THE SAFETY AND CLINICAL APPLICATIONS OF INTRATHECAL GADOLINIUM-ENHANCED MRI: A SYSTEMATIC REVIEW AND CASE REPORT

Oona Hantula
Syventävien opintojen kirjallinen työ
Tampereen yliopisto
Lääketieteen yksikkö
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Gadoliniumpohjaisia kontrastiaineita käytetään magneettikuvauksessa lisäämään kuvien kontrastia ja parantamaan kudosten erottelukykyä. Intravaskulaarisessa käytössä niitä on pidetty erittäin turvallisina ja hyvin siedettyinä, mutta viime vuosina on havaittu, että gadoliniumia voi kertyä aivokudokseen. Vaikka gadoliniumpohjaisten kontrastiaineiden intratekaalinen käyttö ei ole virallisesti hyväksyttyä, menetelmän turvallisuus on osoitettu alustavasti useissa kliinisissä tutkimuksissa. Mahdollisia käyttöaiheita intratekaalisella gadoliniumilla tehostetulle magneettikuvaukselle (GdMK) ovat muun muassa likvorivuotojen ja likvorikierron häiriöiden diagnostiikka. Tämän katsauksen tavoite oli selvittää GdMK:n turvallisuutta ja hyödyllisyyttä aivojen ja selkäydinkanavan poikkeavuuksien diagnostiikassa.

Kirjallisuushaussa Medline- ja Scopus-tietokannoista etsittiin alkuperäisartikkeleita ja tapausselostuksia, joissa 1) arvioitiin GdMK:n turvallisuutta ja/tai hyötyä kliinisessä käytössä, ja 2) kuvattiin toimenpiteen suoritus yksityiskohtaisesti. Täydentävää hakua tehtiin aihetta käsittelevien artikkelien kirjallisuusluetteloista. Katsaukseen otettiin mukaan 28 alkuperäisartikkelia ja 8 tapausselostusta. Neljässä tutkimuksessa GdMK:ta verrattiin suoraan yhteen tai useampaan muuhun kuvantamismenetelmään ja raportoitiin menetelmille diagnostisten testien tunnuslukuja (herkkyys, tarkkuus, PPV, NPV). Näiden neljän tutkimuksen laatua arvioitiin soveltaen QUADAS-2-kriteereitä. Meta-analyysiä ei tehty, koska aineisto oli heterogeeninen.

Yhteensä 790 tutkimushenkilöä kuvannettiin GdMK:lla. Vakavia haittatapahtumia ei raportoitu. Yleisin haitta oli toimenpiteen jälkeinen päänsärky, jota esiintyi 83 potilaalla (11 %). Yhdelle potilaalle nousi toimenpiteen jälkeen kuume, yksi kärsi ohimenevästä täydellisestä muistinmenetyksestä (TGA) ja yksi sairastui bakteerimeningiittiin. GdMK:n herkkyys kallonpohjan likvorivuotojen diagnostiikassa oli 89–98 %. Kolme tutkimusta raportoi GdMK:n olevan varjoaine-TT:tä herkempi selkäydinkanavan likvorivuotojen diagnostiikassa. Lisäksi GdMK todettiin hyödylliseksi araknoidaalikystien, hydrokefaluksen ja neurokystiserkoosin diagnostiikassa.

Gadoliniumpohjaisten kontrastiaineiden intratekaalinen käyttö vaikuttaa olevan turvallista ja hyvin siedettyä. Intravaskulaariseen käyttöön liittyvät haitat tulee kuitenkin huomioida myös intratekaalisessa käytössä, ja gadoliniumpohjaisia kontrastiaineita tulisi käyttää varoen potilailla, joilla on munuaisten vajaatoiminta. Vaikka intratekaaliset annokset ovat intravaskulaarisiin annoksiin nähden pieniä, intratekaaliseen käyttöön voi liittyä vaikeasti ennakoitavia haittoja, sillä annostelureitti vaikuttaa kontrastiaineen kinetiikkaan. GdMK:n etuja ovat säteilyrasituksen puuttuminen ja TT:tä parempi herkkyys muun muassa likvorivuotojen diagnostiikassa, mutta pitkäaikaishaittojen riski on huomioitava gadoliniumin intratekaalista käyttöä harkittaessa.

Abstract

Background: The intravenous use of gadolinium-based contrast agents (GBCAs) in MR imaging is well-established in clinical practice. GBCAs were long considered to be extremely safe, but in recent years some concerns have been raised over possible long-term adverse effects, including deposition of gadolinium in neural tissue. The intrathecal use of GBCAs is not approved by the EMA or FDA, but its relative safety and tolerability has been reported in several clinical studies. When administered intrathecally, GBCAs provide enhancement of CSF and good contrast between CSF and parenchyma. Therefore, potential clinical applications include evaluation of the subarachnoid space, CSF fistulas, and CSF flow dynamics. The objective of this review was to assess the safety and diagnostic value of intrathecal gadolinium-enhanced MRI (GdMRI) in clinical practice.

Materials and methods: A search was carried out in the Medline and Scopus databases up to 30 November 2016. Original articles and case reports that 1) evaluated the safety and/or the diagnostic performance of GdMRI and 2) provided detailed information on the procedure were included. Data was collected on study design, sample size, patient demographics, GBCA type and dose, administration procedure, follow-up, adverse events, and diagnostic performance. Modified QUADAS-2 criteria were used to assess the methodological quality of four studies that compared GdMRI to other imaging modalities and reported diagnostic performance characteristics for GdMRI. Meta-analysis was not attempted due to the heterogeneity of the included studies.

Results: A total of 36 studies with 790 subjects were included. There were no reports of serious adverse events associated with GdMRI. The most frequent adverse effect was mild to moderate postprocedural headache, which was reported in 83 patients (11 %). One patient developed a fever, one had an episode of TGA, and one developed pneumococcal meningitis after the procedure. In detection and localization of skull-base CSF leaks, four studies reported a sensitivity of 89-96 % for GdMRI. Three studies reported improved detection and localization of spinal CSF leaks by GdMRI compared to CECT. The diagnostic value of GdMRI for the evaluation of arachnoid cysts, hydrocephalus, and neurocysticercosis was also reported in small patient series.

Conclusion: The intrathecal use of GBCAs appears to be safe and well-tolerated in the short term. Careful consideration is called for when performing GdMRI in patients with renal insufficiency, and the use of high-risk compounds should be avoided in all patients regardless of renal function. Although intrathecal doses of GBCAs are significantly lower than intravenous doses, no direct comparison can be made between the two due to differences in clearance kinetics. Because the experience on the intrathecal use of GBCAs is limited, the long-term safety of GdMRI remains unclear. In the diagnosis of CSF fistulas, GdMRI appears to have a higher sensitivity than CECT, and several small studies have shown the potential value of GdMRI in various other clinical situations. The benefits of improved diagnostics and lack of radiation exposure need to be weighed against the potential risk of long-term adverse effects when considering the intrathecal use of GBCAs, especially in young patients. More research is needed on the long-term safety of GdMRI before its widespread clinical use can be recommended.

Abbreviations

AS = aqueductal stenosis
CECT = intrathecal contrast-enhanced computed tomography; (general concept including cisternography and myelography)
CISS-3D = Three-dimensional constructive interference in steady state sequence in magnetic resonance imaging
ETV = endoscopic third ventriculostomy
FIESTA = fast-imaging employing steady-state acquisition sequence in magnetic resonance imaging
GBCA = gadolinium-based contrast agent
Gd-BOPTA = gadobenic acid
Gd-DTPA = gadopentetate dimeglumine
GdMRI = intrathecal gadolinium-enhanced magnetic resonance imaging; contrast agent injected via lumbar puncture; (general concept including cisternography and myelography)
GdMRV = intrathecal gadolinium-enhanced magnetic resonance ventriculography; contrast agent injected via ventricular puncture
HRCT = high-resolution computed tomography
NCC = neurocysticercosis
NPH = normal pressure hydrocephalus
NSF = nephrogenic systemic fibrosis
PC-MRI = phase-contrast magnetic resonance imaging
RC = radionuclide cisternography
SIH = spontaneous intracranial hypotension
STV = spontaneous third ventriculostomy
T2MRI = unenhanced T2-weighted magnetic resonance imaging
VPS = ventriculoperitoneal shunting

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1 Background

1.1 Gadolinium-based contrast agents in magnetic resonance imaging

Gadolinium-based contrast agents (GBCAs) are used in magnetic resonance imaging (MRI) to facilitate the detection of disease, e.g. inflammation, infection, and tumors. In GBCAs, gadolinium is attached to a chelating agent to prevent toxicity.[1] GBCAs generate a positive image contrast in T1-weighted sequences by shortening the T1 relaxation time of the hydrogen protons of nearby water molecules.[2] GBCAs were approved for intravenous use in 1988, and by the early 2000s their use had become routine in clinical practice.[3] In intravenous use, GBCAs have been considered to be well tolerated and safe as they rarely cause allergic or other adverse reactions. The incidence of acute hypersensitivity reactions occurring within 24 hours of administration ranges from 0.004 % to 0.7 %, with the majority categorized as minor or moderate. The incidence of severe reactions is 0.001–0.01 %, which is approximately one third of the frequency associated with the use of iodinated contrast agents.[4]

