood vessels are seen in the conjunctiva. (b) Histologic examination of the eye shows numerous ectatic blood vessels in the choroid [Color figure can be viewed at wileyonlinelibrary.com]

conditions are Fibromyalgia, Fetal alcohol spectrum disorders, Gaucher's disease or Gaucher disease, Wilson's disease, Tourette syndrome, African trypanosomiasis/sleeping sickness, sleep apnea, Reye syndrome, Rett syndrome, Kearns–Sayre syndrome, Lyme disease, Machado–Joseph disease, Rasmussen's encephalitis, and Optic neuritis/optic papillitis. Other conditions that fit into this category are described below:

Menkes disease (MNK), also known as Menkes syndrome, is an X-linked recessive disorder caused by mutations in genes coding for copper-transport protein ATP7, which leads to widespread copper deficiency in the bloodstream and brain. This deficiency hinders function of several vital copper-dependent enzymes, leading to the clinical characteristics of kinky hair, growth failure, hypotonia, and nervous system deterioration (Niciu et al., 2007). Astrocytes play an important role in MNK as the mutated copper export protein ATP7A results in copper accumulation within the astrocytes (Kodama et al., 1991) and thus a lack of copper supply to neurons. Excess copper accumulation greatly affects the function of astrocytes by reducing their anti-oxidative and proliferation capacity (Hu et al., 2016). In a mice model of MNK, there appears to be an increase in GFAP positive astrocytic end-feet at the BBB as well as astrocytosis (Niciu et al., 2007). Although the observed astrocytosis is expected (Shafit-Zagardo et al., 1988), the reason for increased astrocytic recruitment near the cerebrovascular domain is not fully understood.

Postherpetic neuralgia (PHN) is a chronic nerve pain caused by the herpes zoster virus (shingles) which damages the peripheral nerves of the body. Activation of spinal astrocytes may contribute to the chronic pain in PHN via increased expression of interleukin-1β and other proinflammatory cytokines (G. H. Zhang et al., 2011). As such, glial inhibitors such as minocycline and fluorocitrate have shown analgesic effects in mice models of PHN (S. Chen et al., 2010; Lei et al., 2016).

Diabetic neuropathy is a common complication in diabetic patients involving peripheral nerve damage. Studies have shown that following peripheral nerve damage, spinal astrocytes produce pro-inflammatory cytokines, matrix metalloproteinases, and chemokines (Machelska & Celik, 2016; F. A. White et al., 2007). In addition, several animal models have shown increased activation of spinal astrocytes in streptozotocin-induced diabetic mice (Barragan-Iglesias et al., 2018; Deng et al., 2017). Administration of astrocytic specific inhibitors to these mice has shown to drastically attenuate mechanical allodynia, suggesting that astrocytes are indeed involved in the physiology of diabetic neuropathy (Y. H. Liao et al., 2011). The exact mechanism has yet to be fully elucidated but this remains an active area of research (G. Chen et al., 2014).

Bipolar disorder is a heterogenous psychiatric disorder characterized by disruption in numerous biochemical pathways including the immune-inflammatory response and glucocorticoid signaling. Clinical manifestations often include oscillation between periods of depressive mood and periods of manic (bipolar I) or hypomanic (bipolar II) episodes. As the cause for bipolar disorder is multifactorial, the functional role of a single cell type such as astrocytes remains unclear. Interestingly, astrocytosis, which is typically observed in several neurodegenerative conditions, has not been observed in bipolar disorder (Damadzic et al., 2001). In addition, there is some emerging evidence that astrocytic densities are reduced in bipolar disorder (Peng et al., 2016), but conflicting findings suggest that this may be location dependent (Altshuler et al., 2010; Toker et al., 2018). Most of what is known about astrocytes in bipolar disorder comes from studying the therapeutic mechanisms of common anti-bipolar drugs including lithium salts, valproic acid, and carbamazepine. In short, these drugs appear to affect astrocytes by inducing gradual intracellular alkalinization which subsequently reduces calcium-mediated gliotransmitter release (B. Li et al., 2007; Song et al., 2012; Yan et al., 2013). This

suggests that aberrant gliotransmitter release from astrocytes may contribute to a disbalance in neurotransmission and to the pathobiology of bipolar disorder, but further conclusive studies are needed to confirm these findings.

Guillain–Barré syndrome (GBS) is an autoimmune inflammatory disorder that can be triggered by viral infection in which the immune system targets the nerves of the peripheral nervous system. Although GBS primarily affects peripheral nerves, CNS involvement has been reported in patients (Gregory et al., 2005). Astrocyte involvement is yet to fully be elucidated but preliminary findings do show the presence of autoantibodies that bind to not only myelin and gangliosides, but also to astrocytes (Gortzen et al., 2004; Rink et al., 2017).

Adrenoleukodystrophy (ALD) is a neurodegenerative, X-linked genetic disease that causes accumulation of expansive fatty acids and subsequent demyelination of neurons. The ALD phenotype is caused by mutations in the ABCD1 gene which encodes for a protein that transfers fatty acids into peroxisomes. The exact pathogenic mechanism of how accumulation of large fatty acids leads to demyelination is unknown, but heat shock proteins and pro-inflammatory cytokines expressed in astrocytes appear to be involved in the initiation of demyelination and inflammation in cerebral ALD (Baarine et al., 2015; Gortz et al., 2018; J. Singh et al., 2009). In addition, astrocytes have been associated with increased amounts of iNOS and human leukocyte antigen (Gilg et al., 2000; Katsuragi et al., 1996; Khan et al., 1998) alongside the presence of lamellar inclusions in lysosomes of swollen astrocytes (Szpak et al., 1996; Takeda et al., 1989). As such, these findings together suggest that the functional role of astrocytes in cerebral ALD is to facilitate an inflammatory response following a build-up of fatty acids which ultimately leads to the observed demyelination.

