



A Diagnostic Algorithm for Patients with Intracranial Calcifications

Algoritmo diagnóstico en pacientes con calcificaciones intracraneales

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Key words (MeSH)

Brain diseases
Brain neoplasms
Central nervous system diseases
Multidetector computed tomography



Palabras clave (DeCS)

Encefalopatías
Neoplasias encefálicas
Enfermedades del sistema nervioso central
Tomografía computarizada multidetector



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Summary

Intracranial calcifications are an occasional finding in computed tomography and cerebral magnetic resonance imaging. Their aetiology is widely diverse and comprises physiological and pathological processes. This review pretends to describe the intracranial calcifications by an easy diagnostic algorithm, using the location, morphology and pattern in order to narrow the differential diagnosis and reduce the interpretation mistakes.

Resumen

Las calcificaciones intracraneales son un hallazgo frecuente en los estudios de tomografía y resonancia magnética cerebral. Su etiología es ampliamente variada y comprende procesos tanto fisiológicos como patológicos. Esta revisión busca describir las calcificaciones intracraneales dentro de un algoritmo diagnóstico fácil de realizar por el radiólogo, en el cual su localización, morfología y patrón pueden ayudar a reducir los diagnósticos diferenciales y a disminuir los errores por mala interpretación.

Introduction

Intracranial calcifications are a common radiographic finding and their pathogenesis varies from benign physiological processes to multiple pathological processes (1), their imaging characterization according to their morphology and location is important to establish a differential diagnosis. Pathological calcifications can be classified into five major groups: congenital, tumor, infectious, vascular and metabolic. The most frequent causes of non-pathological or physiological calcifications are those that occur in: choroid plexus, basal ganglia, dura mater, habenula, parasitic carotid, petroclinoid ligament, pineal gland, tentorium, sagittal sinus, cerebral sickle and blood vessels (2).

Historically, conventional radiography has been used for the detection of calcifications; however, with the advent of technology, tomography has replaced the use of conventional radiography and has become the ideal method for its evaluation due to its high sensitivity in the visualization of bone tissue and calcifications (3). Magnetic resonance

imaging (MRI) is also useful in the detection of calcifications with the use of T2 gradient echo sequences and magnetic susceptibility (4); however, its signal intensity in the T1 and T2-weighted sequences make it a non-specific method for its visualization (5).

Discussion

Physiological calcifications

Intracranial physiological calcifications have no demonstrable pathological cause and are directly proportional to age; they can be found from 5 years of age and without any preference for sex. These may appear in:

Pineal gland: Small conical structure located in the midline between the thalamic bodies posterior to the habenular commissure; this gland has a continuous growth during the first 2 years of life, later stabilizes (6). Its calcification is not pathological unless it is associated with an increase in its size, which suggests a neoplasm when the

calcification is greater than 1 cm (7). The incidence of calcification is 11% (8) and histological reports of early calcium deposits in fetal life have been found in the literature (9); however, starting at age 5 (Figure 1a).

Habenula: Pair of bilateral nuclei located in the dorsomedial inferior thalamus. It has functions in pain processing, reproductive behavior, nutrition, circadian cycle, response to stress and learning. When it is calcified, it has a curvilinear pattern, anterior to the pineal gland. An association between calcification and dysfunction of the habenula and schizophrenia and learning disorders in these patients has been reported in the literature (10). Its calcification is present in up to 10% in over 2 years (11).

Choroidal Plexus: Intraventricular organ responsible for the production of cerebrospinal fluid, located in the lateral ventricles, with a higher concentration in the ventricular atrium called the choroidal glomus. The prevalence of choroidal plexus calcifications varies between 12 and 16% (8, 12) (Figure 1b).

Dura-matter: Meningeal outer layer composed of thick connective tissue that covers the brain and spinal cord, its calcification is more frequent in the tentorium, reported in the literature with a frequency ranging from 2% to 20% (13). They come with a laminar pattern. In another location, in the cerebral sickle, calcifications are visualized with a pattern of dense flat plates in the midline of the brain. It is important to remember that if these are observed in a young population, the sebaceous nevus syndrome should be ruled out (Figure 1c).

Petroclinoid ligament and sagittal sinus: Its calcification is related to degeneration sites, dependent on age, and follow a laminar and discretely nodular pattern.

Basal ganglia: Its calcification is usually of idiopathic etiology with an incidence of 0.3-1.5% that increases with age with a fine, dotted or thick, symmetrical and conglomerate pattern (14); if it appears in patients younger than 30 years of age, metabolic pathology should be suspected (Figure 1b).