While considered safe in the short term, concerns have been raised over long-term adverse effects of GBCAs, foremost the risk of nephrogenic systemic fibrosis (NSF). NSF is a rare but potentially lethal fibrosing disorder that primarily affects the skin but may also involve other organs, including lung, heart, and kidney.[5, 6] The first cases of NSF were reported in the late 1990s, and the connection between NSF and the use of GBCAs was confirmed in 2006. The risk of NSF correlates with the total cumulative dose of GBCAs and delayed elimination of the contrast agent due to renal impairment. After the discovery of the causal relationship between GBCAs and NSF, restrictions were placed on the use of GBCAs in patients with impaired renal function, and the incidence of NSF has since decreased significantly.[7]

Another potential cause for concern is the deposition of gadolinium in brain and bone tissue following intravenous administration of GBCAs. In the early 2000s, traces of gadolinium were discovered in the bone of patients undergoing hip arthroplasty three to eight days after receiving GBCAs intravenously.[8] Accumulation of residual gadolinium in the brain was first suspected in 2014, when areas of hyperintensity were seen on unenhanced T1-weighted sequences of patients with multiple previous intravenous gadolinium-enhanced MRI examinations.[9] Shortly thereafter, McDonald et al. reported gadolinium deposition in the brain of patients who had previously received GBCAs. Unlike NSF, accumulation of gadolinium seems to also occur in patients with

normal renal function. As no studies have been conducted on medical conditions occurring after recurrent GBCA exposure, the clinical significance of gadolinium deposition remains unclear.[1]

According to several studies, some GBCAs are associated with a higher risk of NSF, and it appears that the same compounds are more likely to accumulate in neural tissue.[7] GBCAs may be classified regarding the risk of NSF in several ways. The European Medicines Agency (EMA) has based its classification on the molecular structure of the compounds.[10] In this system, GBCAs with a macrocyclic structure are considered safer, because they are more stable than linear compounds and thus less likely to dissociate and cause toxic damage.[1] Another system, created by The American College of Radiology (ACR), is based on confirmed cases of NSF that have been linked to a specific GBCA in relation to an estimate of administered doses. In both systems, the linear GBCAs gadodiamide and Gd-DTPA are assigned to the group of compounds with a high risk, and restrictions on their use in patients with renal impairment are recommended.[10] Since the risk of NSF correlates with impaired renal function, it has also been suggested that the route of elimination of GBCAs may affect the risk related to their use. However, as the only GBCA compound that has significant biliary elimination is currently only indicated for MRI of the liver, this theory is of limited value in clinical practice.[7]

According to recent guidelines by the European Society of Urogenital Radiology, the use of high-risk GBCAs is contraindicated in patients with severe renal impairment (GFR < 30 ml/min/1.73 m^2) and should be avoided in patients with moderate renal impairment (GFR < 60 ml/min/1.73 m^2). In cases of high-grade renal dysfunction (GFR < 15 ml/min/1.73 m^2), only low-risk GBCAs may be used and only on vital indication. In all cases and regardless of the compound used, GBCAs should be administered in the lowest dose possible for sufficient diagnostic imaging.[10]

1.2 Intrathecal use of gadolinium-based contrast agents

The neurotoxic potential of GBCAs in intrathecal use was demonstrated in animal models in the 1980s and the 1990s. In rat experiments, the medial lethal dose of Gd-DTPA was reported to be 50 µmol/g brain, and signs of toxicity (e.g. myoclonus, ataxia) were seen at doses of 5 µmol/g brain and higher.[11] In one study, histologic examination of the brain and spinal cord of rats after intraventricular Gd-DTPA injection showed loss of oligodendroglia, hypertrophy of astrocytes, and destruction of myelin sheaths.[11] The severity of the neuropathologic changes was dose-related, with first signs of toxic damage seen at 5 µmol/g brain. Some regions of the CNS (e.g. the superior olivary nuclei and the spinal cord) were affected more frequently than others, although the

distribution of the lesions was variable.[11] The same group of researchers carried out a similar study using gadodiamide instead of Gd-DTPA, and found differences in the localization and character of the CNS lesions. The lesions produced by gadodiamide were mostly located in the cerebellum, and unlike with Gd-DTPA, no lesions were seen in the brain stem nuclei or the spinal cord. No morphologic changes or signs of toxicity were seen below a dose of 1.25 µmol/g brain of gadodiamide.[12]

The intrathecal use of GBCAs in humans was first reported in 1997, when a Gd-DTPA-enhanced MR ventriculography (GdMRV) was performed on two patients with leptomeningeal carcinomatosis in order to assess the patency and function of intraventricular catheter systems.[13] In 1999, the safety and imaging characteristics of Gd-DTPA-enhanced MR myelography were evaluated in a pilot study of 11 patients by Zeng et al.[14] At doses of 0.2–1 mL (equal to 0.07–0.36 µmol/g brain) diluted with 5 mL of CSF, they reported no neurologic alterations or other adverse effects immediately after the procedure or during a follow-up of 9 to 15 months, but delayed scans obtained at 4 to 30 hours after administration of Gd-DTPA showed enhancement of the brain parenchyma. High signal intensity of CSF was seen on T1-weighted sequences at all doses. After these preliminary reports, several prospective studies on the subject have been conducted, but the intrathecal use of GBCAs has not been approved by the EMA or FDA and remains an off-label use.[1, 15, 16]

While low doses of intrathecal GBCAs seem to be well tolerated, there are reports of serious adverse events after accidental high-dose injection of GBCAs into the subarachnoid space. Li et al.[17] reported a case of a 34-year-old woman who underwent myelography for brachial plexus injury and was inadvertently administered 15 mL of Gd-DTPA (equivalent to 5.35 µmol/g brain), up to 30 times the recommended dose, via lumbar puncture. The immediate adverse reactions included headache and vomiting, and 1 hour after the injection the patient became comatose and suffered episodic systemic seizures. Cerebral edema and accumulation of Gd-DTPA in the brain parenchyma was seen in MRI, and MR angiography showed vasospasm of major cerebral arteries. The patient was treated with methylprednisolone, chlorpromazine, promethazine, and naloxone, and eventually made a full recovery. Enhancement of the brain parenchyma was still evident in MRI 8 months after the incident.

Samardzic et al.[18] reported a case of gadolinium-induced encephalopathy in a 67-year-old woman who was inadvertently injected with 4 mL of gadodiamide (equivalent to 1.4 µmol/g brain) via lumbar puncture during an epidural steroid injection. Three hours after the procedure, the patient developed nausea, dyspnea, and disorientation. MRI showed progressive enhancement of the brain

parenchyma and EEG showed signs of encephalopathy. The patient received dexamethasone and was discharged two days later in good condition.

Park et al.[19] described a case of 42-year-old man who received 6 mL of Gd-DTPA (equivalent to 2.16 µmol/g brain) intrathecally instead of the intended iodine-based contrast agent. Six hours later, the patient developed confusion, global aphasia, vomiting, focal seizures, and severe rigidity. The patient's CT scan showed diffuse high density, but no specific abnormalities were seen in digital subtraction angiography (DSA). The patient received anticonvulsants and intravenous hydration. In four days his condition improved, and the high-density signal was no longer seen in CT. When all symptoms had subsided, the patient was discharged.

1.3 Target conditions

1.3.1 Cerebrospinal fluid rhinorrhea and otorrhea

Cerebrospinal fluid rhinorrhea or otorrhea refers to the leakage of CSF into the sinonasal cavities or the middle ear cavity and mastoid cells, respectively. The leakage results from a skull base bony defect, or multiple defects, accompanied by a dural tear or tears. The patients present with leakage of clear fluid from the nose or the ear, or, in some cases, recurring bacterial meningitis as a complication of an untreated CSF leak. In CSF otorrhea, the clinical presentation depends on whether the tympanic membrane is intact; CSF leakage from the ear occurs only if the tympanic membrane is perforated. When the tympanic membrane is intact, CSF leaks via the Eustachian tube and otorrhea presents as a nasal leak.[20, 21]

Most skull base CSF leaks are either posttraumatic (80 %) or iatrogenic (16 %) in origin, while only 4 % occur spontaneously.[21] Posttraumatic CSF leaks carry a higher risk of meningitis than iatrogenic or spontaneous leaks but are also more likely to resolve without treatment. In posttraumatic leaks, a delayed onset of the leak, failure to respond to conservative treatment, and a history of meningitis are considered indications for surgical repair.[22] Surgical intervention is also recommended in spontaneous leaks due to the low probability of resolution without treatment.[21]

Differential diagnosis of skull base CSF leaks includes allergic rhinitis, nasal polyps, and chronic sinusitis. When a CSF leak is suspected, the fluid may be tested for β2-transferrin, a protein only found in CSF and perilymph, to determine its origin. If the fluid tests positive for β2-transferrin, imaging studies are needed to localize the leak site. CSF leak repair is almost exclusively performed

via endoscopy, and imaging studies are imperative for preoperative planning. A combination or HRCT and intrathecal contrast-enhanced CT (CECT) has been widely used in the detection of skull base CSF leaks. HRCT facilitates surgical planning by providing an excellent view of paranasal anatomy, but relies on indirect signs of leakage, e.g. bony defects, fracture lines, erosions, pneumocephalus, or fluid levels in the paranasal sinuses. In cases with multiple bony defects, the identification of the exact leak site may not be possible by HRCT alone. In CETC, the use of iodinated contrast agent allows direct visualization of the leak, but its ability to detect low-flow leaks or hairlike communications is limited and therefore its sensitivity is low. Heavily T2-weighted non-contrast enhanced MRI (T2MRI) may allow direct visualization of the leak, but the hyperintense CSF may be difficult to differentiate from mucosal inflammation in the sinuses, and high rates of false positives have been reported.[20, 21]