HTLV-1 associated myelopathy (HAM), which can be caused by infection of the human T-lymphotropic virus type 1 (HTLV-1), is an immune-mediated neurodegenerative disease of the spinal cord that produces chronic inflammation. The HTLV-1 virus is known to target a disproportionate amount of CD4+ and CCR4+ T lymphocytes, inducing increased levels of interferon-y (Araya et al., 2014). Additional immune related findings of HLTV-1 infected patients include the significantly increased secretion of chemokine CXCL10 from astrocytes amidst chronic inflammation in the spinal cord (Ando et al., 2013). Thus, the current postulated mechanism is one of a positive feedback loop where HLTV-1 infected T cells produce interferon-y which then signals astrocytes to secrete increased CXCL10, leading to the recruitment of more infected T cells and ultimately resulting in the observed chronic inflammation (Yamano & Coler-Reilly, 2017). In addition to their role in inflammation, astrocytes appear to also undergo morphological and functional changes when engaging with infected T cells including cell shrinkage, loss of cell to cell contact (Gudo et al., 2015), and impaired glutamate uptake (Szymocha et al., 2000).

Angelman syndrome (AS) is a rare genetic neurodegenerative disease caused by loss of function mutations in the maternally imprinted UBE3A gene, which encodes E3 ubiquitin ligase. In neural tissue, neurons are known to epigenetically silence the paternal allele which is why AS develops as a result of mutations in the maternal allele. The role of astrocytes in AS is only beginning to unfold. As of now, the functional contribution of astrocytes to AS is unknown, but it is known that astrocytes in the brain and spinal cord biallelically express UBE3A, unlike neurons where the gene is imprinted (Grier et al., 2015; Judson et al., 2014).

Attention-deficit hyperactivity disorder (ADHD) is a common heritable neurobehavioral disorder diagnosed by five main criteria outlined in the Diagnostic and Statistical Manual (DSM-IV). ADHD is considerably heterogeneous and so several theories have been proposed to explain the biological foundations of this disorder.

The idea that ADHD is an energy-deficient disorder has been a focal point of many theories. In particular, there is a growing amount of support for a theory based on the Astrocyte-Neuron Lactate Shuttle (ANLS) hypothesis which claims that reduced astrocytic lactate release into neurons causes the symptoms of ADHD by reducing neuronal energy supply (Killeen, 2019; Killeen et al., 2013; Russell et al., 2006). A study by Medin et al. (2019) supports this hypothesis as it was found that the amount of MCT1, a prominent lactate transporter at the BBB, was significantly increased in ADHD mice, suggesting that lactate produced from skeletal muscles may be sent to the brain to compensate for the reduced lactate in the ADHD brain. Aside from lactate related energy supply to neurons, other theories also focus on neuronal-astrocyte interactions as a contributor to hyperactivity. Nagai et. al demonstrate that the secretion of thrombospondin-1 (TSP1) from astrocytes enhanced synaptic transmission among medium spiny neurons in the striatum, producing an ADHD-like phenotype in mice (Nagai et al., 2019).

The search for the cause of this disorder has also expanded into the genetics realm. Although any singular genetic causal with ADHD is unlikely, several astrocyte related genes, including NDRD2 and CADM1 have been proposed to be involved in the pathophysiology of this disorder (Y. Li et al., 2017; Sandau et al., 2012). NDRD2, a tumor suppressor gene primarily expressed in astrocytes, affects numerous astrocyte functions including glutamate clearance, and preliminary studies have shown that downregulation of NDRD2 yields an ADHD phenotype likely as a result of impaired glutamate clearance (X. Li et al., 2020; Y. Li et al., 2017).

Autism spectrum disorder (ASD) is another neurodevelopmental disorder with an elusive etiology and is marked by deficits in social interaction. Neuronal dysfunction is the leading theory for ASD etiology, but the functional contribution of glial cells has also been explored.

The role of neuroinflammation in ASD has been an area of active research (X. Liao et al., 2020), but the question as to whether it is a cause or merely a symptom remains unanswered. In ASD, activated GFAP-positive astrocytes appear to secrete increased pro-inflammatory cytokine IL-6 (Crawford et al., 2015; X. Liao et al., 2020; Wei et al., 2011). Interestingly, inhibiting aberrant IL-6 levels in ASD-derived astrocytes was found to increase synaptogenesis (Russo et al., 2018). Thus, the glial cell induced inflammatory environment may indeed contribute to synaptic dysfunction, which is believed to be a major component in the pathophysiology of ASD (Y. J. Li et al., 2020).

Another observation in ASD is the loss of Purkinje neuron cells in the cerebellum (Becker & Stoodley, 2013; Kern, 2003; Whitney et al., 2009). Since high extracellular glutamate clearance can lead to neuronal apoptosis (Purcell et al., 2001), disruption of the Bergmann glia, which are radial astrocytes of the cerebellum, may be involved as they are responsible for maintaining extracellular glutamate homeostasis (Chrobak & Soltys, 2017).

Canavan disease is a genetic spongiform leukodystrophy characterized by neurodegeneration and demyelination of white matter. The genetic origin is from mutations in the oligodendrocyte specific gene encoding aspartoacylase (ASPA) which hydrolyzes *N*-acetylaspartic acid into acetate and aspartate. The deficiency of ASPA and subsequently the buildup of extracellular NAA in white matter is considered a metabolic hallmark of the demyelination observed in CD. Astrocytes are hypothesized to be primary drivers of increased extracellular NAA as they are responsible for the catabolism of *N*-acetylaspartylglutamate (NAAG) which is an anabolic metabolite of NAA (Baslow, 2000; Baslow & Guilfoyle, 2009). If further proven, this hypothesis would neatly explain and connect the presence of demyelination in CD with the pathological accumulation of NAA in white matter. Morphological changes in astrocytes as a result of ASPA deficiency have been noted and include increased swelling and vacuolation (Bokhari et al., 2020; Merrill et al., 2016).

Another proposed function of NAA is to serve as a molecular water pump removing metabolic water from neurons (Baslow, 2003). Astrocytes are known to be involved with the maintenance of water homeostasis hence why they express numerous water transporters such as aquaporin-4. To delineate if disruption of water homeostasis may be involved with the physiology of CD, Clarner et al. (2014) used a mouse model of CD to observe astrocytic changes with regards to aquaporin-4 expression. They found morphological changes including an increased expression of aquaporin-4 in the cytoplasm rather than in the end-feet which is the norm (Clarner et al., 2014).