Pathological calcifications

Pathological calcifications are divided into several groups, as shown in Table 1.

Table 1. Classification of pathological calcifications

Congenital	Non-congenital infections	Metabolic	Vascular	Neoplastic
Sturge-Weber syndrome	Chronic viral encephalitis	Farh's disease	Primary atherosclerosis	Oligodendroglioma
Tuberous sclerosis	Granulomatous infection	Hypothyroidism	Cavernomatous malformation	Craniopharyngioma
Neurofibromatosis	HIV infection	Hypoparathyroidism	Arteriovenous malformation	Germ cell neoplasm
Lipoma		Hyperparathyroidism	Aneurysms	Neurocytoma
Cockayne's syndrome		Pseudohyperparathyroidism	Chronic infarction	Neuroectodermal primitive Tumor
Gorlin Syndrome		Postthyroidectomy	Chronic vasculitis	Ependymoma
TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes simplex)				Ganglioma
Zika				Meningioma
				Meduloblastoma
				Pilocytic astrocytoma

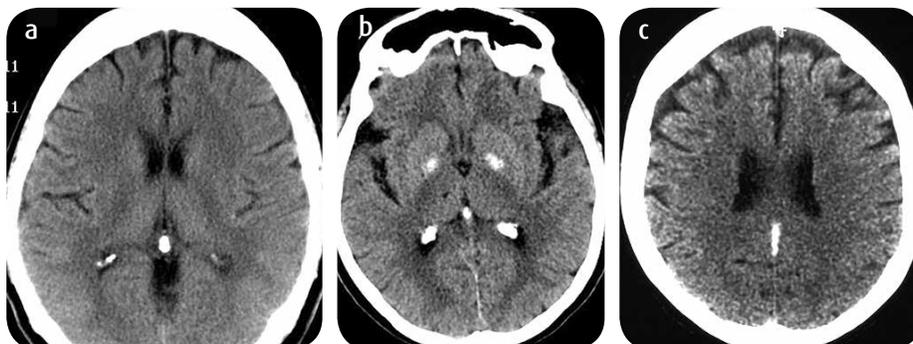


Figure 1. Axial CT cuts of the simple skull: a) calcified pineal gland, located in the midline between the lateral thalamic bodies, posterior to the third ventricle, b) calcification of the basal ganglia, choroid plexus and c) calcification of the sickle interhemispheric in its posterior portion.

Congenital calcifications

Sturge-Weber syndrome: An uncommon neurocutaneous syndrome, of sporadic occurrence, with a prevalence of 1 in 50,000 live births (15). It is characterized by the appearance of facial nevus of port wine color, congenital glaucoma and leptomeningeal angiomatous malformation. The latter generates venous hypertension and hypoperfusion of the cortex, causing chronic ischemia, atrophy and cortical calcifications with a linear pattern, in a double or curvilinear contour, predominating in convolutions, parietal and occipital (14) (Figure 2).

Tuberous Sclerosis: Also known as Bourneville's disease is another autosomal dominant neurocutaneous disorder (facomatosis), with a clinical prevalence / penetrance of approximately 1 in 6,000 to 12,000 live births (16); is characterized by multiple benign tumor lesions derived from the ectoderm that affect the skin, nervous system and eyes. Presents the clinical triad of Vogt: mental retardation, epilepsy and sebaceous adenoma. Its most common manifestations include cortical-subependymal tubers, abnormalities in white matter, cardiac rhabdomyomas and renal angiomyolipomas. There are multiple intracranial manifestations, the 4 most common are: cortical tubers, subependymal nodules, giant cell astrocytomas and abnormalities of the white matter; subependymal nodules represent hamartomatous changes and are associated with calcifications in 88%, more common than cortical tubers (17), and the ventricular atrium is located along the caudothalamic groove (Figure 3).

Neurofibromatosis type 1: Known as Von Recklinghausen disease is the most common facomatosis, with autosomal dominant inheritance, but with spontaneous onset in up to 50% of cases; affects the skin, nervous system, bones and endocrine glands; its incidence is 1 per 2,000 live births. Within their intracranial manifestations, gliomas, dysplasias and hamartomas that affect the globus pallidus are present, but rarely are calcified (18, 19)

Lipomas: They are benign congenital malformations, approximately 80-90% are located in the midline; in its periphery and towards its capsule can be observed curvilinear or focal calcifications that limit with the surrounding parenchyma (20).