1.3.2 Spontaneous intracranial hypotension

Spontaneous intracranial hypotension (SIH) is a disorder characterized by signs and symptoms associated with low CSF pressure, most commonly postural headache. While the exact pathophysiology of SIH is not known, the low CSF pressure is thought to result from slow CSF leaks via dural defects in the spinal area, typically at the nerve root sleeves of the cervicothoracic junction or the thoracic spine. It is unclear why some individuals develop non-traumatic CSF leaks, but Marfan syndrome, meningeal diverticulae, and other connective tissue abnormalities have been suggested as predisposing factors.[23, 24]

The patients present with postural headache which occurs or worsens while standing upright and subsides in a supine position, usually within 15 to 30 minutes after lying down.[23] Other signs and symptoms may include nausea, meningism, hypacusis, tinnitus, or cognitive disturbances.[23] The headaches associated with low CSF pressure are considered to result from intracranial venous dilatation, which may cause meningeal traction, subdural effusions, or subdural hematomas due to the rupture of bridging veins.[24]

SIH is diagnosed based on symptoms, typical findings in clinical tests (e.g. low CSF opening pressure during lumbar puncture), and imaging. Cranial MRI findings in SIH may include downward sagging of the brain, diffuse pachymeningeal enhancement, engorged venous structures, and subdural fluid collections. However, SIH cannot be excluded based on a normal finding in MRI.[23]

The first line of treatment in SIH is conservative, i.e. bed rest, oral caffeine and hydration. When conservative treatment fails, one or several blind blood patches may be performed. If the symptoms prevail after blind blood patches, measures that require localization of the leak site, such as targeted blood patching or surgical repair of the dura, may be considered.[23] Imaging modalities for localizing the leak site include CECT and radionuclide cisternography (RC).[25] While indirect signs indicating spinal CSF leakage may be seen in RC, its ability to localize the leak is limited by its poor spatial resolution and lack of cross-sectional images.[26, 27] CECT is considered to be the most sensitive technique for detection of spinal CSF leaks, but as it involves considerable exposure to ionizing radiation (> 10 mSv), there is a need for an alternative imaging technique.[25]

1.3.3 Arachnoid cysts

Arachnoid cysts are benign fluid collections within the arachnoid membranes typically diagnosed in children and adolescents. Most patients with arachnoid cysts are asymptomatic and do not require further examinations or treatment. However, cysts may obstruct CSF flow or compress neural structures, leading to nonspecific or localized symptoms or hydrocephalus.[28] In symptomatic patients, surgical intervention may be considered. Since cranial surgery involves considerable risk, appropriate patient selection is important. It has been suggested that patients with cysts that do not communicate with the surrounding CSF space are more likely to benefit from surgery than patients with communicating cysts. Therefore, determining the fluid dynamics of the cysts via imaging studies may be helpful in patient selection. CECT and RC have been used for this purpose, but in pediatric patients, radiation exposure is a concern.[28] Non-enhanced MRI sequences such as three-dimensional constructive interference in steady state (CISS-3D) or phase-contrast MRI (PC-MRI) have been proposed as alternative techniques, but CISS-3D only provides morphologic information and in PC-MRI complex CSF flow patterns may lead to false positives.[29]

1.3.4 Neurocysticercosis

Neurocysticercosis (NCC) is an infectious disease caused by the helminth *Taenia solium*. Although rare in first world countries, it is a leading cause of acquired epilepsy in tropical low-income countries.[30] In NCC, vesicles or cysts containing larva may be seen in the brain or spinal cord parenchyma, the subarachnoid space, or the ventricles. Eventually the cysts degenerate and calcify.

Depending on the location, number, and size of the lesions, patients present with a range of neurological symptoms and signs, including epileptic seizures. In extraparenchymal forms of NCC, the cysts may obstruct CSF flow, leading to hydrocephalus and intracranial hypertension.[30]

The diagnostic work-up of NCC includes neuroradiological imaging, CSF analysis, and blood tests for antibodies. In extraparenchymal NCC, the cysts may be difficult to detect in CT scans because the cyst membrane is thin and the cyst fluid isodense with CSF. MRI is more sensitive than CT in detecting viable cysts, but calcified lesions are better seen on CT. The use of intrathecal contrast may help to ascertain the presence of cysticerci and avoid unnecessary antiparasitic therapy in patients without active disease.[30,31]

1.3.5 Hydrocephalus

In hydrocephalus, obstruction of CSF flow leads to excessive accumulation of CSF and dilatation of the cerebral ventricles. It may or may not be associated with increased intracranial pressure. In obstructive (non-communicating) hydrocephalus, CSF flow is obstructed proximal to the apertures of the fourth ventricle, typically due to a tumor, a cyst, or postinflammatory arachnoid adhesions.[32] The most common site of obstruction is the cerebral aqueduct.[33] In communicating hydrocephalus, the obstruction is distal to the apertures of the fourth ventricle, e.g. in the arachnoid granulations or in the basal cisterns. Communicating hydrocephalus is often secondary to meningitis, subarachnoid hemorrhage, or cranial trauma.[32]

Normal pressure hydrocephalus (NPH) is a type of communicating hydrocephalus seen in elderly patients. It is characterized by a typical triad of symptoms: dementia, urinary incontinence, and gait ataxia.[34] While there is no consensus on the pathophysiology of NPH, impaired re-absorption of CSF by arachnoid granulations has been considered a contributing factor.[35] Imaging examinations are useful in differentiating between NPH and other causes of dementia, e.g. Alzheimer's disease and vascular dementia. Typical MRI findings in NPH include ventriculomegaly, narrowed sulci, and deep white matter ischemia.[36, 37] In RC, radioactive contrast material seen in the ventricles for more than 24 hours after intrathecal administration is considered indicative of NPH.[38] CSF diversion by shunting leads to clinical improvement in some but not all patients, and thus far predicting which patients will benefit from the procedure has been difficult, although it has been suggested that patients with a history of meningitis or subarachnoid hemorrhage may respond better than patients with idiopathic NPH.[32]

In obstructive hydrocephalus, typical MRI findings include dilatation of the lateral and third ventricles, and bulging of the floor of the third ventricle. The patency of the cerebral aqueduct may be assessed with conventional T2MRI, in which a hypointense signal extending into the third and fourth ventricles (flow-void signal) is considered a sign of a patent aqueduct.[37] Treatment options for obstructive hydrocephalus include ventriculoperitoneal shunting (VPS) and endoscopic third ventriculostomy (ETV).[37] In ETV, a small opening is made in the floor of the third ventricle, allowing CSF to bypass the obstruction by flowing directly into the basal cisterns. In the case of a spontaneous third ventriculostomy (STV), which is sometimes seen in obstructive hydrocephalus, surgical treatment is considered unnecessary as it is unlikely to provide further benefit. The presence of an STV may be assessed by CISS-3D, which provides detailed anatomical information of the third ventricle, or PC-MRI, which allows assessment of CSF flow.[36]

Multiloculated hydrocephalus refers to the presence of isolated fluid-filled compartments within the ventricles. The formation of septae results from a disruption of the ependymal lining and often arises following intraventricular hemorrhage or meningitis. The septae may obstruct CSF flow and cause symptoms by mass effect. Imaging studies are needed for evaluating possible benefits of operative treatment, as patients with communicating intraventricular compartments are considered less likely to benefit from a procedure.[39]

2 Case report

A 33-year-old man presented with symptoms of intracranial hypotension, including postural headache and dizziness, but conventional MRI of the brain did not demonstrate typical findings for SIH. After conventional spinal MRI, conventional myelography, and CT myelography, GdMRI was performed with 0.4 mL of Gd-DTPA mixed with 4 mL of saline. A spinal drain was used for intrathecal contrast administration, and T1-weighted sequences were obtained before and 5 minutes after administration of Gd-DTPA. A fluid collection anterior to the medulla was seen in all imaging studies and enhancement of the fluid collection was seen with intrathecal contrast. However, no fluid compartment was found on surgical exploration. It was concluded that the fluid collection is located subdurally and communicates with the subarachnoid space. While GdMRI did not provide additional information in this case, it proved feasible and useful in situations where repeated imaging of the entire spine is required, with the advantage of no radiation exposure. Case and images courtesy of Jussi Numminen, HUS Radiology.