Cerebral palsy (CP) is a movement disorder usually caused by brain injury during gestation or after birth. A common way white matter damage occurs in infants is by hypoxic-ischemic encephalopathy (HIE). Similar to other diseases, neuroinflammation involving activated astrocytes plays a vital role in the pathogenesis of CP. Under HIE and other ischemic-type conditions, astrocytes secrete pro-inflammatory cytokine IL-1β and become activated. Several studies in mice and humans have looked at astrocytic changes in HIE conditions. Some of the findings include increased astrocytic activation (Yang et al., 2019), upregulated astrocytic cyclooxygenase type 2 (COX2) as a result of IL-1β (Shiow et al., 2017), disruption in astrocytic connexin 43 hemichannel opening (Chavez et al., 2019; Mallard et al., 2014), and increased astrocytic expression of glutamate transporter EAAT2 (Desilva et al., 2008). Some morphological changes have also been noted including an increase in the number of astrocytic processes (Chavez et al., 2019) and the presence of astrocytic swelling in minimal extracellular Ca^{2+} (Thomas et al., 2004). Overall, it seems that ischemic-type injuries that lead to CP appear to have several downstream functional and morphological effects on astrocytes, likely in part because of the activated inflammatory environment created which interferes with several different astrocyte dependent homeostatic processes.

Down syndrome (DS) is a genetic disorder caused by trisomy of chromosome 21 and is a major cause of intellectual disability. Although much is already known about neurons in DS, the functional and morphological changes of astrocytes are beginning to be unveiled. From a genetic standpoint, RNA seq analysis of human iPSC-derived astrocytes shows dysregulation in transcription of genes related to neurodevelopment and cell adhesion (Ponroy Bally et al., 2020). However, DS implications from these RNA seq results are limited as it focuses primarily on isolated astrocytes rather than the crosstalk between astrocytes and neurons, which is of more relevance.

To better understand the functional contribution of astrocytes to the pathogenesis of AD, recent studies have used human iPSCs (Araujo et al., 2018; C. Chen et al., 2014). C. Chen et al. (2014) observed that astrocytes secreted increased amounts of reactive oxygen species and failed to sufficiently modulate synaptic activity and synaptogenesis in neurons. Other iPSC studies built upon these findings (Araujo et al., 2018) with one of them showing that astrocytes in DS had spontaneous Ca^{2+} oscillations (Mizuno et al., 2018). These findings are consistent with other studies showing that calcium homeostasis and signaling in astrocytes is disrupted in DS (Bambrick et al., 2003; Muller et al., 1997). In regard to the Chen et. al study mentioned above, the observed higher levels of reactive oxygen species in trisomic astrocytes is interesting as it is one of the first studies to show the functional contribution of astrocytes to the oxidative stress commonly observed in DS. Trisomic astrocytes also appear to have a lower intracellular concentration of zinc (Ballestin et al., 2014), which is a common antioxidant used to neutralize reactive oxygen species (Prasad, 2014).

Taken together, these findings suggest that increased astrocytic free radicals in tandem with reduced astrocytic zinc concentration may be one of the causes of oxidative stress in DS. In addition, major disruptions in calcium signaling and homeostasis in DS astrocytes may be of pathophysiological relevance as there are a myriad of calcium-mediated effects in the brain.

Cerebral vasculitis or CNS vasculitis is a condition characterized by inflammation in the brain and spinal cord vasculature. Astrocytes appear to be involved in two ways by forming physical and molecular barriers that seal the injury site and localize the neuroinflammatory response (Cekanaviciute & Buckwalter, 2016). In addition, activated astrocytes regulate and activate the inflammatory response by secreting various inflammatory cytokines as seen in several conditions above.

Cushing's syndrome is characterized by elevated levels of plasma glucocorticoid cortisol. To date, only one study has looked into the function and morphology of astrocytes in Cushing's syndrome; Tata et al. (2006) administered larger amounts of corticosterone to induce the Cushing phenotype in rats and found enlarged astrocytic processes in the tissue of the proximal hippocampal subfield.

Gray matter heterotopia is a group of neurological disorders characterized by the presence of gray matter in imprecise locations of the

