The possible causes for sulcal hyperintensities on FLAIR images on brain MRI: the dataset derived from a systematic review

Digital Object Identifier (DOI):
10.17632/pskc7cfmrt.1

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Cerebrospinal fluid (CSF) is normally dark with low signal on magnetic resonance imaging (MRI) fluid-attenuated inversion recovery (FLAIR) images, but the signal may increase (become whiter) if there is protein or gadolinium compounds or other materials in the CSF. We performed a systematic review to document all causes of increase in CSF signal on FLAIR MRI.

A systematic literature search was conducted in PubMed and EMBASE (from inception to June 2020) in line with the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). We searched for relevant articles reporting sulcal FLAIR hyperintensities using Boolean operator terms and restricted the search to MR imaging in humans. Various combinations of the following search terms were employed: “inferior frontal sulci”, “inferior frontal sulcus”, “sulcal”, “CSF”, “cerebrospinal fluid”, “FLAIR”, “hyperintensity” and “hyperintensities”.

Initial search specifically relating IFSH on FLAIR on 3T MRI sequences yielded no relevant results on PubMed and EMBASE (search syntax entered on PUBMED listed as **Figure I**). Hence, the search was subsequently expanded to look more generally at causes for sulcal hyperintensities on FLAIR images which yielded more results (search syntax used on PubMed is listed in **Figure II**). Additional papers were also reviewed by hand-searching the references of the relevant papers found. We excluded non-English articles, animal-based studies and articles that were not available via full-text.

Results of literature review

A summary of the number of papers found is shown as below in **Figure III** with the corresponding flow-chart summarizing the search. Out of the initial 83 potentially relevant papers identified, after de-duplication, 64 were screened and 39 full papers assessed for relevance. Of 25 records removed, 24 papers were excluded as they were not available as full articles, and one was excluded as it was not in English language. Fifteen full-text articles were subsequently excluded as they were deemed not relevant to the focus of the study. Overall, only 24 articles were deemed relevant.

1) (((inferior frontal sulci OR inferior frontal sulcus)) AND (sulcal OR CSF OR cerebrospinal fluid OR FLAIR)) AND (hyperintensity OR hyperintensities)
2) (((((inferior frontal sulci OR inferior frontal sulcus)) AND (sulcal OR CSF OR cerebrospinal fluid OR FLAIR)) AND (hyperintensity OR hyperintensities)) AND (MRI OR magnetic resonance imaging)) AND (3T OR 3 Tesla)
3) ((((inferior frontal sulci OR inferior frontal sulcus)) AND (sulcal OR CSF OR cerebrospinal fluid OR FLAIR)) AND (hyperintensity OR hyperintensities)) AND (MRI OR magnetic resonance imaging)
4) (((inferior frontal sulcus OR inferior frontal sulci)) AND (hyperintensity OR hyperintensities)) AND (MRI OR magnetic resonance imaging)
5) ((inferior frontal sulcus OR inferior frontal sulci)) AND (hyperintensity OR hyperintensities))

Figure I: Search syntax on PubMed regarding inferior frontal sulci hyperintensities on FLAIR on 3T MRI sequences

6) ((((sulcal OR sulci OR sulcus)) AND (hyperintensity OR hyperintensities)) AND (MRI OR magnetic resonance imaging)) AND (3T OR 3 Tesla)
7) ((((((sulcal OR sulci OR sulcus)) AND (hyperintensity OR hyperintensities)) AND (MRI OR magnetic resonance imaging)) AND FLAIR) AND (CSF OR cerebrospinal fluid)