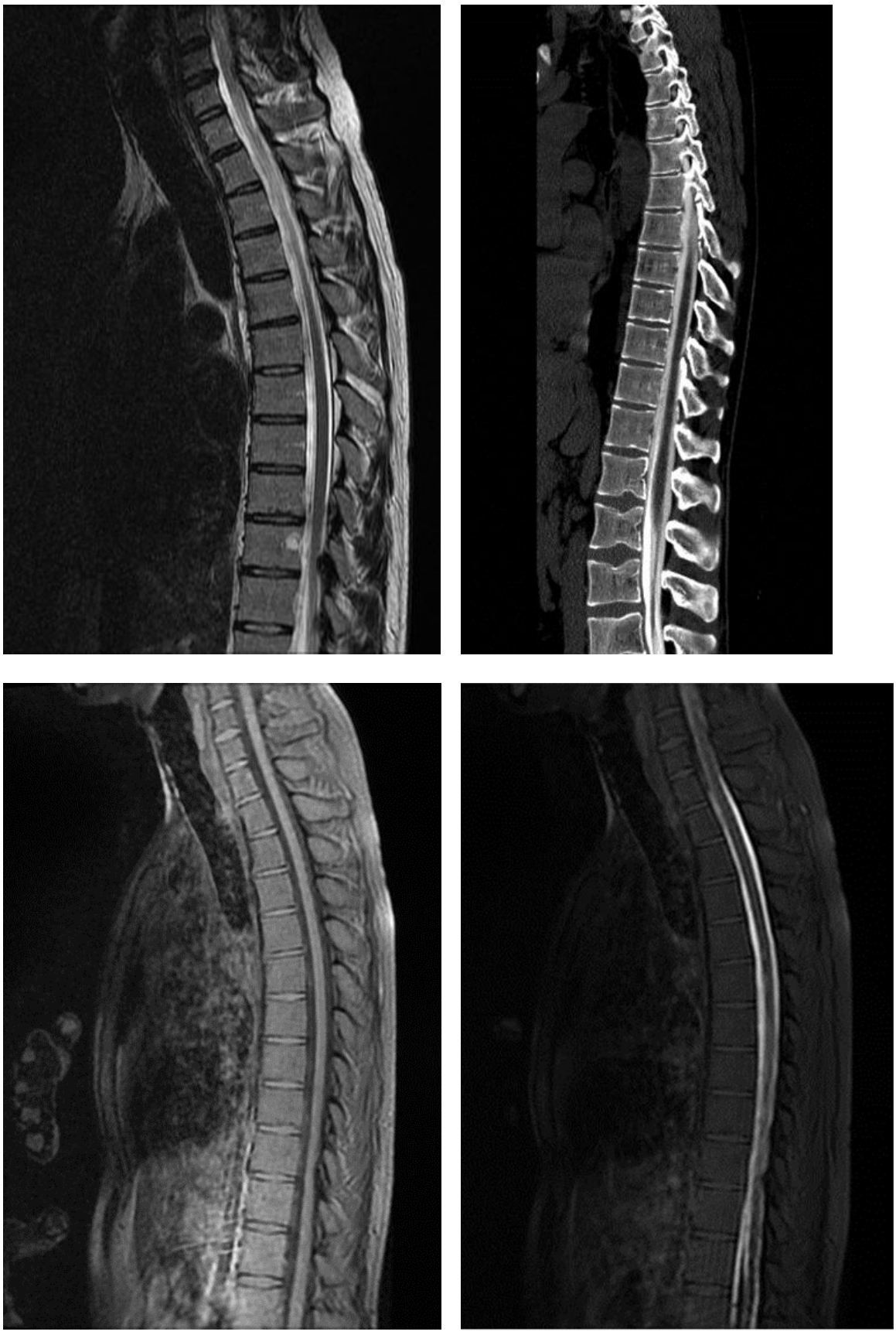

Figure 1. T2-weighted MRI (upper left); CT myelography (upper right); unenhanced T1-weighted MRI (lower left); T1-weighted MRI with intrathecal Gd-DTPA (lower right). The fluid collection is not apparent in sagittal images.

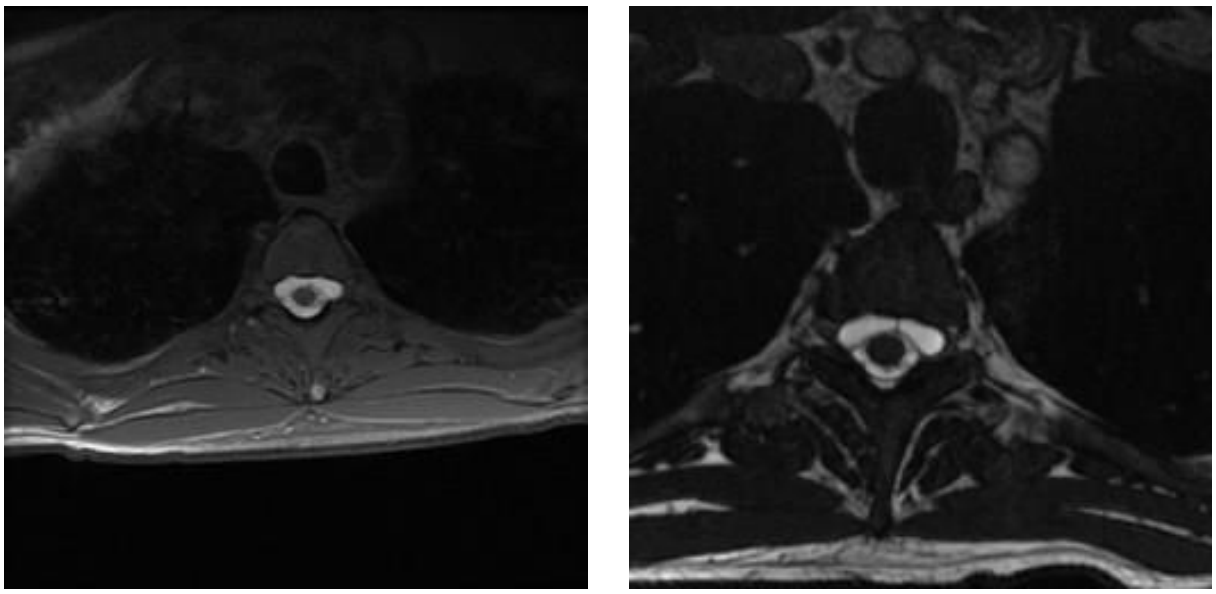

Figure 2. T1-weighted MRI with intrathecal Gd-DTPA (left); fast-imaging employing steady-state acquisition (FIESTA) MRI (right). Fluid exhibiting high signal intensity is seen anterior to the medulla.

3 Materials and methods

For this review, a search was carried out in the Medline and Scopus databases up to 30 November 2016. The search strategies for the two databases are described in Appendix 1. The citation lists of relevant articles, including reviews, were searched by hand for additional references. Original articles and case studies that 1) evaluated the safety and/or diagnostic performance of GdMRI, and 2) provided detailed information on the procedure were included in this review. The search was limited to English language articles available in full text via Tampere University Library.

The abstracts and titles of 51 studies were screened and full text articles of 23 potentially relevant studies were retrieved and assessed for eligibility by the author. An additional 13 eligible studies were identified by searching the citation lists of relevant articles. A summary of the study selection process is shown in Appendix 2.

The following data was extracted from full text articles: year of publication, sample size, patient demographics, target condition, imaging techniques, reference standard test, diagnostic performance characteristics, follow-up, and adverse events.

Four studies compared GdMRI to other imaging techniques and reported diagnostic performance characteristics (sensitivity, specificity, PPV, and/or NPV) for GdMRI. For these studies, the applicability and risk of bias were assessed based on modified QUADAS-2 criteria.

Due to the heterogeneity of the studies included in this review, statistical analysis was not attempted.

4 Results

4.1 Basic characteristics of included studies

Thirty-six studies (28 original articles and 8 case reports) met the inclusion criteria and were included in this review. The objective of the included studies was to evaluate the safety and/or diagnostic value of GdMRI. A total of 790 subjects (756 patients and 34 controls) were assessed. In the original articles, the sample size ranged from 5 to 95 patients, with a mean of 26 patients. The mean age of patients was available for 15 studies, with an average of 38 years (range 1 month to 85 years). Ten studies included pediatric patients (age 16 or younger), and in two of these all subjects were children. Out of eight case reports, two included pediatric patients. The proportion of men ranged from 33 % to 87 %. Out of 790 subjects, 437 were male and 353 female. (Table 1.)

All subjects underwent at least one GdMRI examination. Four studies included controls and in three of these, the controls also underwent GdMRI and were included in the analysis.[36, 40, 41] Controls who underwent GdMRI were suspected with intracranial abnormalities other than the target condition. In most studies, both immediate and delayed imaging was performed. Delayed images were obtained up to 96 hours after the administration of GBCAs. Imaging findings were evaluated by one to three experienced neuroradiologists. The reported follow-up ranged from an observation period of 24 hours to annual evaluations for up to six years, with an estimated average of 12 months.

GBCAs were administered via lumbar puncture in 29 studies. Gd-DTPA (with a concentration of 0.5 mmol/mL) was used in 25 of these studies with a total of 663 subjects (629 patients and 34 controls), with doses ranging from 0.2 to 1 mL, equal to 0.07–0.36 µmol/g brain. Gadodiamide (0.5 mmol/mL) was used in three studies with a total of 33 patients in doses of 1–2 mL, equal to 0.36–0.72 µmol/g brain. Gadobutrol (1 mmol/mL) was used in one study of 26 patients with a dose

of 1 mL, equal to 0.72 µmol/g brain. The use of Gd-BOPTA (0.5 mmol/mL) was reported in two patients with doses of 0.3 mL and 1 mL, equal to 0.11 and 0.36 µmol/g brain, respectively. In three studies GBCAs were injected simultaneously with an iodine-based contrast agent (iohexol or iomeprol).[24, 42, 43] In one study, 0.5–1 mL of iotrolan 240 was injected prior to the injection of Gd-DTPA to control needle placement.[44] (Table 2).