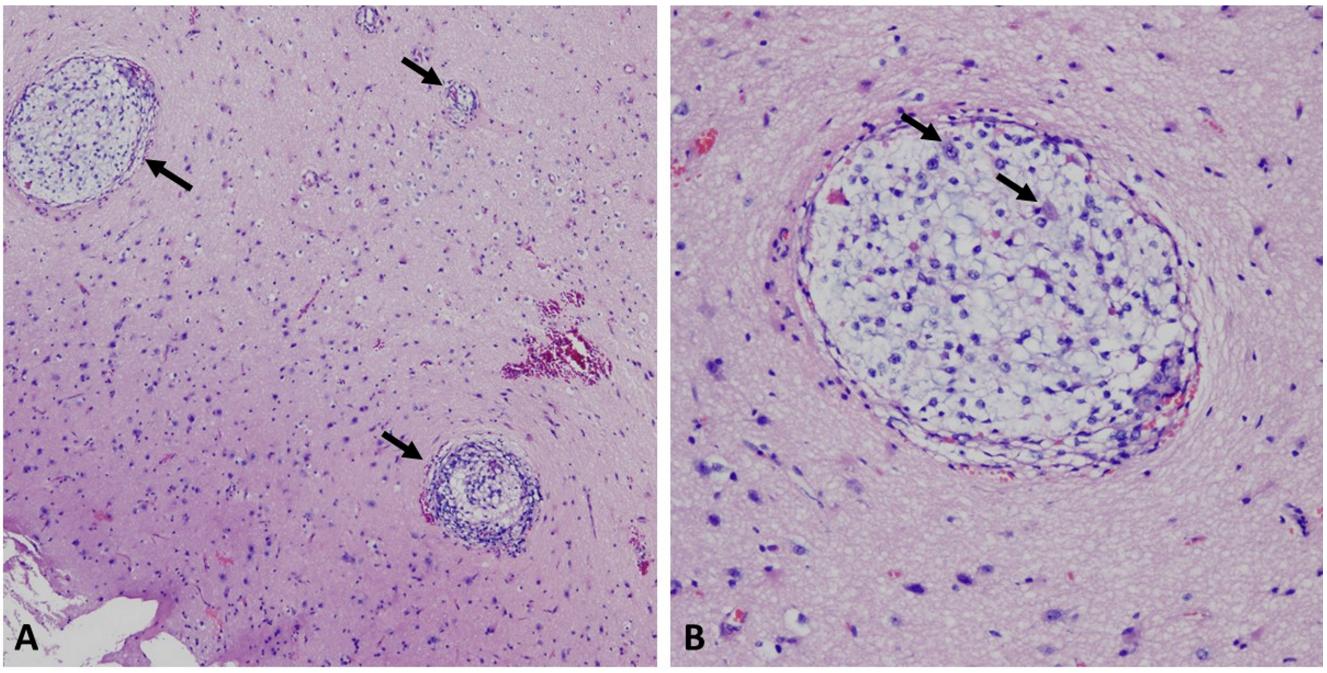

FIGURE 10 Gray matter heterotopia: (a) multiple glioneuronal nodules (arrows) are noted in the white matter and at the gray-white matter junction. (b) Higher magnification shows a well circumscribed nodule with scattered neurons (arrows) [Color figure can be viewed at wileyonlinelibrary.com]

brain. It is caused by a disruption in neuronal migration to the cerebral cortex during cortical development and can lead to the accumulation of glioneuronal nodules in the white matter (Figure 10(a),(b)). Gray matter heterotopia on histologic studies showed the presence of cytoplasmic inclusions containing filamin in some GFAP positive astrocytes of the human cerebral cortex (Alshafai et al., 2014). Another study showed that in mice numerous astrocytes were present in the heterotopic cell mass, suggesting that these astrocytes may have been derived from a separate precursor cell (Sun et al., 2001).

Acute disseminated encephalomyelitis (ADEM) also known as acute demyelinating encephalomyelitis, is an immune-mediated encephalomyelitis that is characterized by white matter inflammation. Activated myelin-reactive T cells and CD3+ perivascular T cells perpetuate can perpetuate the ongoing inflammation (Figure 11(a),(b)). ADEM is often misdiagnosed with multiple sclerosis but its clinical presentation and prognosis is different (Brinar & Poser, 2008). To date, current knowledge of astrocytes in relation to ADEM is restricted to case reports. Morphological changes have been observed including astrocytic clasmatodendrosis with the loss of processes leading to more rounded astrocytes (Di Pauli et al., 2015).

Prader–Willi syndrome (PWS) is a rare genetic disease caused by deletion of paternally imprinted genes on chromosome 15. Clinical manifestations include hypotonia, obesity, short stature, and intellectual disability. Almost no information is known about astrocytic involvement in PWD with the exception of a single study which found that astrocytic GFAP immunoreactivity was decreased in the human PWS hypothalamus (Bochukova et al., 2018).

Tarlov cysts are cysts filled with cerebrospinal fluid found at the base of the spine. Astrocytes within the cyst wall may stain positively for GFAP (Ferrand et al., 2015). Syringomyelia is another cyst, also known as syrinx, disorder of the spinal cord in which the syrinx can expand and damage the spinal cord. Astrocytic involvement in syringomyelia remains largely unknown but GFAP-positive astrocytes were observed in tissue surrounding syrinx cavities (Hemley et al., 2013).

Neuromyelitis optica (NMO), also known as Devic's disease, is an inflammatory and demyelinating autoimmune disorder. It predominately impacts the optic nerves and spinal cord, causing loss of myelin sheaths around myelinated nerves (Figure 12(a)–(d)). In NMO, it has been shown that damage to perivascular astrocytes by an IgG anti-aquaporin-4 antibody (NMO-IgG), also known as NMO antibody, is the primary cause (Kezuka et al., 2012). Upon binding to AQP4, NMO-IgG induces astrocytic secretion of various inflammatory cytokines and chemokines (Howe et al., 2014). As perivascular astrocytes provide constant input to microvascular endothelial cells, astrocytic dysfunction in NMO can impact the integrity of the BBB. Several in-vitro and in-vivo studies have shown that the binding of NMO-IgG to astrocytic AQP4 channels increases the permeability of the BBB and alters the location of AQP4 expression by inducing internalization of AQP4 (Bennett et al., 2009; Hinson et al., 2007; Melamud et al., 2012; Vincent et al., 2008; Zhou et al., 2008). The exact link between the NMO antibody and the observed demyelination and BBB hyperpermeability remains largely elusive. However, glutamate-mediated excitotoxicity caused by decreased astrocytic glutamine synthetase expression has been shown in-vitro to cause secondary damage to myelinating oligodendrocytes, revealing a potential explanation for

