

CNS imaging studies in cystic fibrosis patients presenting with sudden neurological events

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ABSTRACT

Background Acute neurological events may present as an extrapulmonary complication in patients with cystic fibrosis (CF). These events can be secondary to a range of different aetiologies.

Methods A retrospective analysis of 476 medical records of CF patients attending a large teaching hospital between 2000 and 2018 was performed. Patients presenting with acute neurological events who had MRI brain imaging were evaluated. Patients who had headaches without associated neurological symptoms were excluded from this analysis.

Results Acute neurological presentations, excluding headaches without associated neurological symptoms, were reported in 27 index patients out of the 476 patients. Of these, 16 patients had MRI brain imaging for review. Three patients suffered pathology secondary to vascular events, both ischaemic and haemorrhagic; four patients had evidence of ischaemia or infarction not consistent with a vascular territory stroke and the remaining patients experienced a range of different neurological events. The most common presentation among these patients was seizure activity, followed by a transient motor or sensory deficit.

Conclusions Neurological complications are recognised among individuals with CF. Although rare, they can be secondary to a range of different aetiologies, including dysfunctional cell energetics. Additional studies are required to further evaluate this association.

BACKGROUND

Cystic fibrosis (CF) is characterised by chronic infection and inflammation and is attributed to dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein.¹ It is a multisystem disease with the major cause of morbidity and mortality being secondary to mucus accumulation, airway obstruction and bronchiectasis leading to respiratory failure.² Orally active gene modulator therapy has the potential for altering disease progression. However, these agents are not currently suitable for all CF genotypes and so many patients ultimately will still require lung transplantation.³ Depending on genotype, individuals with CF also experience a range of extrapulmonary manifestations

Key messages

- ▶ What neurological extrapulmonary complications are observed in a cohort of cystic fibrosis (CF) patients?
- ▶ CF patients can present with a range of different neurological events, with some having evidence of recent of remote ischaemia or infarction that is not consistent with a single vascular territorial stroke on MRI brain imaging.
- ▶ This is the first study to describe acute neurological events in individuals with CF that could be secondary to dysfunctional cell energetics.

that significantly add to morbidity.^{4 5} As CF patients experience longer life expectancy, extrapulmonary disease requires greater consideration.⁶

Of the extrapulmonary presentations, neurological sequelae are less well described.^{7 8} Isolated case reports and small studies have identified neurological events related to vitamin deficiency; prolonged vitamin E deficiency leads to neurological dysfunction^{9 10} and vitamin K deficiency can result in cerebral haemorrhage as a rare, early complication of CF.^{11 12} Paradoxical embolism has been reported in some patients resulting in stroke¹³ and instances of cough have led to altered consciousness and hemiplegic migraine.¹⁴ Interestingly, individuals with CF appear to have a higher risk of central nervous complications post lung transplantation.^{15 16}

The CFTR protein has also been implicated in the regulation of mitochondrial function.^{17–21} This is of interest because a wide spectrum of neurological disease is attributable to dysfunctional mitochondria.²² Among these include conditions where acute neurological events (stroke-like syndromes) occur in young subjects,^{23 24} which are radiologically distinct from ischaemic strokes.²⁵ Acute interventions that may have therapeutic benefit in such incidences are available, including L-arginine.²⁶



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Table 1 Baseline demographics

Baseline demographics n=27/476	
Number with MRI brain imaging for review	16
Age (mean, years)	37.1 (23–51)
Male	9 (56.3%)
Genotype	
F508del homozygous	9 (56.25%)
F508del+ another mutation	3 (18.75%)
Other mutations	2 (12.5%)
Heterozygote (F508del/unknown*)	2 (12.5%)
Lung function	
Mean percentage predicted FEV ₁ (forced expiratory volume in 1 s)	43.3% (22–83)
Mean percentage predicted FVC (forced vital capacity)	59.6% (39–93)

*Both patients presenting prior to extended genotype testing but with elevated sweat chloride levels and classic CF symptoms. CF, cystic fibrosis.

This report details imaging findings in a single-centre experience with acute neurological events seen in CF patients.

METHODS

A retrospective review of the clinical records of 476 patients with CF treated in a university teaching hospital between 2000 and 2018 was undertaken. These were the total number of patients managed by the CF service over this time period whose notes and images were readily available. Of these patients, 27 index patients were identified that had experienced various neurological events. Patients with headaches as their only neurological symptom were excluded from this analysis. MRI brain scans, performed within the same hospital, were available for review on 16 subjects. Low risk ethics was approved

for this study by the Alfred Ethics Committee: project number 123/9.

Patient and public involvement

Patients and the public were not involved in the design, conduct or reporting of this research. There were no time or funds allocated for patient and public involvement and so the study was unable to involve them.

RESULTS

The CF individuals within this retrospective cross-sectional case-review study experienced a range of neurological events. The baseline demographic data are shown in [table 1](#). Some of these subjects were identified as having intracerebral pathology consistent with underlying vascular events. The vascular events occurring within this cohort included intracerebral haemorrhage and ischaemic strokes. The results for these patients are described in [table 2](#).