In three studies and two case reports with a total of 39 patients, GBCAs were administered directly into the ventricles via ventricular puncture. In two other studies, GBCAs were administered to some patients via lumbar puncture and some via ventricular puncture, transfontanelle ventriculostomy (TF), or ventriculoperitoneal shunt reservoir (VPS). Gd-DTPA was used in four studies, with doses ranging from 0.01 mmol to 1 mmol, equal to 0.0072–0.72 µmol/g brain. Gadodiamide was used in three studies, with doses of 0.02–0.5 mmol, equal to 0.014–0.036 µmol/g brain. (Table 2.)

4.2 Adverse events

There were no reports of gadolinium toxicity immediately after the procedure or during follow-up. One pediatric patient developed a fever after the administration of 1 mL of Gd-DTPA; the fever resolved with antihistamines and was attributed to a hypersensitivity reaction to the contrast agent.[45] There were no other reports of immediate or delayed hypersensitivity reactions. One patient with a suspected skull base CSF leak developed meningitis caused by *Streptococcus pneumoniae* 12 hours after the administration of Gd-DTPA via lumbar puncture,[46] and one patient who was being examined for SIH had an episode of transient global amnesia (TGA) after the administration of gadobutrol via lumbar puncture.[24] Apart from these two cases, no significant adverse events were reported.

Mild or moderate post-procedural headache was reported in 13 studies, with an incidence of 8–36 %. The headache resolved in all cases with conservative treatment (e.g. mild analgesics and/or bed rest) within 24–72 hours. In one study of 95 patients, nausea was reported in six patients and vomiting in two.[47] The symptoms resolved with bed rest within 24 hours. Adverse events are reported in Table 2.

Table 1. Basic characteristics of included studies.

	Year of publication	Type of study	No. patients; controls	Male, female	Age in years (mean, range)	Target condition
Wenzel et al.	2000	Case report	4	1, 3	26–62	CSF rhinorrhea
Jinkins et al.	2002	Prospective	15	8, 7	9–68	CSF rhinorrhea
Reiche et al.	2002		10	7, 3	42	CSF rhinorrhea
Aydin et al.	2004	Prospective	20	12, 8	19–56	CSF rhinorrhea
Arbeláez et al.	2007		24	15, 9	37, 7–61	CSF rhinorrhea
Goel et al.	2007	Prospective	10	5, 5	13–52	CSF rhinorrhea
Aydin et al.	2008	Prospective	51	32, 19	36, 19–61	CSF rhinorrhea
Algin et al.	2010	Prospective	17	13, 4	32, 11–70	CSF rhinorrhea
Selcuk et al.	2010		85	45, 40	15–72	CSF rhinorrhea
Vanopdenbosch et al.	2011	Prospective	27	9, 18	45, 18–73	CSF rhinorrhea, SIH
Ecin et al.	2013		60	33, 27	37, 18–70	CSF rhinorrhea
Mehdi et al.	2014	Case report	1	0, 1	9 mo	CSF rhinorrhea
Ragheb et al.	2014		24	16, 8	33–62	CSF rhinorrhea
Kraemer et al.	2005	Case report	1	0, 1	19	SIH
Albayram et al.	2007	Case report	1	0, 1	32	SIH
Albayram et al.	2008		19	7, 12	40, 25–77	SIH
Akbar et al.	2012	Retrospective	41	14, 27	61, 22–80	SIH
Albes et al.	2012	Prospective	26	15, 11	21–72	SIH
Chazen et al.	2014	Retrospective	24	14, 10	51, 20–85	SIH
Sharma et al.	1999	Case report	1	1, 0	60	Neurocysticercosis
Higuera-Calleja et al.	2015	Prospective	14	8, 6	32–64	Neurocysticercosis
Tali et al.	2004	Prospective	20	12, 8	37, 5–67	Arachnoid cysts
Tan et al.	2015		23	20, 3	0.3–9.7	Arachnoid cysts
Singh et al.	2008	Prospective	12	9, 3	12, (2 mo–50 y)	Hydrocephalus, ETV
Algin et al.	2010	Prospective	25; 9	14, 11; 4, 5	23, 1–67	Hydrocephalus, AS
Algin et al.	2011	Prospective	36; 15	14, 22; 9, 6	63, 46–75	NPH
Algin et al.	2011	Prospective	11; 10	8, 3; 6, 4	17, 2–35	Hydrocephalus, STV
Gandhoke et al.	2013		18	11, 7	2–14 mo	Multiloculated hydrocephalus
Zeng et al.	1999	Prospective	11	9, 2	40, 23–66	Various
Tali et al.	2002	Prospective	95	50, 45	1 mo–78	Various
Joseph et al.	2003		5	2, 3	6 mo–49	Various
Munoz et al.	2007		10	8, 2	1 mo–16	Various
Siebner et al.	1997	Case report	2	0, 2	60, 52	Drug device patency
Kraemer et al.	2002	Case report	1	0, 1	58	Spinal cyst
Hattingen et al.	2009	Retrospective	8	3, 5	27–73	CSF leakage
Munoz et al.	2014	Case report	4	2, 2	4–17	Craniophraryngiomas

AS = aqueductal stenosis; ETV = endoscopic third ventriculostomy; NPH = normal pressure hydrocephalus; STV = spontaneous third ventriculostomy; SIH = spontaneous intracranial hypotension

Table 2. Adverse events and administration technique.

	Type of GBCA	No. patients + controls	Dose (mL)	Dilution	Administration procedure	Follow-up (mean, range)	Adverse events (headache, other)
Siebner et al.	Gd-DTPA	2	0.01 mmol	Saline	VP	NA	-
Zeng et al.	Gd-DTPA	11	0.2, 0.5, 1	CSF	LP	9–15 mo	-
Wenzel et al.	Gd-DTPA	4	1	Saline	LP	NA	-
Jinkins et al.	Gd-DTPA	15	0.5	CSF	LP	6–12 mo	20 %
Reiche et al.	Gd-DTPA	10	1[1]	Saline	LP	0–2 y	-
Tali et al.	Gd-DTPA	95	0.5–1	CSF	LP	6–12 mo	20%, nausea (6 pt), vomiting (2 pt)
Albayram et al.	Gd-DTPA	1	0.5	Saline	LP	12 mo	-
Aydin et al.	Gd-DTPA	20	0.5	-	LP	1 mo, 3 mo	20 %
Tali et al.	Gd-DTPA	20		CSF	LP	6 mo	27 %
Arbeláez et al.	Gd-DTPA	24	1	-	LP	0–9 mo	36 %
Munoz et al.	Gd-DTPA	10	0.8–2	CSF	LP, VPS, TF	48 h	20 %
Albayram et al.	Gd-DTPA	19	0.5	Saline	LP	12 mo	26 %
Aydin et al.	Gd-DTPA	51	0.5	-	LP	4.1 y, 3–6 y	24 %
Hattingen et al.	Gd-DTPA	8	0.5	CSF	LP	24 h	NA
Algin et al.	Gd-DTPA	25 + 9	0.5–1	-	LP	NA	NA
Algin et al.	Gd-DTPA	17	1	-	LP	24 h	30 %, fever (1 pt)
Selcuk et al.	Gd-DTPA	85	0.5	Saline	LP	38.6 mo	8 %
Algin et al.	Gd-DTPA	36 + 15	1	-	LP	72 h	27 %
Algin et al.	Gd-DTPA	11 + 10	0.5–1	-	LP	NA	NA
Vanopdenbosch et al.	Gd-DTPA	27	0.5	-	LP	NA	meningitis (1 pt)
Akbar et al.	Gd-DTPA	41	0.5	Saline	LP	24 h–6.8 y	2 %
Ecin et al.	Gd-DTPA	60	0.5–1	-	LP	24 h	10 %
Chazen et al.	Gd-DTPA	24	0.3[2]	-	LP	NA	-
Munoz et al.	Gd-DTPA	4	0.1–0.2	Saline, CSF	VP	NA	-
Mehdi et al.	Gd-DTPA	1	0.5	Saline	LP	6 mo	-
Ragheb et al.	Gd-DTPA	24	0.5	-	LP	NA	25 %
Tan et al.	Gd-DTPA	23	0.5	CSF	LP, VP	1–10 mo	4 %
Sharma et al.	Gadodiamide	1	0.5	-	LP	NA	-
Joseph et al.	Gadodiamide	5	0.02–0.04 mmol	CSF	VP	9–15 mo	-
Goel et al.	Gadodiamide	10	2.0[3]	-	LP	1–12 mo	10 %
Singh et al.	Gadodiamide	12	1	CSF	VP	0–14 mo	-
Gandhoke et al.	Gadodiamide	18	0.02–0.04 mmol	-	VP	10 mo, 3 mo–2 y	-
Higuera-Calleja et al.	Gadodiamide	14	1	-	LP	18 mo, 12–24 mo	-
Kraemer et al.	Gd-BOPTA	1	1	-	LP	NA	-
Kraemer et al.	Gd-BOPTA	1	0.3	Saline	LP	4 mo	-
Albes et al.	gadobutrol	26	1[4]	-	LP	NA	TGA (1 pt)

[1] with 0.5–1.0 mL iotrolan; [2] with 10 mL iohexol; [3] with 5 mL iohexol; [4] with 9 mL iomeprol; NA = not available; LP = lumbar puncture; VP = ventricular puncture