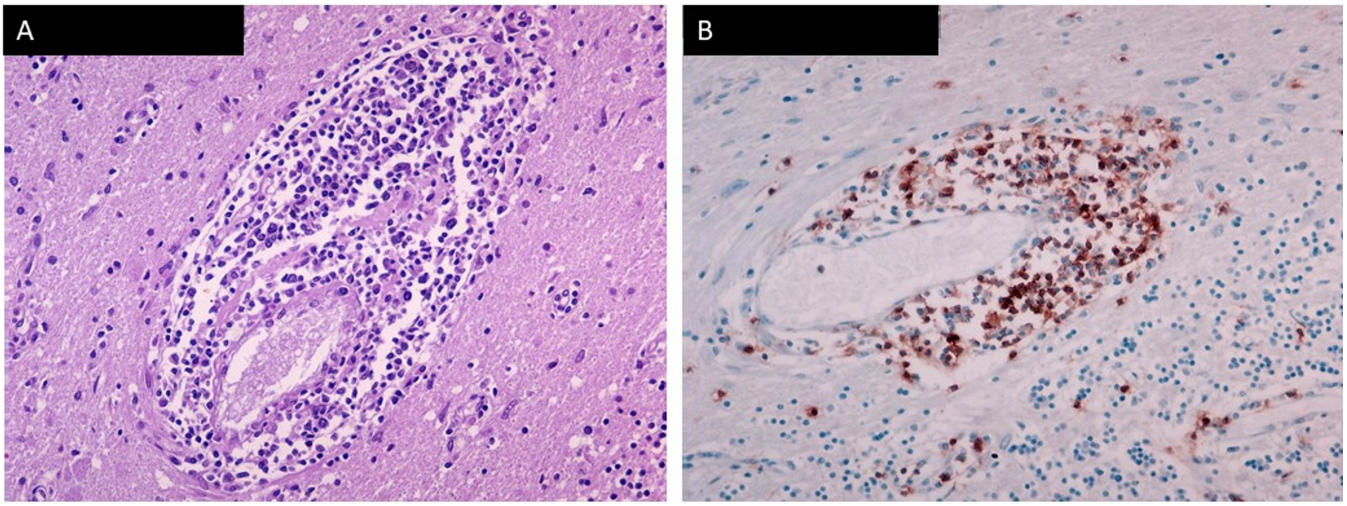

FIGURE 11 Acute disseminated encephalomyelitis (ADEM): (a) ADEM is characterized by perivenous lymphocytic infiltrate of T-cells. Note the absence of fibrinoid necrosis of the vascular wall. (b) CD3 immunostain is positive in the majority of perivenous lymphocytes confirming their T-cell immunophenotype [Color figure can be viewed at wileyonlinelibrary.com]

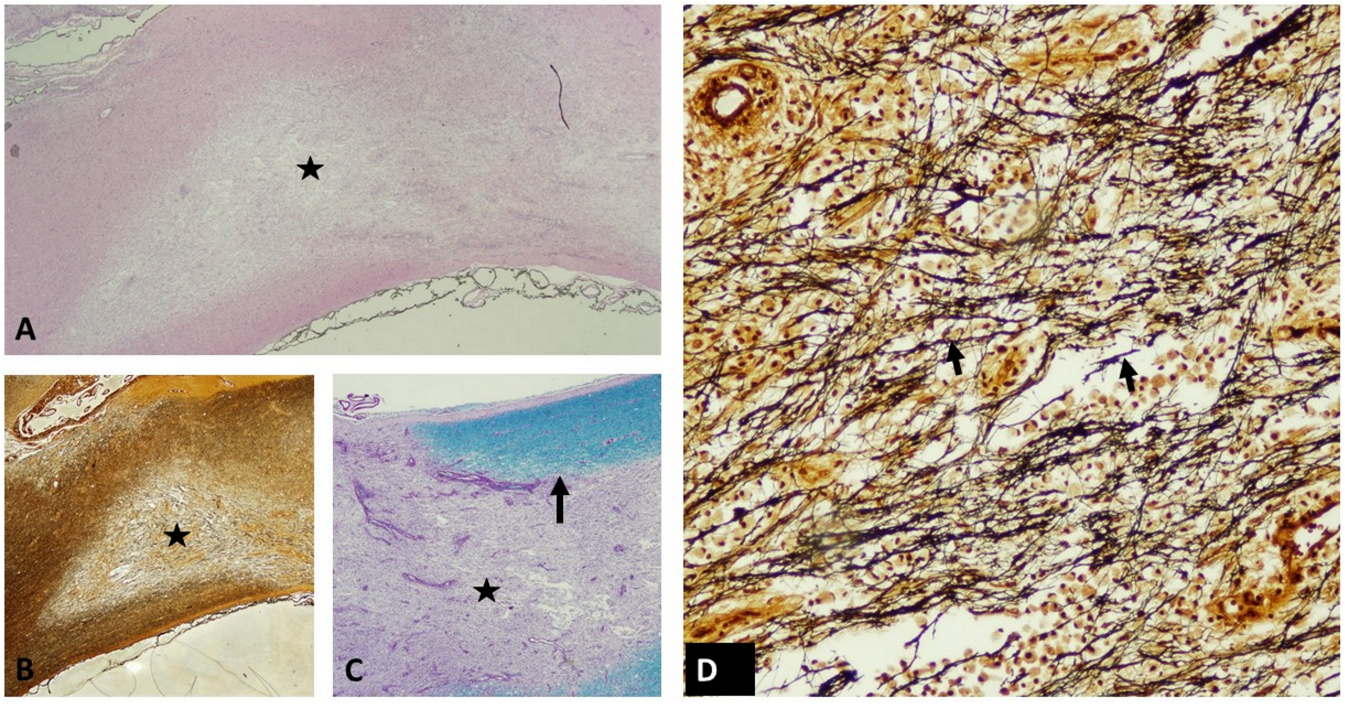

FIGURE 12 Neuromyelitis optica (NMO), longitudinal section of the optic nerve in a patient with neuromyelitis optica (Devic's disease): (a) there is a central area of demyelination (star). (b) Bodian (axonal) stain shows preservation of axons. (c) Myelin stain confirms the presence of demyelination (star). Note the presence of residual (blue, arrow) myelin at the periphery of the optic nerve (d) higher magnification of Bodian stain shows preserved axons (arrows). It is important to show that the axons are intact because similar findings may be present in lacunar infarcts. However, in infarcts, axons are destroyed [Color figure can be viewed at wileyonlinelibrary.com]

how astrocytic dysfunction leads to demyelination in NMO (Marignier et al., 2010).

An emerging area of research is the cross-talk between astrocytes and microglia in NMO. It has been previously established that microglial activation is observed in NMO (Lucchinetti et al., 2014). In a murine model of NMO, Chen et. al continuously infused human NMO-IgG into the mice to induce motor impairment (T. Chen et al., 2020). When staining for Iba1, a microglia marker, they found significant microglial activation as marked by increased Iba1 immunoreactivity and a change in microglial morphology in the mice that received NMO-IgG. Staining for GFAP and Iba1 revealed that the processes of astrocytes and microglia overlap significantly following NMO-IgG

infusion compared to control. In particular, they found that there was an increase in complement component C3 secretion from astrocytes as well as an increase in microglial expression of the corresponding C3 receptor in mice that received NMO-IgG. This was the first study in NMO to reveal the previously underappreciated interactions that occur between astrocytes and microglia. Further studies will build upon these findings.