Figure II: PubMed search syntax

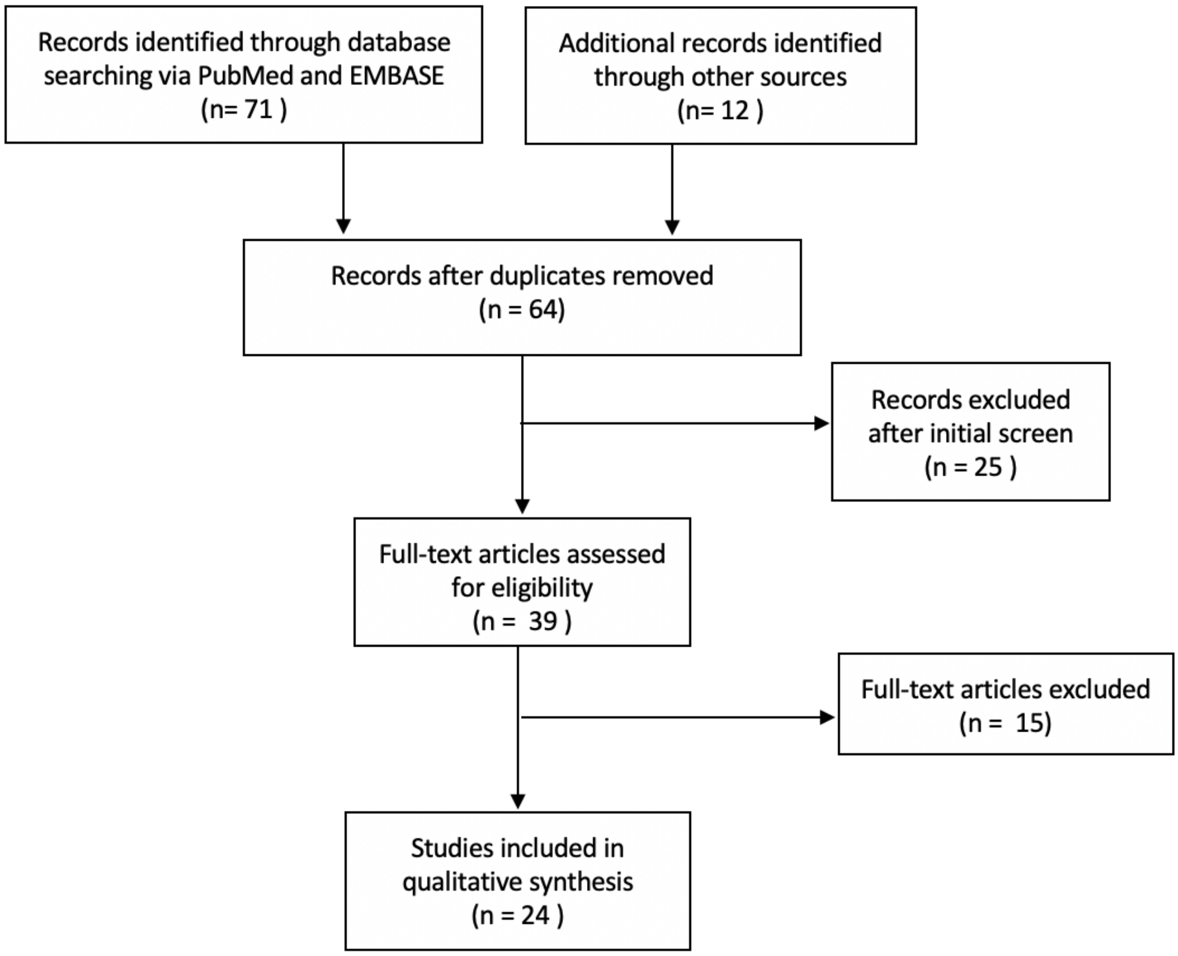

Figure III: Flow-chart of the systematic literature search

A summary of the various papers is shown in **Table I** which includes the field strength of the scanner used, number of patients, age ranges, gender demographic, disease association with sulcal hyperintensity on FLAIR and proposed pathological process behind sulcal hyperintensity.

Of the 24 included papers, 2 concerned acute stroke, 3 were on haemorrhage, 4 on meningitis, 2 on malignancies, 4 post-interventions (CSF drainage, oxygen administration), 3 on migraine with aura and the remaining 6 on a number of other topics. Though there were varied causes of increased cerebrospinal fluid (CSF) signal on FLAIR, a number of studies attributed sulcal hyperintensity to blood brain barrier (BBB) disruption or increased CSF protein concentration/leakage, eg due to blood products. Specifically, increased CSF protein concentration was mentioned in association with conditions such as meningitis, cryptococcal meningoencephalitis and intracranial meningeal carcinomatosis (tumour cells thought to induce increased CSF protein). BBB breakdown was mentioned in association with conditions such as stroke and central nervous system (CNS) haemorrhage. The increased CSF signal on FLAIR was usually located at the site of the brain pathology and therefore could relate to any sulci.

Most studies used 1.5T scanners. The range of total number of participants across the studies is from 1 – 578 (1 being a case report). Age range of participants across studies range from 3 months – 88 years.