4.3 Clinical applications

4.3.1 CSF rhinorrhea and otorrhea

In 10 original articles and two case reports, the main objective was the detection and localization of a CSF leak in patients with clinically suspected CSF rhinorrhea or otorrhea. One additional study included patients suspected with either CSF rhinorrhea or SIH. A total of 334 patients were assessed for CSF rhinorrhea. Excluding case reports, the sample size ranged from 10 to 85 patients, with a mean of 32 patients. The mean age was available in five studies, with an average of 37 years (range 9 to 72 years). One study and one case report included pediatric patients (children under the age of 16). Gender distribution was available for all but one study with two target conditions, in which the gender distribution for each patient group was not reported. In the remaining 12 studies, the proportion of men ranged from 50 % to 76 %. Of 321 patients, 187 were male and 134 female. Beta2-transferrin testing was performed in some or all patients as part of the clinical evaluation in five studies.[22, 45, 48, 49, 50]

Direct comparisons between imaging modalities were made in four studies. Out of these four, surgical or endoscopic findings were used as a reference standard in three studies,[42, 45, 51] while in one study,[48] β2-transferrin testing was also accepted as a reference standard. In one study,[45] only eight out of ten positive findings were confirmed surgically. The range for sensitivity and specificity of GdMRI in the detection of CSF rhinorrhea was 89–96 % and 80–100 %, respectively. Methodological evaluation of the four studies is described in Table 3.

Ragheb et al.[51] compared GdMRI with HRCT in a series of 24 patients. Sensitivity, specificity, PPV, and NPV for GdMRI were 96 %, 100 %, 100 %, and 50 %, respectively, and for HRCT, 65 %, 33 %, 88 %, and 11 %, respectively. Ecin et al.[48] compared GdMRI with unenhanced T2-weighted MRI (T2MRI) in a series of 60 patients. Sensitivity, specificity, PPV, and NPV calculated for GdMRI were 92 %, 80 %, 76 %, and 93 %, respectively, and for T2MRI, 56 %, 77 %, 64 %, and 71 %, respectively. Goel et al.[42] described a series of 10 consecutive patients, nine of whom underwent GdMRI, CECT, and CISS-3D, while one patient only underwent GdMRI. Sensitivity and specificity for GdMRI were 89 % and 100 %, respectively; for CISS-3D, 75 % and 100 %, respectively; and for CECT, 37.5 % and 100 %, respectively. Algin et al.[45] compared GdMRI to CISS-3D and HRCT in a series of 17 patients. Beta2-transferrin testing was carried out in eight

Table 3. Diagnostic performance characteristics of imaging modalities in detection of skull base CSF leaks in surgically confirmed groups.

	Modalities	Sensitivity	Specificity	Accuracy
Goel et al.	GdMRI	89 %	100 %	100 %
	CISS-3D	75 %	100 %	100 %
	CECT	38 %	100 %	100 %
Algin et al.	GdMRI	100 %	-	-
	HRCT	88 %	-	-
	CISS-3D	76 %	-	-
Ecin et al.	GdMRI	92 %	80 %	-
	T2MRI	56 %	77 %	-
Ragheb et al.	GdMRI	96 %	100 %	96 %
	HRCT	65 %	33 %	61 %

GdMRI = intrathecal gadolinium-enhanced MRI
CISS-3D = Three-dimensional constructive interference in steady state
CECT = intrathecal contrast-enhanced computed tomography
HRCT = high-resolution computed tomography
T2MRI = unenhanced T2-weighted MRI

Table 4. Methodological assessment by modified QUADAS-2 criteria.

	Goel et al.	Algin et al.	Ecin et al.	Ragheb et al.
Consecutive or random patient sample	Yes	Yes	Unclear	Unclear
Selection criteria clearly described	No	No	Yes	Yes
All patients received the same reference standard test	No	No	No	Yes
Patients received the same reference standard test regardless of index test results	No	No	Yes	Yes
Index test results interpreted without knowledge of results of the reference standard	No	No	Yes	Yes
Reference standard results interpreted without knowledge of results of the index test	No	No	No	Unclear
Criteria for a positive imaging result defined clearly	Yes	Yes	No	No

patients. Ten patients had a positive GdMRI, and leaks were confirmed surgically in eight of these patients. The same eight patients were tested for β2-transferrin and all eight tested positive. Sensitivity for GdMRI, HRCT, and CISS-3D were 100 %, 88 %, and 76 %, respectively. Specificity was not calculated due to the lack of a reliable reference standard. Diagnostic performance characteristics are reported in Table 3.

In the remaining seven studies, no direct comparison between modalities was made. However, in two of these studies all patients underwent both HRCT and GdMRI. [49, 52] A total of 105 patients were assessed, and GdMRI found a leak in 80 patients, 78 of which were confirmed surgically (one patient refused surgery and one was referred to another hospital). HRCT showed bony defects in all patients. The patients with a negative GdMRI were followed conservatively for 3 to 12 months and

did not require surgical treatment during follow-up. No false negative or false positive findings in GdMRI were reported.

In five studies, no other imaging modalities besides GdMRI were used. A total of 113 patients were evaluated. GdMRI showed a leak in 92 patients, 77 of which were confirmed surgically. The remaining 15 patients with a positive GdMRI were followed conservatively, and their symptoms resolved during follow-up. One patient with a negative GdMRI had a history of recurring bacterial meningitis and was therefore also referred for surgery, which revealed a leak in the ethmoidal region (false negative). Reasons for refraining from surgery in patients with a positive GdMRI included low-flow fistulas or intermittent leakage.[44, 46, 50, 52, 53]

The two case reports described a 9-month-old child with CSF otorhinorrhea and four adults with CSF rhinorrhea. GdMRI was performed due to inconclusive findings in previous imaging studies or surgical exploration. In all patients, the leak site was successfully localized by GdMRI.[54, 55]

4.3.2 Spontaneous intracranial hypotension

In five original articles and two case reports, patients with clinically suspected SIH underwent GdMRI for the detection and localization of spinal CSF leaks. In one additional study, 14 out of 27 patients underwent GdMRI due to suspected SIH, while the remaining 13 patients were suspected with skull base CSF leaks. A total of 136 patients were evaluated. In the study with two target conditions, the gender distribution for patients suspected with SIH was not available. Of the remaining 112 patients, 51 were male and 61 female. The patients' age range was 19–85 years, with an estimated average of 40 years. Two of the studies were retrospective. In three studies, the patients underwent both CECT and GdMRI, and in one study, GdMRI was the only imaging modality used. Imaging findings were not confirmed surgically, and no reference standard for detection of spinal CSF leaks was defined.[25, 43, 46, 56, 57, 58, 59, 60]

Albayram et al.[56] reported a series of 19 consecutive patients with suspected SIH, who did not undergo other imaging in addition to GdMRI. Of these 19 patients, 17 were found to be positive for a CSF leak on GdMRI, and the leak was successfully localized in 14 cases. The remaining three patients showed diffuse leakage due to a high-volume fistula. The writers suggest GdMRI for patients in whom blind epidural blood patches fail to sufficiently alleviate symptoms.

Albes et al.[24] reported a series of 26 patients with clinically suspected SIH. Twenty-three patients underwent both CECT and GdMRI, while three patients only underwent GdMRI. Leaks were

detected in all patients at the cervical, thoracic, and/or lumbar spine. GdMRI identified at least one leak site in 10 patients with no leaks detected in CECT. The writers concluded that GdMRI is more sensitive than CECT in detecting spinal CSF leaks, especially leaks associated with meningeal diverticula.

Chazen et al.[43] conducted a retrospective study of 24 patients, who underwent both CECT and GdMRI. CECT detected a leak in three patients, while GdMRI identified a leak in nine. All three leaks seen in CECT were also identified by GdMRI. Of the six cases where a leak was only seen in GdMRI, four were related to meningeal diverticula. The writers concluded that GdMRI is more sensitive than CECT in the diagnosis of spinal CSF leaks.

A retrospective study by Akbar et al.[58] looked at patients who underwent GdMRI after at least one prior CECT examination. Out of 41 patients, 24 had a negative finding in CECT and were considered the target population of the study. GdMRI detected a leak in five patients with a previous negative CECT, and the site of the leak was identified in four out of five cases. Out of 17 patients with a positive finding in prior CECT, GdMRI detected a leak in 12 cases but only identified the leak site in five cases. These cases were typically complex, with persisting symptoms despite multiple previous interventions. The writers concluded that GdMRI is useful in patients with a strong clinical suspicion of SIH and a negative finding in previous CECT, but in patients with a positive CECT, GdMRI is of limited value.

In a retrospective study by Hattingen et al.,[59] eight patients with suspected spinal CSF leaks underwent GdMRI, while six controls underwent unenhanced T1-weighted MRI with a frequency-selective fat saturation pulse (SPIR). In all subjects, a hyperintense signal imitating a CSF leak was seen at the apex of the lungs. The writers concluded that the described artefact may lead to false positives for spinal leaks.

In a study by Vanopdenbosch et al.,[46] 13 patients with suspected SIH underwent GdMRI. Leaks were detected in nine patients, eight of which were repaired surgically. Although no comparison to other imaging modalities was made, the writers suggest that GdMRI is more sensitive than CECT in detecting spinal CSF leaks.