There were four subjects who had evidence of recent or remote ischaemia or infarction not consistent with a single vascular territorial stroke on MRI brain imaging. These results are described in [table 3](#). The MRI brain imaging from two of these patients who had imaging that did not fit a vascular territory stroke are shown in [figures 1 and 2](#).

The remaining patients presenting with other conditions are described in [table 4](#).

Subject 4 who has clear evidence of cerebral ischaemia crossing more than one vascular territory has presented on multiple occasions with neurological deficits. The initial ([figure 1A,B](#)) and latest MRI brain images ([figure 1C,D](#)) are included and demonstrate signal change in the precentral and postcentral gyrus on the right. This would be consistent with recurrent neurological events in mitochondrial disease.

DISCUSSION

Our study examined the abnormal findings on MRI brain imaging in a small cohort of CF patients presenting with

Table 2 Intracerebral injury secondary to underlying comorbidity

Subject	Presentation	MRI brain findings	Underlying comorbidity
1	Expressive dysphasia, facial paralysis	T2 hyperintensities in left corona radiata extending to left lentiform nucleus with associated susceptibility artefact without diffusion restriction	Hypertension, diabetes mellitus
2	Delayed presentation of a 'thunderclap' headache associated with diplopia and ataxia	T2 hyperintensities in right MCP cavernoma with minimal oedema. Scattered T1 hyperintensities. Intracerebral haemorrhage	Right MCP cavernoma
3	Grand mal seizure and occipital headache	Low attenuation in left middle temporal lobe. Right MFG microhaemorrhage	Right MFG cavernoma

MCP, middle cerebellar peduncle; MFG, middle frontal gyrus; T1, T1-weighted images; T2, T2-weighted images.

Table 3 MRI findings in primary cerebral injury

Subject	Presentation	MRI brain findings
4	Grand mal seizure with left sided motor deficit and cognitive impairment	Bilateral frontoparietal and right temporo-occipital FLAIR, T2 and DWI changes.
5	Cerebellar tremor	Periventricular white matter bilateral T2/FLAIR hyperintensities
6	Facial numbness	Bilateral peritrigonal white matter T2 hyperintensity
7	Left sided motor deficit with ataxia and Vllth nerve palsy	T2 hyperintensity in the corona radiata

DWI, diffusion-weighted intensity; FLAIR, fluid-attenuated inversion recovery image.

neurological events, including seizure activity or stroke-like events.

Impairment of central nervous system activity in CF may be attributable to hypoxia,²⁷ vitamin E or K deficiency,^{9–12} antibiotic adverse effects,²⁸ fluid depletion/imbalance,²⁹ use of psychotropic agents,³⁰ stroke from paradoxical emboli¹³ or other causes. A cause for the neurological presentations in this report, based on clinical presentation and investigations, were identified in 12 out of the 16 patients who had available imaging for review. Seizures were the most common presentation, followed by localised motor or sensory deficits. The majority of these events were transient episodes. There was no identifiable precipitating event in any of the cases of unknown cause.

Brain injury in healthy adults with CF has been identified in case reports.³¹ In this retrospective study, lesions thought to be consistent with ischaemia were seen in the

hippocampus, occipital cortex, posterior thalamus and parietal cortex. Behavioural and cognitive defects have been reported in CF and are consistent with possible involvement of these areas.^{27 32}

The CFTR protein has been identified in human brain tissue³³ and its expression may be conditional on local factors.³⁴ It was initially thought that CFTR expression was localised to the hippocampus but in fact there is evidence of widespread expression throughout the human brain. However, in humans this appears to be only within neuronal cells, and not in astrocytes or radial glial cells.^{33 35} Although animal models have found evidence of CFTR in both microglia and Schwann cells.^{36 37} The CFTR protein is involved in various functions, including neuronal development³⁸ and neuronal cell apoptosis, with reduced neuronal CFTR protein function associated with mitochondrial oxidative stress.³⁹

CFTR is a complex protein and is a member of the subclass C family of the ATP binding cassette transporter proteins. It consists of two membrane-spanning domains that function as the ion channel, each connected to two nucleotide-binding domains (NBD1 and NBD2) to which ATP binds, and a regulatory domain (RD). Phosphorylation of the RD together with ATP binding to the NBDs is required for channel opening to occur.⁴ It functions as a chloride and bicarbonate channel but also regulates several other functions within the cell. Neuronal activity is modulated by the transport of anions and thus the

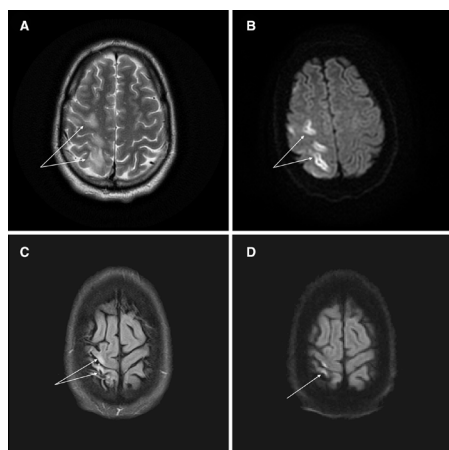


Figure 1 MRI brain images of case 4, one of the patients presenting with neurological events, which were not consistent with a single vascular territory stroke—initial presentation: two images (1) T2-weighted image: precentral and postcentral gyrus ischaemia (A). (2) Diffusion-weighted image: precentral and postcentral gyrus ischaemia (B). Subsequent presentation: two images (1) diffusion-weighted image: precentral and postcentral gyrus ischaemia (C). (2) FLAIR image: precentral and postcentral gyrus ischaemia (D). FLAIR, fluid-attenuated inversion recovery image.