Table I: Literature review summary table by diseases

First Author and paper title	Field strength	No of patients	Age range (years)	Gender (Male/ Female)	Postulated underlying pathology for sulcal hyperintensity
Stroke					
Lee H et al. Clinical Implications of Sulcal Enhancement on Postcontrast Fluid Attenuated Inversion Recovery Images in Patients with Acute Stroke Symptoms[1]	1.5T, 3T	578	-	-	Hyperintense acute reperfusion marker is thought to be a useful marker for indicating BBB disruption in an acute stroke, because gadolinium does not cross the intact BBB. The contrast medium is believed to cross the BBB injury site after reperfusion, enter the perivascular space, and then diffuse into the CSF via a perivascular pathway.
Kim et al. Sulcal Hyperintensity on Fluid-Attenuated Inversion Recovery Imaging in Acute Ischemic Stroke Patients Treated With Intra-Arterial Thrombolysis: Iodinated Contrast Media as Its Possible Cause and the Association With Hemorrhagic Transformation[2]	1.5 T	14	43-75	7 /7	May be caused by disruption of the BBB, which may result in leakage of contrast medium as well as protein into the CSF space.
Haemorrhage					
Noguchi et al. MR of Acute Subarachnoid Hemorrhage: A Preliminary Report of Fluid- Attenuated Inversion-Recovery Pulse Sequences[3]	0.5 T	3	30-68	1/2	Increased signal from bloody CSF because of shortening of the Tl relaxation time. Thus, acute subarachnoid haemorrhage is seen as hyperintense relative to normal CSF.
Kidwell et al. Hyperacute injury marker (HARM) in primary hemorrhage: a distinct form of CNS barrier disruption.[4]	1.5T, 3T	46	Mean age = 65	-	Likely involves a combination of BBB and B-CSF-B disruption.
Oshida et al. A Case of Chronic Subdural Hematoma Demonstrating the Epileptic Focus at the Area With Sulcal Hyperintensity on Fluid-Attenuated Inversion Recovery Image[5]	-	1 (case report)	77	1/-	The epileptogenic area corresponding to that with sulcal hyperintensity on FLAIR might be in an activated electrophysiological state, with the activated area exhibiting a hypermetabolic state, thereby causing compensatory regional hyperperfusion.
Meningitis					
Kamran et al. Role of fluid-attenuated inversion recovery in the diagnosis of meningitis: comparison with contrast-enhanced magnetic resonance imaging.[6]	1.5 T	28	1 month to 69 years	20/8	FLAIR high signal may be seen in meningitis due to increased CSF protein concentration.
Kuwahara et al. Cryptococcal meningoencephalitis presenting with an unusual magnetic resonance imaging appearance--case report.[7]	Not stated	1 (case report)	61	- /1	Increased CSF protein concentration from inflammation in localised subarachnoid space

Boban et al. Leptomeningeal form of Immunoglobulin G4-related hypertrophic meningitis with perivascular spread: a case report and review of the literature.[8]	-	1 (case report)	58	1/-	These changes probably represented vasogenic edema (no signs of restricted diffusion were present), due to venous congestion and deprived venous outflow.
Melhem et al. Fluid-attenuated inversion recovery MR imaging: identification of protein concentration thresholds for CSF hyperintensity. [24]	1.5 T	1 (case report)	60	- /1	FLAIR high signal may be seen in acute meningitis due to increased CSF protein concentration.
Malignancies					
Yasuyuki et al. Epithelial Ovarian Carcinoma Associated with Metastases to Central Nervous System: Two Case Reports[9]	-	2 case reports	55 and 63	- / 1	-
Tsuchiya et al. FLAIR MR imaging for diagnosing intracranial meningeal carcinomatosis[10]	1.5 T, 0.5T	9	21- 73	4/5	Tumour cells in meningeal carcinomatosis thought to induce an increase in cerebrospinal fluid proteins.
CSF removal and oxygen administration					
Yazdani et al. Sulcal FLAIR hyperintensity after CSF removal in two patients with intracranial hypertension[11]	-	2 (case reports)	27 and 28	- / 2	Proposed mechanism of sulcal FLAIR hyperintensity is possibly due to decrease in CSF to blood pool ratio in the involved voxels from decrease in sulcal CSF space hence the blood pool becomes the dominant contributor to sulcal FLAIR signal rather than CSF, and the blood pool is not attenuated by the inversion recovery.
Anzai et al. Paramagnetic Effect of Supplemental Oxygen on CSF Hyperintensity on Fluid-Attenuated Inversion Recovery MR Images[12]	1.5 T	6	34-40	3/3	Oxygen has a known paramagnetic effect and increases CSF signal intensity on fluid-attenuated inversion recovery (FLAIR) MR images
Frigon et al. Fraction of Inspired Oxygen in Relation to Cerebrospinal Fluid Hyperintensity on FLAIR MR Imaging of the Brain in Children and Young Adults Undergoing Anesthesia[13]	1.5 T	70	-	-	Likely related to the fact that oxygen, being slightly paramagnetic, also produces a mild shortening in T1.
Goetz et al. Hyperintense Cerebrospinal Fluid on FLAIR Images Induced by Ventilation with 100% Oxygen[14]	1.5 T	40	3 months to 8 years	27 /13	Increased CSF signal intensity changes thought to be caused by paramagnetic effects of supplemental oxygen.
Migraine with aura					