Two case reports described one patient with Marfan syndrome and one patient with Behcet's disease. The patients presented with symptoms of SIH and underwent GdMRI after other imaging modalities failed to localize dural leaks. Multiple dural defects were revealed by GdMRI in both patients.[57, 60]

4.3.3 Arachnoid cysts

In a series of 23 pediatric patients (age range 3 months to 9.7 years) reported by Tan et al., GdMRI was performed to evaluate communication between arachnoid cysts and surrounding CSF spaces. The cysts were classified as complete communicating, incomplete communicating, or non-communicating based on the enhancement pattern seen in GdMRI. The patients were randomized into two groups: in one group, all patients underwent surgery regardless of the GdMRI findings (n = 10); in the other group, only patients with non-communicating or incomplete communicating cysts were operated on (n = 5) and patients with communicating cysts were followed conservatively (n = 8). Although there was no significant difference in the clinical outcome or cyst shrinkage between the two groups, the writers concluded that GdMRI may be of use in treatment planning for patients with arachnoid cysts, as surgery may be unnecessary in patients with communicating cysts.

In a study by Tali et al, 20 patients with a mean age of 37 years (age range 5–67 years) underwent GdMRI. All patients had been diagnosed with arachnoid cysts based on previous CT or MR imaging. Cyst enhancement was evaluated in both immediate and delayed post-contrast imaging, with delayed imaging carried out 24 hours after the injection of contrast media. Immediate enhancement of the cyst fluid was seen in nine patients, and delayed enhancement was seen in another six patients. In the remaining five patients, no enhancement of the cyst fluid was demonstrated. Of these five, symptomatic patients (n = 3) were referred for surgery, while clinical and imaging follow-up was planned for asymptomatic patients (n = 2). Of the patients with communicating cysts, three underwent surgery because their symptoms were believed to result from regional mass effect caused by the cysts. Clinical improvement was seen in all patients who underwent surgery. In the patients who were not treated surgically, no change was seen in follow-up at 6 months. The writers concluded that GdMRI may be useful in patient selection for arachnoid cyst surgery.

4.3.4 Neurocysticercosis

In a study by Higuera-Calleja et al.,[31] 14 patients (8 males, 6 females; age range 32–64) with suspected neurocysticercosis underwent GdMRI. In the patients' prior CT examinations, no cysts or vesicles had been seen, but one patient had a finding suggestive of a cysticercus vesicle in a previous MRI examination. GdMRI showed vesicles or cysts in 10 patients in the basal

subarachnoid space, the lateral ventricle, the fourth ventricle, or the spinal canal. In four patients, no vesicles or cysts were detected. The writers concluded that GdMRI is useful in the detection of cystic lesions, especially ones located in the basal cisterns, spinal subarachnoid space and ventricles.

Sharma et al.[61] reported the case of a 60-year-old man presenting with seizures, ataxia, dementia, and urinary incontinence. The patient's CT scans showed mild ventricular dilatation, focal dilatation of sulci, and calcified lesions in the brain parenchyma, but no cysticercal cysts or vesicles. MRI exams showed cysticercal cysts in the parenchyma and strands resembling a cobweb in the dilated sulci. GdMRI confirmed the presence of cisternal cysticerci, which were clearly demonstrated as filling defects in the cisternal spaces. The patient was diagnosed with intraparenchymal and cisternal cysticercosis.

4.3.5 Hydrocephalus

In a study by Singh et al.,[61] intrathecal gadolinium-enhanced MR ventriculography (GdMRV) was performed in 10 patients with communicating hydrocephalus to evaluate the success of an ETV procedure. In preoperative GdMRV, flow of contrast media beyond the fourth ventricle was seen in all patients. Postoperative GdMRV showed immediate flow of contrast media into the prepontine and basal cisterns in seven patients, and ETV was considered successful in these cases. No symptoms indicating failure or closure of ETV were seen during a follow-up time of 7 to 14 months. In three patients, ETV was considered unsuccessful as there was no flow of contrast seen in the prepontine cistern postoperatively and symptoms of raised ICP persisted after the procedure. The writers concluded that GdMRV was useful in determining the patency of ETV and the subarachnoid space.

Algin et al.[41] compared GdMRI, PC-MRI, and CISS-3D in the evaluation of the presence of STV in patients with obstructive hydrocephalus. Eleven patients and 10 controls underwent GdMRI, PC-MRI, and CISS-3D. STV was seen in six patients in PC-MRI, three patients in CISS-3D, and two patients in GdMRI. GdMRI was considered as the reference standard, and surgical treatment was offered to the eight patients with no STV seen in GdMRI. Two of these patients refused surgery, and the remaining six underwent VPS, cyst fenestration, or ETV. Surgical findings were consistent with imaging findings, and the surgically treated patients improved clinically after surgery. The writers concluded that due to their noninvasive nature, PC-MRI and CISS-3D should be considered

primary examinations for the evaluation of the presence of STV, and positive findings should be verified by GdMRI.

In another paper by the same group,[40] PC-MRI and CISS-3D were compared to GdMRI in the evaluation of aqueductal stenosis. Aqueductal patency was evaluated in 25 patients with suspected AS and nine controls by GdMRI, PC-MRI, and CISS-3D. GdMRI was considered as a reference standard, but imaging findings were not confirmed surgically. In eight patients, PC-MRI or CISS-3D showed partial flow while GdMRI showed complete obstruction or normal flow. The writers suggest that if partial narrowing of the aqueduct is suspected based on PC-MRI and CISS-3D, GdMRI should be performed to verify the presence of AS.

Gandhoke et al.[39] performed GdMRV in 18 pediatric patients (age range 2–14 months) with suspected multiloculated hydrocephalus to evaluate the presence of ventricular septae and obstruction of CSF flow. GdMRV verified the diagnosis of multiloculated hydrocephalus in 17 patients and excluded it in one patient. Four cases showed free flow of CSF within the ventricular system, leading to simplification of the planned surgical procedure. In 13 cases, multiple isolated compartments were seen in the ventricles, and endoscopic treatment was planned accordingly. Postoperative GdMRV was obtained in eight patients. Findings included a closed or non-functioning ETV in four patients and the successful fenestration of septae in four patients. During a follow-up of 3 months to 2 years, 9 out of 13 endoscopically treated patients remained shunt free. The writers concluded that GdMRV is complementary to CISS-3D in the assessment of multiloculated hydrocephalus and may reduce the number of unnecessary procedures.

Algin et al.[38] performed GdMRI in 36 patients with suspected NPH and 15 controls in order to assess whether imaging findings predict response to shunt surgery. The presence of contrast material in the lateral ventricles was assessed at 12, 24 and 48 hours after the injection of Gd-DTPA. The presence of contrast material in the lateral ventricles at 24 and 48 hours after the injection was significantly more prevalent in the patient group than in the control group, but it did not correlate with response to shunt treatment. The sensitivity and specificity for GdMRI in predicting response to shunt surgery were 100 % and 17 %, respectively.

Joseph et al.[63] described a series of five nonconsecutive patients presenting with symptoms of hydrocephalus. GdMRV was performed in all five to evaluate obstruction of CSF flow or the patency of third ventriculostomy. The writers concluded that GdMRV is useful in the evaluation of CSF dynamics.

4.3.6 Other

In three studies, patients were enrolled based on various symptoms and signs for which cranial or spinal imaging with intrathecal contrast was requested. A total of 116 patients were assessed. The purpose of these studies was to evaluate the safety and imaging characteristics of GdMRI. In a pilot study by Zeng et al.,[14] 11 adult patients presenting with symptoms of the lower extremities or lower back underwent GdMRI. The largest series of patients was reported by Tali et al.,[47] who performed GdMRI in 95 patients (50 males, 45 females; age range 1 month to 78 years). Imaging indications included paraparesis, subcutaneous paraspinal mass, and suspected cranial or spinal CSF leaks. Muñoz et al.[64] performed GdMRI in 10 pediatric patients (age range 1 month to 16 years) with various suspected intracranial abnormalities, in whom previous standard MRI provided insufficient information for diagnosis or treatment planning. In all three studies, there were no reports of severe adverse events. Tali et al. reported postprocedural headache in 19 patients, nausea in six, and episodes of vomiting in two. All symptoms resolved within 24 hours with bed rest. Imaging findings included spinal cysts, intraventricular and intraparenchymal cysts, spinal stenosis, intervertebral disc herniation, meningomyelocele, and arachnoiditis. It was concluded that GdMRI is a relatively safe and feasible procedure with potential clinical applications in assessment of CSF-filled spaces and CSF flow.

In the first report of intrathecal use of GBCAs, Siebner et al.[13] performed GdMRV in two patients with leptomeningeal carcinomatosis to evaluate the function of intraventricular drug devices. Both patients tolerated the procedure well, and good contrast between CSF and brain parenchyma was achieved. The writers concluded that GdMRI may be valuable in imaging of CSF-related disorders.