Cockayne Syndrome: An autosomal recessive disease manifested by progressive encephalopathy associated with intracranial calcifications and white matter lesions. Calcifications are characterized by their subcortical localization, in basal ganglia and dentate nuclei, are visualized with a thick pattern (13).

Gorlin-Goltz Syndrome: Also known as basaloid cell nevus syndrome, it is a rare autosomal dominant facomatosis, manifested with multiple odontogenic keratocysts and basal cell carcinomas. Its incidence is 1 per 60,000 live births. For its diagnosis it is necessary to fulfill two major criteria or one major and two minor; bilamellar calcification is one of the largest.

Infectious calcifications

Can be classified into congenital and acquired.

Infection of the central nervous system (CNS) in the fetus can be seen in a large group called TORCH, which includes toxoplasmosis, rubella, cytomegalovirus and herpes virus infections. In herpes simplex there is extensive neuronal destruction, multicystic encephalomalacia and manifests with scarring calcifications as sequels, with thalamic, periventricular and in the convolutions. In the case of congenital toxoplasmosis, calcifications occur predominantly in basal ganglia, periventricular and cerebral cortical, with dystrophic appearance and random location; their size correlates with the time of infection (3) (Figure 4).

Congenital rubella is associated with meningitis, ventriculitis, ventriculomegaly, and periventricular calcifications in the white matter, basal ganglia and brain stem. Cytomegalovirus infection is caused by a DNA virus member of the herpes virus family, is the most common congenital infection and affects 0.5 - 2.5% of the born. Transmission to the fetus requires close and prolonged contact with respiratory secretions, urine, blood, transfusions. The most frequent findings due to central nervous system involvement are microcephaly, hydrocephalus, cortical and periventricular calcifications, punctiform or plaque, periventricular pseudocysts and malformations of cortical development (Figure 5).

Within this group of congenital infections should be added the infection by Zika virus, an arbovirus of the family Flaviviridae that in 2016 was found in 28 countries. This virus identified in the cerebral parenchyma of the newborn destroys the developing brain, generates microcephaly and craniofacial disproportion; the intracranial calcifications are thick, localized in the basal ganglia and in the corticosubcortical transition (21) (Figure 6).

Among the acquired infectious diseases are viral encephalitis in its chronic phase, with encephalomalacia and residual calcifications in the parenchyma; tuberculous granulomatous infections; and opportunistic fungal infections. In the intraparenchymal tuberculomas the sign of the "white" has been described, by the representation of a central nest of calcification, surrounded by a ring of enhancement, findings highly suggestive of tuberculosis compromise. Other acquired infectious pathologies where intracranial calcifications are visualized are HIV, neurocysticercosis and hydatid cysts. In neurocysticercosis it is possible to observe a densely calcified cyst that may contain an eccentric dense nodule; findings that represent a dead larva, similar to that visualized in the hydatid cyst where the dead parasite is observed as single septate or multiloculated calcification (Figures 7 and 8).

Metabolic calcifications

Fahr's disease: Rare neurological disorder characterized by extensive symmetrical bilaterally calcifications of basal ganglia (striatum-pale). According to their location they generate progressive dystonia, parkinsonism and neuropsychiatric manifestations. It begins to be symptomatic after about 20 years, and one of its most common causes is parathyroid disease (22) (Figure 9).

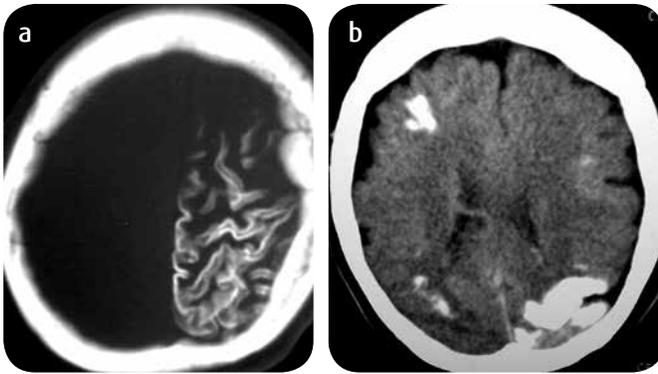


Figure 2. a and b) Axial CT cuts of the single skull: multiple frontal and parietal cortical calcifications with a linear pattern, in a rail or double curvilinear contour, compatible with the Sturge-Weber diagnosis.