de Oliveira et al.Reversible Sulcal FLAIR Hyperintensity on MRI in a Migraine Patient With Aura[15]	1.5T	1 (case report)	66	- / 1	Changes in the occipital lobe possibly related to a hyper excitable visual cortex as trigger for the headache and also vasodilatation with tissue hyperoxygenation and decreased energy reserves as part of the central pain process pathway. A suggested mechanism is increased leptomeningeal vascularity leading to plasma extravasation and increased local protein concentration in the sulci.
Gómez et al. Migraine with Aura Associated with Reversible Sulcal Hyperintensity in FLAIR[16]	-	1 (case report)	22	- / 1	Transient increase of leptomeningeal vascular permeability during the aura phase might have led to gadolinium leakage during the first/prior MR head examination. It would accumulate within the pia mater and arachnoid membrane in sufficient concentration to cause the signal changes observed during the second MRI study.
Kang et al. Transient Sulcal Hyperintensities on Fluid-Attenuated Inversion Recovery in Migraine With Aura: Transient Sulcal Hyperintensities in Migraine[17]	-	1 (case report)	33	- / 1	It is suggested that sulcal hyperintensities on FLAIR images could be caused by a slow flow of the pial artery which transiently occludes the microcirculation from micro- emboli via PFO.
Others					
Taoka et al. Sulcal hyperintensity on fluid-attenuated inversion recovery mr images in patients without apparent cerebrospinal fluid abnormality[18]	1.5 T	291	2- 88	-	Protein leakage, alteration of vascular haemodynamic and increased blood pool.
Hacein-Bey et al. Hyperintense ipsilateral cortical sulci on FLAIR imaging in carotid stenosis: ivy sign equivalent from enlarged leptomeningeal collaterals[19]	Not stated	1 (case report)	69	- / 1	Slow flow within enlarged leptomeningeal collaterals.
Bozzao et al. Cerebrospinal fluid changes after intravenous injection of gadolinium chelate: assessment by FLAIR MR imaging[20]	1.5 T	33	-	-	In pathological conditions with BBB breakdown or neovascularisation, gadolinium can leak in the subarachnoid spaces and cause CSF signal changes.
Liu et al. MRI Abnormalities Predominate in the Bottom Part of the Sulcus with Type II Focal Cortical Dysplasia: A Quantitative Study[21]	3T	58	-	35/23	Cortical FLAIR hyperintensity, which predominate in the bottom part of the sulcus, seen in Type II focal cortical dysplasia.
van Veluw et al. Hippocampal T2 hyperintensities on 7 Tesla MRI[22]	7T	58	43-78	31/37	Study done in patients with no known neurological disease. Found that hippocampal T2 hyperintensities are extremely common.

Stephen et al. Hyperintensity in the Subarachnoid Space on FLAIR MRI[23]	- (pictorial essay of various conditions)	-	-	-	Acute subarachnoid haemorrhage, meningitis, leptomeningeal malignancy, leptomeningeal melanosis, moyamoya disease, elevated Blood Pool to CSF Ratio, IV contrast in context of altered blood-brain barrier or neovascularisation near subarachnoid space/ ventricles, artefacts (supplemental oxygen, CSF pulsation, motion artefact, magnetic susceptibility artefact)

Abbreviations: BBB, blood brain barrier; CSF, cerebrospinal fluid; CNS, central nerve system; FLAIR, Fluid-attenuated inversion recovery; PFO Patent Foramen Ovale.

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