Gadolinium-based contrast agents in neurofibromatosis type 1 (Review)

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Abstract. Gadolinium (symbol Gd) is the chemical element with atomic number 64 and is aductile rare-earth metal, and +3 is its most frequent oxidation state. Gadolinium has an ionic radius of 0.99 Å and is nearly identical to the one of Ca^{2+}. Gd^{3+} and Ca^{2+} can become toxic to biological systems if complete. It slowly reacts with atmospheric oxygen to form a black coating and in nature it is usually found only in an oxidized form. Gadolinium usually has impurities similar to those of other rare-earth metals, when separated, because of their similar chemical properties. Neurofibromatosis type 1 (NF1) or von Recklinghausen's disease is an autosomal dominant disorder of tissues of ectodermal origin, accounting for over 90% of neurofibromatosis cases. Diagnosis is primarily clinical and the central nervous system is commonly involved. The screening of the brain with magnetic resonance (MR) imaging is utilised to evaluate the patients with neurofibromatosis type 1 and as an aid in the diagnosis of asymptomatic patients when clinical criteria are not met.

Contents

1. Introduction

Gadolinium (Gd) has the atomic number 64. It is a heavy metal and belongs to the family of lanthanides. The oxidation state of gadolinium that is met often is +3. Gadolinium has an ionic radius of 0.99 Å and is almost identical to the one of Ca^{2+} (1). Gd^{3+} and Ca^{2+} can become toxic to biological systems if it compete. When administered to humans in chelated forms the presence of free gadolinium is avoided, thereby reducing its toxicity (2,3). Gd is capable of inducing a strong magnetic field that influences the degree of relaxivity of the protons of water molecules, resulting in a signal increase in MRI (4-6).

2. Development of gadolinium complexes

Runge first introduced the term of gadolinium-based contrast agent (GBCA) in 1982 at the Radiologic Society of North America meeting in Chicago (7,8). GBCAs were thereafter produced commercially because this increases detection of the lesion. Fig. 1 shows the combined form of Gd-DTPA-Magnevist (also known as gadopentetate dimeglumine). In 1988, this complex was first authorized for use. Subsequently, gadolinium was used in the following complexes:

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Gd-DOTA-Dotarem (also known as gadoterate meglumine) (Fig. 2), Gd-HP-DO3A-ProHance (gadoteridol) (Fig. 3), and Gd-DTPABMA-Ominiscan (gadodiamide) (Fig. 4) (9). Following identification of the complexes, GBCAs were used for more than 30 years in more than 100,000,000 patients (1).

3. Findings

The administration of gadolinium complexes rarely induces side effects and they can be divided into two groups: i) non-allergic reactions (fatigue, headache, arthralgia, gustatory perversion, flushed feeling, nausea, vomiting) and ii) idiosyncrasic allergy-like reactions (periorbital edema, rash, erythema, respiratory failure, chest pressure) (10,11). The frequency of side effects is similar to medical systemic or topical drugs used for various clinical conditions (12-21). Classified by the severity, the acute reactions to GBCA are: Mild, moderate and severe (10). The mild ones are auto-limited events, show no progress, are the most common and do not require medical treatment, except for skin reactions for which an antihistamine drug can be administered. Skin reactions occur in 0.07 and 2.4% of cases. Moderate reactions require medical treatment such as antihistamines, or transport to emergency room and occur in 0.004-0.7% of cases. The patient life is subjected to immediate risk by severe reaction; however, such reactions do not exceed 0.001-0.01% (10,11). If patients have a history of allergy, hypersensitivity to a gadolinium-based contrast agent or if they receive the contrast agent at a rapid rate, complications may occur (6).