Alexander disease is a rare astrocytopathy caused by missense mutations in the GFAP gene. Similar to other leukodystrophies, Alexander disease is characterized by white matter degeneration. It is believed that astrocyte dysfunction due to accumulation of mutated GFAP sets of a cascade of secondary pathological features including the activation of a pro-inflammatory environment, increased oxidative stress, proteasome inhibition, and increased glutamate toxicity, among others. The culmination of these functional pathologies appears to explain the relationship between astrocytic dysfunction and the observed myelin pathology. Compared to other diseases mentioned in this paper, functional and morphological changes of astrocytes in Alexander disease is much better understood. Sosunov et. al review this topic in great detail (A. Sosunov et al., 2018).

In Alexander disease, astrocytes acquire several morphological changes including the accumulation of intracellular aggregates known as Rosenthal fibers. These aggregates contain predominantly GFAP protein but several other proteins as well including hsp27 and alphaB-crystallin (Heaven et al., 2016). Multinucleation and enlarged somas are also commonly observed (A. Sosunov et al., 2018).

Astrocytic dysfunction has shown to contribute to neuronal apoptosis in areas of the brain with large glutamatergic input such as the striatum and hippocampus (Borrett & Becker, 1985; Minkel et al., 2015; Tian et al., 2010). Tian et. al performed immunohistochemical staining for Glut-1 on tissue from Alexander disease patients and found significantly reduced levels in astrocytes of the hippocampus (Tian et al., 2010). They then overexpressed GFAP-mutant and WT astrocytes in culture and found that neurons cocultured with the mutant astrocytes displayed increased apoptosis when exposed to normal amounts of extracellular glutamate. This suggests that dysfunction in astrocytic glutamate uptake may be the driving force of the observed neuronal apoptosis.

A pro-inflammatory response is another observed characteristic of Alexander disease. Evidence is emerging that the cross talk between astrocytes and microglia may be responsible for the enhanced inflammatory environment in Alexander disease (de Waard & Bugiani, 2020; Olabarria et al., 2015; A. Sosunov et al., 2018). For one, enlarged and activated microglia with increased levels of Iba1 have been observed in mice models of Alexander disease (Olabarria et al., 2015). RNA sequencing data showed substantially increased levels of cytokines and chemokines, mainly CXCL10 and CCL2. Spatial analyses showed that CXCL10 was expressed in solely astrocytes, while CCL2 was highly expressed in microglia.

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a progressive condition characterized by myelin degeneration and subsequent atrophy leading to the formation of subcortical cysts. In MLC, myelin is often found to be swollen with several fluid-filled vacuoles. Clinical characteristics include macrocephaly, motor function deterioration, epileptic seizures, and spasticity. Mutations in the MLC1 or GLIALCAM gene, which are membrane proteins expressed by perivascular astrocytes, are related to the development of MLC. To our knowledge, there exists only one human autopsy study of a patient with MLC (Lopez-Hernandez et al., 2011). Histological analysis of this patient revealed cytoplasmic aB-crystallin inclusions and decreased amounts of oligodendrocytes and astrocytes. Increased levels of aB-crystallin are believed to be indicative of cellular stress (Head et al., 1994).

MLC1 and GlialCAM are involved in maintaining ion-water homeostasis and are expressed primarily in perivascular astrocytes as opposed to oligodendrocytes (Boor et al., 2005; Teijido et al., 2004). Hence, the observed myelin degeneration may be directly as a result of astrocyte dysfunction, which has been corroborated by several murine studies (Sugio et al., 2017; van der Knaap et al., 2012). Furthermore, the loss of functional MLC1, as seen in most MLC patients, is believed to disrupt cellular volume regulation, leading to astrocytic swelling. As MLC1 is highly expressed at astrocyte-astrocyte gap junctions (Lanciotti et al., 2020) and is implicated in glial crosstalk, loss of functional MLC1 in astrocytes may hinder normal astrocyte-oligodendrocyte and astrocyte-microglia interactions, reducing the ability of astrocytes to support oligodendrocytes (de Waard & Bugiani, 2020). Further studies are needed to validate this hypothesis.

Landau–Kleffner syndrome (LKS) is a rare childhood neuropathology that often clinically manifests as aphasia and loss. As LKS is significantly rare, astrocytic involvement remains elusive. A single case report has shown occasional fibrous astrocytes throughout cortical gray matter (Cole et al., 1988).

3 | IMPORTANT NEUROLOGICAL CONDITIONS IN WHICH ASTROCYTIC MANIFESTATION AND FUNCTION HAVE NOT BEEN INVESTIGATED

There are numerous neurological conditions that have been shown to have neuronal pathologies but have not been researched to have astrocytic changes thus far. Some of the conditions manifest as:

Motor neuronal pathologies where the main symptom revolves around muscles in the extremities that gradually weaken. These conditions are Multifocal motor neuropathy, Myasthenia Gravis, Lambert–Eaton Mysathenic Syndrome (LEMS), congenital myotonia, Morvan's syndrome, neuromyotonia, paramyotonia congenita, periodic paralysis, centronuclear myopathies (CNM), and distal hereditary motor neuropathy type V.

Other than motor neuronal pathologies, psychiatric diseases may vary from well-known conditions to rare diseases with no examined astrocytic dysfunction. These are abulia, Alien Hand syndrome (Dehghani et al.), Capgras delusion, cloclothymia, delayed sleep phase disorder, disorders of consciousness, epilepsy intellectual disability in females, generalized anxiety disorder, trichotilliomania, tardive dysphrenia, tardive dyskinesia, sensory processing disorder, lupus

erythematosus neurological conditions, Kleine–Levin syndrome (KLS), Sleeping Beauty syndrome, Non-24-h sleep–wake disorder, phantom limb, rapid eye movement (REM) sleep behavior disorder, restless legs syndrome, and rhythmic movement disorder.

Infectious agents and some toxins can cause a variety of neuropathologies some of which the role of astrocytes remains unknown. They can present as a manifestation of fever and a host of neurological symptoms such as seizures, confusion, and memory loss. These include Viliuisk Encephalomyelitis, tetanus, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), poliomyelitis, and postpolio syndrome.