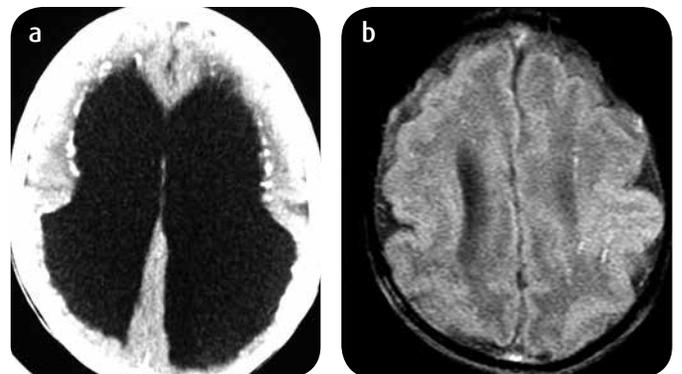


Figure 5. a and b) Axial CT scan of the skull and axial sequence with T1 information in a patient with cytomegalovirus congenital infection: hydrocephalus, fine cortical calcifications and punctiform periventricular plaques forming.

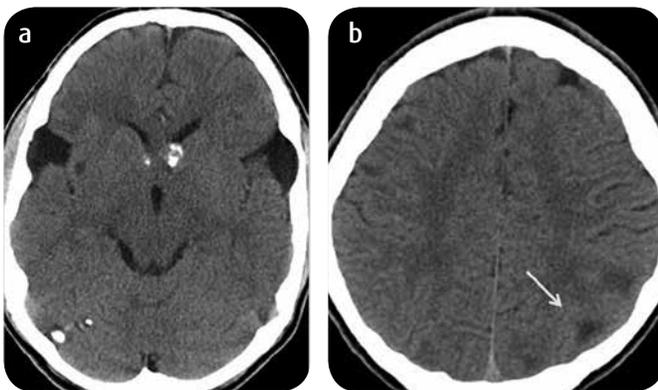


Figure 3. a and b) Axial CT scans of a patient with a diagnosis of tuberous sclerosis: subependymal nodules and calcified parenchymal hamartomas, as well as cortical tubers.

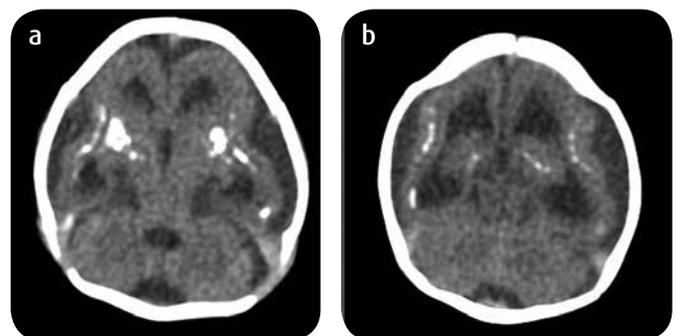


Figure 6. a and b) Axial CT cuts of a single skull in a newborn with congenital infection by Zika: Microcephaly, craniofacial disproportion and gross intracranial calcifications are evident in the basal ganglia and in the area corticosubcortical.

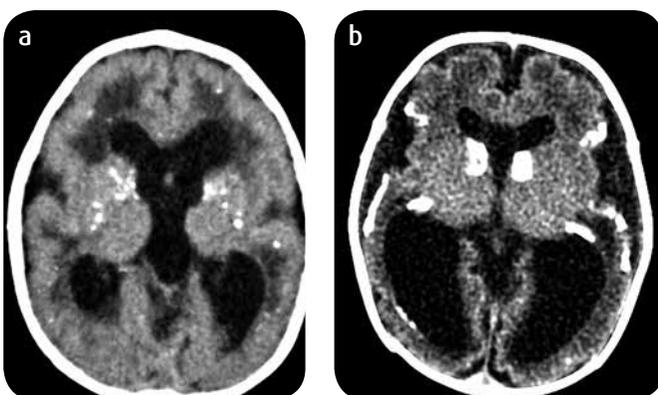


Figure 4. a and b) Axial CT scans of single skull: multiple calcifications in basal ganglia, periventricular and cerebral cortical, dystrophic appearance and random localization in a newborn with congenital toxoplasmosis infection.