One case report described the use of intracystic GdMRI in the evaluation of residual giant-cystic craniopharyngiomas in four pediatric patients (age range 4 to 17 years). GdMRI was performed to rule out communication between the intracystic space and the surrounding structures before intracystic therapy. In three cases, no communication was seen, and in one case, GdMRI showed leakage of contrast material from the cyst despite a previous negative finding in contrast-enhanced CT cystography. The writers concluded that GdMRI is superior to contrast-enhanced CT in the evaluation of cyst leakage.[65]

Kraemer et al.[66] performed GdMRI with 1 mL of Gd-BOPTA in a 58-year old female patient with a spinal cyst. Sedimentation of the contrast material was seen in the lumbosacral subarachnoid space. The writers suggested that a lower concentration of contrast agent be used and mixed with a small volume of CSF before administration to avoid sedimentation.

5 Discussion

For this paper, 28 original articles and 8 case reports were reviewed, with a total of 790 subjects undergoing at least one GdMRI examination. The most frequently used GBCA was Gd-DTPA, which was administered to 663 patients in 29 studies. The other GBCAs used were gadodiamide, gadobutrol, and Gd-BOPTA. Gd-DTPA was most commonly administered at a dose of 0.5 mL (equal to 0.17 µmol/g brain), which was sufficient to achieve excellent contrast between CSF and brain or spinal cord parenchyma.

The neurotoxicity of GBCAs has been established in animal models, and there are several reports of neurotoxic effects in humans following accidental high-dose injection of GBCAs. In the studies included in this review, GBCAs were used at diagnostic doses and no signs or neurotoxicity were reported. There were no reports of allergy or hypersensitivity to GBCAs apart from one case of fever that was attributed to a hypersensitivity reaction to the contrast agent (Gd-DTPA). One patient with CSF rhinorrhea developed pneumococcal meningitis 12 hours after the intrathecal administration of Gd-DTPA, but this was likely a complication of a CSF leak and not the procedure. Also, one patient had an episode of TGA after the intrathecal administration of gadobutrol, but it remains unclear whether the procedure caused or contributed to the event. Mild to moderate postprocedural headache was reported in 13 studies, with an incidence ranging from 8 to 36 %. The headache resolved in all patients with conservative treatment within 24–72 hours and should be attributed to lumbar puncture and not GBCAs. Higher rates of postprocedural headache have been reported in patients after CECT examinations, most likely because the high viscosity of iodine-based contrast agents requires the use of larger diameter needles.[26]

For the time being, it is unclear whether intrathecal administration of GBCAs has any long-term adverse effects. Even though such effects have not been reported thus far, the risk of long-term neurotoxicity cannot be excluded, as the procedure has been performed in a fairly small number of patients and mostly in studies conducted 10 years ago or less. The longest reported mean follow-up in a study was 4.12 years and as seen with intravenous use of GBCAs and NSF, it may take considerably longer for an adverse effect to manifest and be recognized as such. It should be presumed that the risk of NSF and gadolinium deposition is inherent in both intravenous and intrathecal use of GBCAs. Although the doses of GBCAs in intrathecal use are significantly lower than intravenous doses (e.g. a total dose of 0.25 mmol and 0.1–0.2 mmol/kg for Gd-DTPA, respectively), no direct comparison can be made between the two because the kinetics of clearance of contrast agents differ depending on the route of administration. However, since both the risk of

NSF and gadolinium deposition seem to correlate with the total cumulative dose of GBCAs administered, the risk associated with a single dose of intrathecal GBCAs should be small.

The reported clinical applications of GdMRI included detection and localization of CSF leaks, assessment of obstructions of CSF flow, demonstration of cysts, and evaluation of communication between cysts and surrounding structures. In the studies reviewed for this paper, GdMRI was most frequently used to assess patients with suspected CSF rhinorrhea or otorrhea. Compared to CECT, GdMRI was found to have a higher sensitivity and specificity in detection and localization of skull base CSF leaks. This has been attributed to improved detection of low-flow leaks and hairlike CSF fistulas by GdMRI.[42] Iodinated contrast agents have a higher viscosity than GBCAs and are thus less likely to flow past narrow bony and dural defects, which may lead to false negatives. Also, contrast between CSF and bone is poor in CECT as both appear hyperdense, whereas GdMRI provides good contrast between hypointense bone and hyperintense CSF. Fat-saturated sequences are recommended for suppressing the signal intensity of bone marrow.[42]

A recent review on diagnostic imaging of CSF rhinorrhea suggests HRCT as the primary imaging modality in all patients with suspected skull base CSF leaks.[20] HRCT provides a detailed view of the bony structures and is considered necessary for surgical planning. In cases where a single bony defect is seen in HRCT, no further imaging may be needed. If multiple defects are identified or if the clinical presentation does not match the findings in HRCT, fat-suppressed T2MRI may be recommended as a second-line imaging modality due to its noninvasive nature. T2MRI has a high sensitivity, but the hyperintense CSF may be difficult to differentiate from mucosal inflammation in the sinuses, and high rates of false positives have been reported.[42, 44] In cases where HRCT and T2MRI fail to provide sufficient information for surgical planning, GdMRI may be recommended.

Surgical findings were used as a reference standard for diagnosing CSF rhinorrhea in most of the studies, but apart from one study, patients with a negative finding in GdMRI were not referred for surgery or endoscopy, so the negative results were not confirmed. However, the patients with a negative GdMRI were followed conservatively and their symptoms were relieved during follow-up. This suggests that GdMRI correctly identified the patients who did not require surgery, either because they did not have a CSF leak or because the leak resolved spontaneously. In three studies, the selection criteria included a minimum duration of symptoms (range 2 weeks to 3 months). Since the probability of spontaneous cessation of a posttraumatic CSF leak is fairly high during the first weeks, it seems appropriate to require a minimum duration of symptoms in order to avoid unnecessary invasive imaging procedures. Also, a β2-transferrin test should be performed in all patients to differentiate a CSF leak from other causes of nasal discharge.

In patients with suspected spinal CSF leaks, GdMRI was considered superior to CECT in showing diffuse or low-flow leaks and in detecting meningeal diverticula. The longer imaging half-life of GBCAs as compared to iodine-based contrast agents enables delayed imaging and better visualization of slow, low-flow leaks.[43, 56] The improved detection of diffuse leaks by GdMRI was attributed to the lower viscosity of GBCAs.[56] CECT was considered superior to GdMRI in the localization of high-flow leaks due to the shorter acquisition time of CECT.[43] Two out of three studies that compared GdMRI to CECT found GdMRI to be more sensitive in the detection and localization of spinal CSF leaks.

The primary imaging examination in patients with suspected SIH is cranial MRI.[23] In patients who remain symptomatic despite conservative treatment and blind epidural blood patches, the leak site should be localized so that a targeted blood patch or surgical repair of the dural tear may be performed. Since CECT involves considerable exposure to ionizing radiation and does not appear to be safer or more sensitive than GdMRI, the latter may be suggested as a primary imaging procedure for localization of spinal CSF leaks.

In the assessment of patients with suspected obstructive hydrocephalus, GdMRI was compared to PC-MRI and CISS-3D in two studies by the same group.[40, 41] Due to their noninvasive nature, PC-MRI and CISS-3D may be considered primary imaging modalities in patients with suspected aqueductal stenosis or spontaneous third ventriculostomy, while GdMRI may be recommended in cases where the results of PC-MRI and CISS-3D are inconclusive. GdMRI was also considered useful in the evaluation of endoscopic third ventriculostomy patency.[62] In patients with suspected normal pressure hydrocephalus, GdMRI failed to predict response to shunt surgery, whereas CECT has previously been shown to predict surgical outcome.[38, 63] In children with multiloculated hydrocephalus, preoperative GdMRI reduced the number of unnecessary procedures and was deemed useful.[39]

GdMRI was also found to be useful in the evaluation of arachnoid cysts, and although it was not compared to other imaging methods, it may be a viable alternative to CECT due to radiation concerns, especially since most patients are children or adolescents.[28, 29] In patients with suspected neurocysticercosis, GdMRI improved the detection of cysticerci in the cisternal spaces, ventricles, and spinal subarachnoid space.[31, 61]

6 Conclusion

The intrathecal administration of GBCAs appears to be a relatively safe and well-tolerated procedure in the short term. As with intravenous use, careful consideration is called for when administering intrathecal GBCAs to patients with renal insufficiency, and the use of high-risk compounds should be avoided in all patients regardless of renal function. Although intrathecal doses of GBCAs are significantly lower than doses in intravenous use, no direct comparison can be made between the two regarding possible long-term risks, because the kinetics of clearance differ depending on the route of administration. There is limited experience of the intrathecal use of GBCAs and it may therefore involve risks that have yet to be recognized. GdMRI appears to be more sensitive than CECT in the detection and localization of cranial and spinal CSF leaks, and several small studies have reported the diagnostic value of GdMRI in various other clinical situations. The benefits of improved diagnostics and lack of radiation exposure need to be weighed against the risk of long-term adverse effects when considering intrathecal administration of GBCAs, especially in young patients. More research is needed on the long-term safety of the intrathecal use of GBCAs and the diagnostic value of GdMRI in different clinical situations.

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Appendix 1. Search strategies.

Database(s): Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)

#	Searches	Results
1	Gadolinium DTPA/ or Gadolinium/	19730
2	Magnetic Resonance Imaging/	336136
3	intrathecal gado*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	45
4	Injections, Spinal/	11856
5	3 or 4	11880
6	1 and 2 and 5	43
7	limit 6 to (english language and humans)	34

Database: Scopus

(TITLE-ABS-KEY (*"intrathecal gado*"*) AND TITLE-ABS-KEY (*mri*))

Appendix 2. Study selection process.