Autoimmune and neurological conditions with inflammation as the main pathophysiology may present in various forms like ulcers, radiating pains, and skin problems. Some examples are Behçet's disease, central pontine myelinosis, spinal stenosis, lumbar herniated disc dermatomyositis, erythromelalgia, giant-cell arteritis, hemicrania continua, inclusion body myositis, inflammatory myopathy, toxic encephalopathy, Sjögren syndrome, and Ohtahara syndrome. No research has been done to show astrocytic pathology in these conditions.

There are vast amounts of genetic and hereditary conditions that affect the population that have neurological manifestations but again research on morphology and dysfunction of astrocytes in them are exceedingly rare or not present. These conditions are Allan–Herndon–Dudley syndrome, alternating hemiplegia of childhood Chiari malformation ATR-16 syndrome, Auditory processing disorder, Septo-optic dysplasia Cephalic disorders, Cerebral dysgenesis, neuropathy, ichthyosis, palmoplantar keratoderma syndrome/CEDNIK Cerebral gigantism, Sotos syndrome, Charcot–Marie–Tooth disease, Coffin–Lowry syndrome, congenital facial diplegia, craniosynostosis, Dandy–Walker syndrome, Kufor Rakeb disease, Dejerine–Sottas disease,

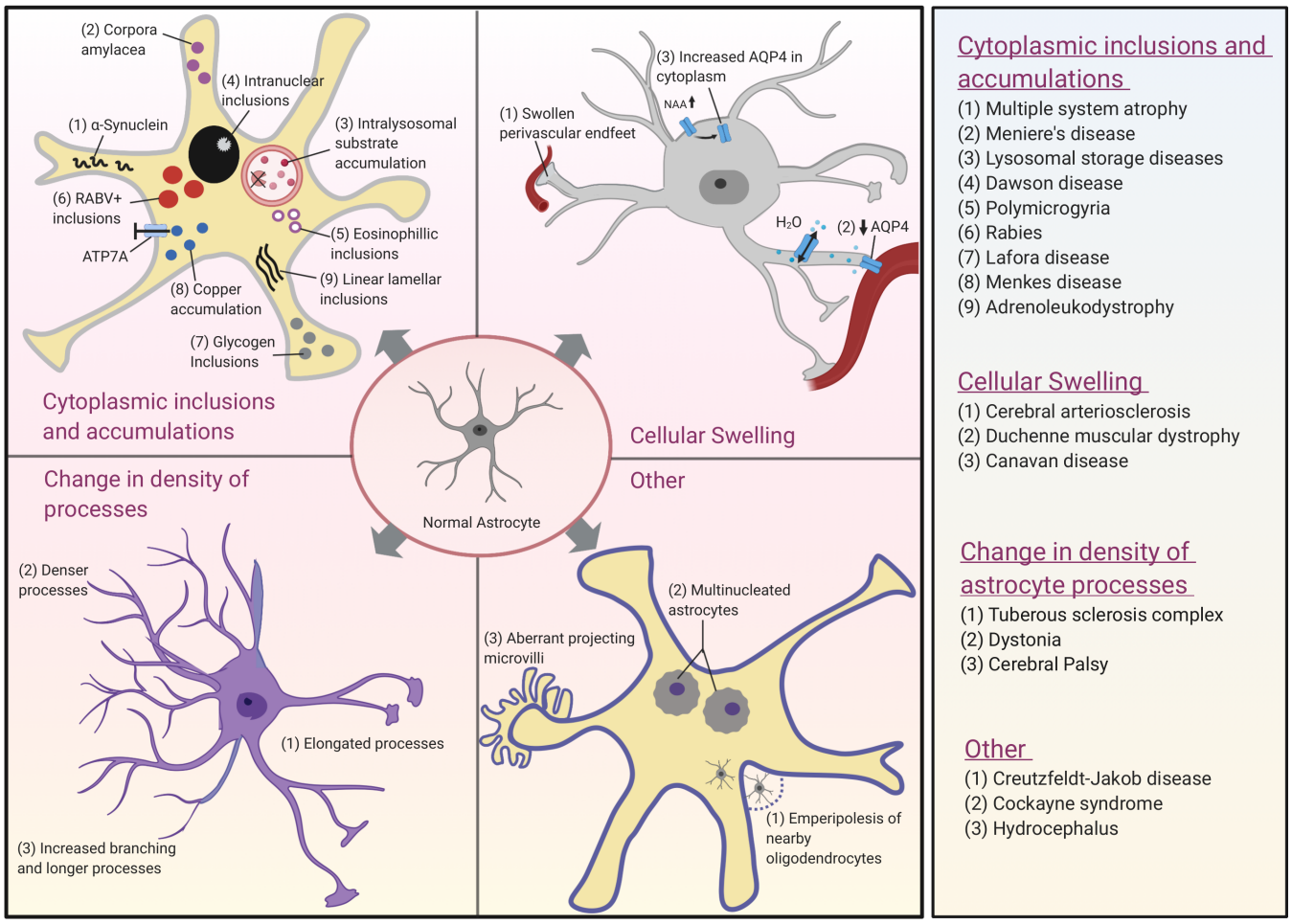

FIGURE 13 Morphological changes in astrocytes of various neurological conditions: This figure is a schematic representation of the key morphological changes observed in astrocytes of all neurological conditions discussed in this review. There are four main quadrants branching from the normal astrocyte in the middle, each describing a different morphological alteration. The four main changes include cytoplasmic inclusions and accumulations (top left), cellular swelling (top right), changes in density of processes (bottom left), and other unique morphologies (bottom right). In each quadrant, a single astrocyte is shown with various changes detailed in different parts of the cell. Each example is representative of the observed morphology in a single disease. The number given to each depiction corresponds to the far-right panel which displays the disease that specific morphology is pertinent toward. AQP4, aquaporin-4; NAA, *N*-acetylaspartic acid; RABV, rabies virus [Color figure can be viewed at wileyonlinelibrary.com]

Dravet syndrome, encephalocele, Sturge–Weber syndrome, hereditary spastic paraplegia, incontinentia pigmenti, isodicentric 15, Joubert syndrome, deafness Y-linked 1, Williams syndrome, Von Hippel–Lindau disease, Lesch–Nyhan syndrome, Leigh syndrome, Klippel–Feil syndrome, Melkersson–Rosenthal syndrome, Otosclerosis, and Brody myopathy.