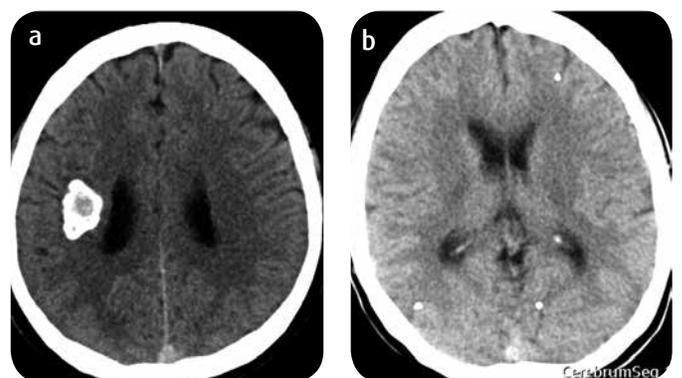


Figure 7. (a) Axial CT scans of single skull in a patient with intracerebral tuberculoma located at corticosubcortical junction. b) Patient with history of neurocystocercosis in the chronic or calcified phase: Several punctiform calcifications are visualized.

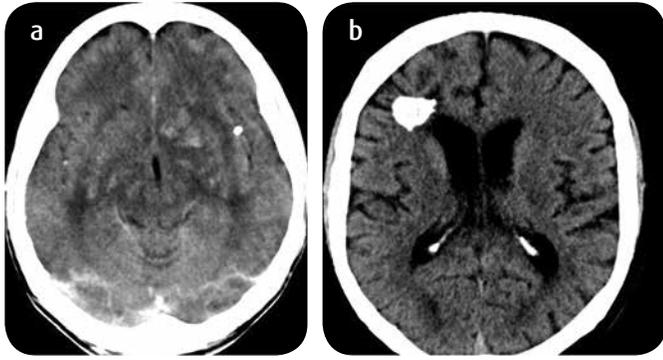


Figure 8. a) Single skull CT scan in patients with HIV diagnosis: calcified lesion of left insular localization, high gangliobasal lesions on the same side and occipital leptomeningeal enhancement corresponding to the diagnosis of cryptococcosis, infection caused by *Cryptococcus neoformans*. b). Patient with a unique dystrophic calcification, adjacent to the anterior horn of the right lateral ventricle, with diagnosis of toxoplasmosis in chronic phase, opportunistic infection more frequent in the patient with HIV.

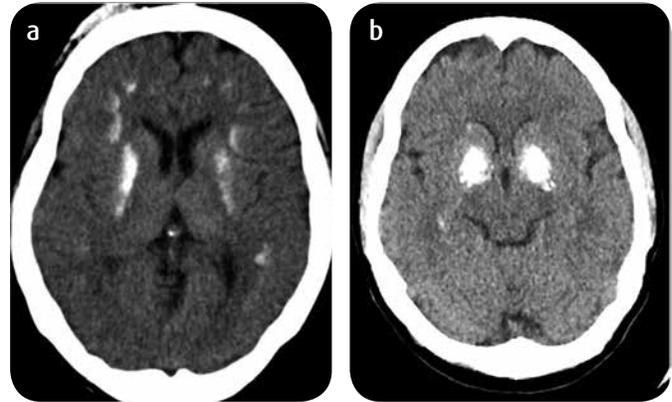


Figure 9. Simple cranial CT in patients diagnosed with Fahr's disease: bilateral symmetrical calcifications of the basal ganglia.

Parathormone metabolism disorders (hypo/hyper/pseudohyperparathyroidism): The parathormone has the function of maintaining serum calcium levels, then any alteration in the production of this hormone can generate intracranial calcifications. These are of preferential location in the dentate nuclei, basal ganglia, thalamus and peripheral subcortical white matter (22) and may be associated with dyskinesias and signs of extrapyramidal (Figure 10).

Vascular calcifications

Calcifications due to primary atherosclerosis are proportional to age, common in the elderly, preferentially located in the internal carotid artery, in its clinoid portion (60%), vertebral arteries (20%), middle cerebral artery and basilar artery (5%) (23) (Figure 11).

Other vascular causes include arteriovenous, cavernomatous malformations and aneurysms. Arteriovenous malformations may appear as dystrophic calcifications in the nest and others with serpentine distribution along the vessels by 25-30%. Cavernomatous malformation or vascular hamartomas show typical calcifications in "corn popcorn" with an incidence of 40-60%; the aneurysms may contain mural calcifications and more frequently if they are partially or totally thrombosed. Pathophysiologically, the mechanism of calcification of most of these lesions is secondary to chronic venous ischemia and formation of dystrophic calcifications by hemorrhage (23) (Figures 12 and 13).