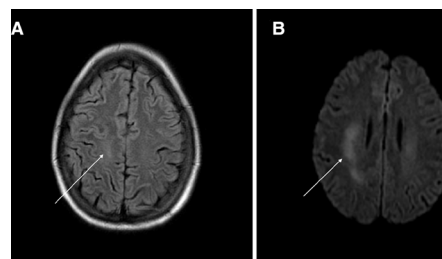


Figure 2 MRI brain images of case 7, one of the patients presenting with neurological events, which were not consistent with a single vascular territory stroke—two images (1) diffusion weighted (A) and (2) FLAIR images (B) subtle changes seen in the corona bilaterally. FLAIR, fluid-attenuated inversion recovery image.

Table 4 Other neurological presentations in CF patients resulting from a range of aetiologies

Subject	Presentation	MRI brain findings	Diagnosis
8	Left sided motor deficit and tonic left sided seizure	T2 hyperintensity in the PVWM, posterior pons and MCP	Multiple sclerosis
9	Syncopal episode while undergoing haemodialysis	Diffuse cerebral oedema	Dialysis disequilibrium syndrome
10	Reduced conscious level requiring intubation	No focal intracerebral abnormality	Metabolic lactic acidosis and hyperammonemia
11	Atypical seizure with reduced consciousness	No focal intracerebral abnormality	Drug reaction to ceftazidime
12	Grand mal seizure	No focal intracerebral abnormality	Epilepsy
13	Fall with loss of consciousness	Scattered supratentorial white matter changes, likely representing chronic small vessel disease	Vasovagal syncope secondary to dehydration
14	Tonic clonic seizure	T2 hyperintensity in the periventricular white matter	Isolated seizure
15	Vertigo, tinnitus and dysphasia	Multiple T2 hyperintensity punctate lesions	Sinusitis and dehydration
16	Grand mal seizure. Right upper limb and left lower limb paraesthesia	Focal right occipital cortex and subcortical T2/FLAIR hyperintensity with T1 hypointense lesion	Epilepsy

FLAIR, fluid-attenuated inversion recovery image; MCP, middle cerebellar peduncle; PVWM, periventricular white matter.

transport of chloride by CFTR within the cells could have implications for neuronal excitability.

Prior to the discovery that CFTR was a chloride channel, several studies highlighted a variety of mitochondrial abnormalities in CF, including dysfunctional mitochondrial calcium uptake.^{40–44} The functions of the CFTR protein and cell mitochondria appear to be intrinsically linked; some mitochondrial proteins are encoded by CFTR-dependent genes that are downregulated in CF.^{20–21} These include MT-ND4 and CISD1, with the MT-ND4 protein being a subunit of the respiratory chain complex I within the mitochondria.¹⁹ Interestingly MT-ND4 is associated with the human mitochondrial encephalomyopathy Leber's hereditary optic neuropathy and mesial temporal lobe epilepsy.^{22–45} Human mitochondrial encephalomyopathies are a heterogeneous group of diseases, which due to the complexities of mitochondrial genetics are not completely understood.²² They have an impact on the mitochondria and cell energetics, which is also seen in CF.¹⁷ Also included within this group is mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome, which can give rise to early stroke-like episodes with the potential to develop progressive muscular weakness, lactic acidosis, cognitive dysfunction, seizures, encephalopathy and premature death.⁴⁶ As individuals with CF may have dysfunctional cell energetics, and early stroke-like events and seizures can occur secondary to mitochondrial abnormalities, the pathology of some of the patients presented are consistent with those which occur in mitochondrial encephalomyopathies such as MELAS. Also, of note is that individuals

with CF have an increased incidence of neurological complications post lung transplantation when compared with other lung transplant recipients.^{15–16} The calcineurin inhibitors, particularly tacrolimus, are commonly used as part of the immunosuppressive regimen post lung transplantation.^{47–48} Tacrolimus alters mitochondrial calcium uptake and uncouples oxidative phosphorylation.^{49–51} The combination of altered mitochondrial function secondary to the downregulated CFTR protein and the effect of calcineurin inhibitors on an organ with high oxidative demands such as the brain, could explain the increased neurological events in these patients.

The importance of this case series in individuals with CF is that some of these neurological events may be amenable for treatment. L-arginine is a recognised treatment for MELAS, and this therapy may be of benefit for some individuals with CF who present with acute neurological events.²⁶ Further evaluation is required to assess this therapy within the CF cohort.

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