Some neuropathologies can be caused by nerve impingements or overuse of joints. These can cause pain that radiates down the affected nerve dermatome and ultimately hindering muscular function of the particular muscle that the nerve supplies. These conditions are brachial plexus injury, tarsal tunnel syndrome, overuse syndrome, carpal tunnel syndrome, accumulative trauma disorder, thoracic outlet syndrome. No astrocyte research has been done for these conditions as well so far.

There are also unique neurological conditions which do not fit into one given category that present with neuronal changes, but there is lack of study on astrocytic changes in them. These conditions include prosopagnosia, anosognosia, cyclic vomiting syndrome, dysautonomia, dyskinesia, nonverbal learning disorder, exploding head syndrome, febrile seizure Foville's syndrome, Hallervorden–Spatz syndrome, hemifacial spasm, Hirayama syndrome Holmes Adie syndrome, misophonia, vestibular schwannoma, Todd's paresis, synesthesia, Stiff-person syndrome, macropsia, Mal de debarquement syndrome, developmental coordination disorder, Moyamoya disease, empty sella syndrome, Parry–Romberg syndrome, autosomal compelling helio-ophthalmic outburst, and Ramsay Hunt syndrome (RHS) type 1 and 2.

4 | CONCLUSION

Overall, research efforts over the last few decades have begun to unveil the role of astrocytes in many rare neuropathologies. As these cells have numerous functions responsible for neuronal and overall CNS homeostasis, astrocytic dysfunction appears to occur in tandem with widespread detrimental neurobiological effects. Common functional changes that appear to span over several of these rare diseases include astrocytosis, disruption in calcium-mediated effects, activation of neuroinflammatory responses, disruption of BBB integrity, and impaired extracellular glutamate clearance. One major similarity we have identified in many of these conditions is the presence of reactive astrocytes. It is still unclear if the overall effects of astrocytosis are detrimental or beneficial. One hypothesis is that reactive astrocytosis may be a necessary response in the early stages of destructive CNS injuries, but it may have deleterious effects in latter stages such as neuroinflammation or neuronal apoptosis. Aberrant astrocytic morphologies have also been observed in several of these diseases including cytoplasmic inclusions, cellular swelling, and changes in the density of processes (Figure 13). While over 40 rare neurological conditions were covered in this review, there remain hundreds of other known conditions where the exact functional involvement of astrocytes leans enigmatic.

Interestingly, there is a growing body of literature looking into how astrocytes communicate and interact with microglia and how this crosstalk is implicated in several diseases. Astrocyte-microglial interaction has already begun to be explored in MSA, KD, Rabies, NMO, Alexander disease, and CRPS. It appears that a primary point of interaction between astrocytes and microglia centers around neuroinflammation. This may likely be because both activated microglia and astrocytes can exhibit a pro-inflammatory phenotype (M1 and A1 types, respectively) and anti-inflammatory phenotype (M2 and A2, respectively). Additionally, both astrocytes and microglia respond and interact with each other via various factors which include amino acid neurotransmitters (glutamate), cytokines/chemokines, reactive oxygen species, and ATP-induced extracellular vesicles (Drago et al., 2017; Reemst et al., 2016). The secretion of various inflammatory factors can induce a positive feedback whereby activated M1 microglia subsequently trigger A1 reactive astrocytes, which further amplifies the inflammatory response (Liu et al., 2020). As astrocytes and microglia actively communicate with neurons and help promote angiogenesis and synaptogenesis, the exact consequences of disruption of astrocyte-microglial crosstalk are not fully understood. Future studies are needed to better understand how disruption in the crosstalk between astrocytes and microglia is connected to the pathogenesis of various neurological conditions.

It is important to note that while astrocytic dysfunction directly drives pathology in some of the diseases covered, there is not sufficient evidence for the vast majority of these diseases to conclude that astrocytic changes cause a certain diseased phenotype. As this remains an active gap in current research, minimal causal extrapolations for now can be made based on observed astrocyte behavior. Thus, further studies which favor a controlled single-variable experiment design over the common histological observational study design are warranted. This will greatly advance the current knowledge of astrocytic contribution to neurological disorders as it will begin to uncover whether the observed astrocytic functional and morphological changes underlie a diseased phenotype or if they merely occur as accompanying phenomena.

Current knowledge about the astrocyte phenotype in these neurological conditions is quite preliminary likely in part due to how rare some of these conditions are in the general population. However, as diagnostic approaches continue to improve, the prevalence of several of these conditions may continue to steadily increase as most rare neurological conditions are underdiagnosed. Thus, it is vital that better treatment strategies be developed. Since various markers that are released from neurons and astrocytes have been targeted to gain a better understanding of disease progression and for diagnostic and treatment purposes, it is of increasing importance that the functional pathologies of astrocytes and other glia are better understood.

Last, it should be proposed that, by continuing to explore the means by which perturbations in the function of glia impact the spectrum of neuropathology, we are moving closer toward a comprehensive understanding of how the brain works, in addition to new insights into disease prognosis, diagnosis, and potential targeted treatment.

ACKNOWLEDGMENTS

This research was supported by the Stanley J. Glaser Research Grant and AASLD/American Liver Foundation grant. The authors thank Drs. Michael D. Norenberg and Carol K. Petito (deceased December

15, 2018) for their careful evaluation of the manuscript and their fruitful discussions regarding astrocytic morphology in rare neurological conditions. Select figures were created with BioRender.com.

CONFLICT OF INTEREST

Karthik Ravi, Ali Saad, and Arumugam R. Jayakumar disclose no conflicts. Michael J. Paidas has received grant funding, is a Scientific Advisory Board member and has stock options in BioIncept, LLC, Westport, CT.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed in this review article.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/cne.25118.

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How to cite this article: Ravi K, Paidas MJ, Saad A, Jayakumar AR. Astrocytes in rare neurological conditions: Morphological and functional considerations. *J Comp Neurol*. 2021;529:2676–2705. https://doi.org/10.1002/cne.25118