Neurofibromatosis type 1 (NF1) or von Recklinghausen's disease is an autosomal dominant disorder involving tissues of ectodermal origin and represents over 90% of neurofibromatosis cases. Initially, the diagnosis is clinical (22). Symptoms manifest differently in each patient with a highly variable expression, even those within the same family (23,24). The diagnostic criteria take into account the cutaneous, neurological, ocular and skeletal manifestations to which is added the genetic component. These criteria were established in 1988 during the Neurofibromatosis - NIH Consensus Development Conference (22). If two or more criteria out of the seven are present, a clinical diagnosis can be made. The criteria are: i) prepubertal: Six or more than six 'café-au-lait' spots >5 mm and >15 mm, postpubertal; ii) two or more neurofibromas or one or more plexiform neurofibroma; iii) axillary or inguinal freckle (Crowe sign); iv) glioma of the optic nerve; v) two or more than two iris hamartomas; vi) sphenoid wing dysplasia, cortex of long bones thin(with/without pseudarthrosis); vii) a 1st degree relative with neurofibromatosis type 1 diagnosed using the above criteria (25).

The central nervous system is commonly involved in NF1. The screening of the brain with magnetic resonance (MR) imaging is utilised to evaluate the disease progression and as an aid in the diagnosis of asymptomatic patients when clinical criteria are not met (26-29). The most common intracranial abnormalities in NF1 patients are astrocytomas of the optic pathways, as indicated in the MRI of an 8-year-old female patient (Fig. 5). Surfaces with abnormal T-2 signal intensity are observed with high frequency and represent hamartomas or heterotopias as identified in an 8-year-old patient (Fig. 6).

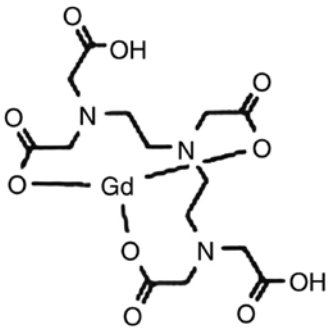

Figure 1. Chemical structure of gadopentetate dimeglumine.

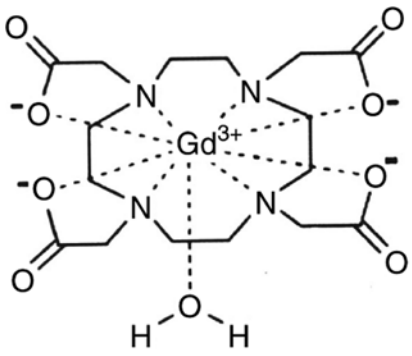

Figure 2. Chemical structure of gadoterate meglumine.

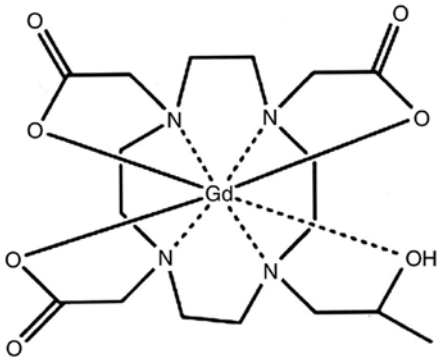

Figure 3. Chemical structure of gadoteridol.

4. Discussion

Progression of these lesions in the second decade of life dictates the need for strict monitoring to exclude neoplasia. In adults the safety of contrast material has been well established, and according to preliminary data that it is also safe for use in children. Contrast administration is recommended when pre-contrast studies show abnormalities, when tumor is suspected, when improved lesion delineation is necessary, and when postoperative evaluation is required to ascertain tumor recurrence (30). Approximately 15% of all patients with NF1 have brain anomaly on MRI (27). The lesions are often multiple (29,30), in characteristic locations: The pons, cerebellar white matter, midbrain, splenium of the corpus callosum and internal capsule. Cerebellar tumors can compress the brain and the fourth ventricle (appearing hydrocephalus) and

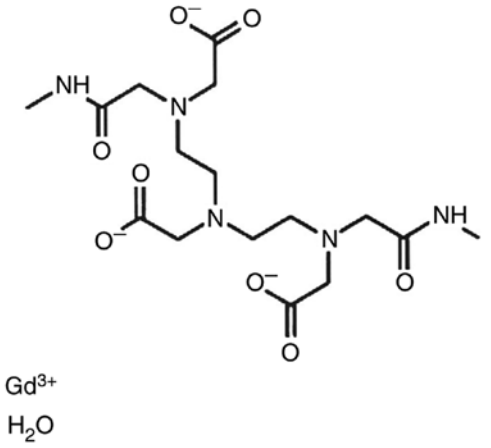

Figure 4. Chemical structure of gadodiamide.

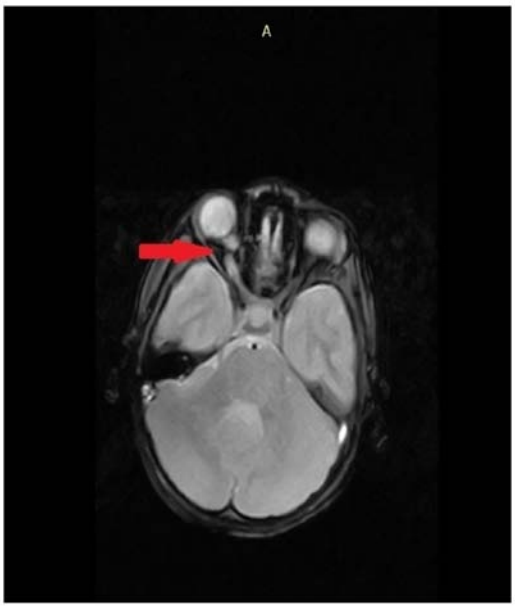

Figure 5. Anterior view of a MRI image in T-2 transversal section and the right optic nerve thick and sinuous of a patient, aged 8 years presenting to the Clinical Hospital for Children, Galati, Romania. A, anterior view.

treatment may require surgical resection. On suspicion of a tumor, administrating contrast material can be helpful to fully delineate and help characterize it, with other investigations being performed for genetic or congenital disorders (30-34).

Rehabilitation of patients can be applied at any stage of disease; consequently, the objectives change as the disease advances. The use of preventive rehabilitation ensures the maintenance of maximum functional independence. A decline in functional skills due to tumor progression leads to rehabilitation playing a supportive role via accommodating patients with anatomic and physiologic limitations. Palliative rehabilitation is recommended for the terminal stages of illness and isused to improve and maintain comfort and quality of life.

5. Conclusions

Contrast administration may be used to maximize tumor detection in basic MR and to determine the stability of

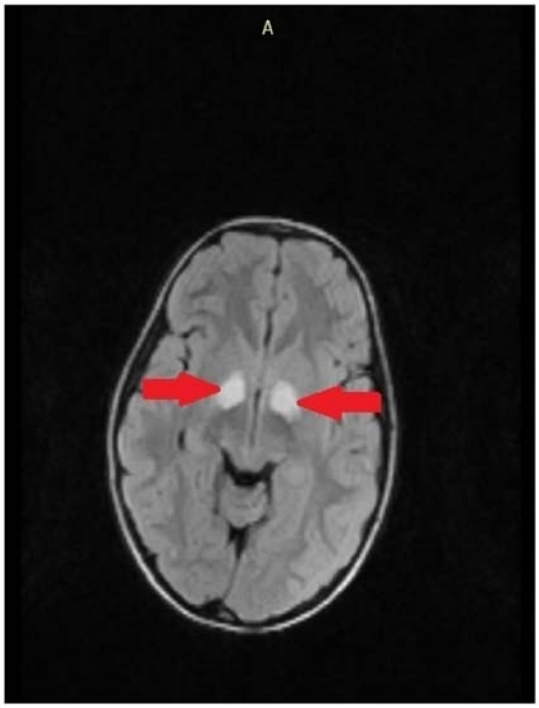

Figure 6. Anterior view of MRI showing FLAIR transversal section-midbrain hamartomas identified in an 8-year-old patient, obtained at the Clinical Hospital for Children, Galati, Romania. A, anterior view.

neoplasms in follow-up exams. However, if there no new symptoms develop the contrast may not be necessary in patients with, for example, myelin vacuolization. Nevertheless, GBCA is safe and the patients tolerate it well.

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Availability of data and materials

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Authors' contributions

All authors have had equal participation and equal rights to this article. FN and ALT were major contributors in writing the manuscript. FN, ALT, DM, AM, LB, DSR, BIS, AN and EN contributed to the conception and design of the work, as well as revising the manuscript. DM, BIS, AN and LB helped analyze the data for the work. AM revised it for important intellectual content. ALT and AN approved the final version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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