Neoplastic calcifications

In intracranial neoplasms with calcifications, its evaluation in conjunction with the patient's age, morphology and tumor location narrows the diagnostic possibilities. They can be divided into two groups: extraaxial and intra-axial. Extraaxial tumors, such as craniopharyngiomas occurring in adults, present with visual,

endocrinological or intracranial hypertension, have suprasellar localization and show amorphous and lobulated calcifications (Figure 14); meningiomas of dural origin are frequent in elderly people and may have variable calcifications in 3% (Figure 15). Intra-axial tumors are associated with hemorrhage by combination of neovascularization, arteriovenous shunts, and rapid tumor growth leading to necrosis and disruption of intracellular calcium regulation, which ultimately leads to calcium deposition. Within this group are the slow-growing oligodendrogliomas, located preferentially in the frontal lobe, show calcifications in a 40 - 90%, central, microcalcifications or lumpy (23) (Figure 16).

Medulloblastomas are calcified by 10-20%. Other tumors do so in lesser percentages, such as those of the pineal gland and germ cells, in which it is rare for them to generate their own calcifications. Pineal tumors are believed to encompass existing calcifications, with the exception of pinealblastoma that may have multiple and peripheral calcifications of its own. Other less frequent tumors that are calcified include primitive neuroectodermal tumor, dysembryogenic tumor, gangliogliomas, pilocytic astrocytoma and metastatic tumors of osteogenic sarcoma and mucinous adenocarcinoma or secondary to radiotherapy (24).

Tumor calcifications have no pathological significance, but may suggest adequate response to treatment (25) (Figures 17 and 18).

Residual calcifications posttreatment or posttrauma

Another possible aetiology of acquired calcifications is scarring, either by surgical treatment or by radiotherapy or post trauma, in which case it is of vital importance to know the antecedents and ideally to have the previous diagnostic images to assess if calcifications appear after the traumatic event or treatment, whether or not this type of tumor is associated with calcifications per se and evaluated in relation to the other findings in the image and clinical evolution (Figure 19).

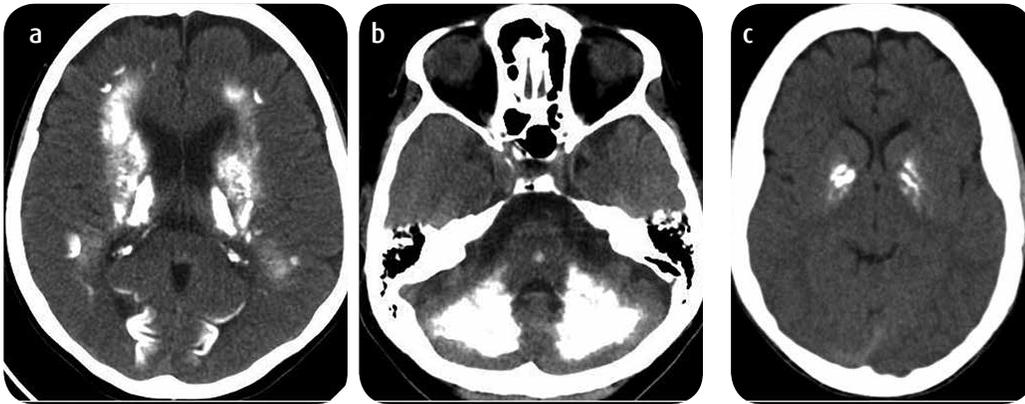


Figure 10. a and b) Axial CT cuts of the single skull in patients with idiopathic hypoparathyroidism, pseudohypoparathyroidism and hyperparathyroidism, who present in 70-80% calcifications in the basal ganglia, subcortical, in dentate nuclei and cerebellum.

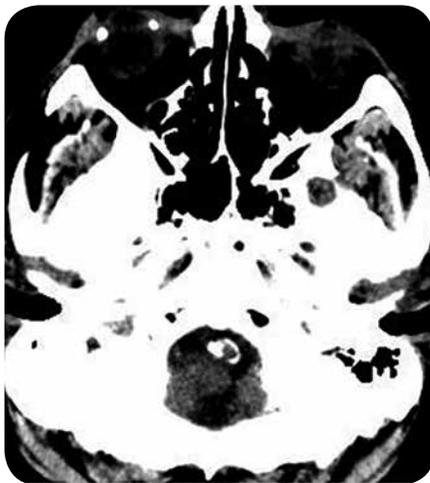


Figure 11. a and b) Axial CT scan of the skull: calcification of the vertebral arteries in their intracranial portion at height of the great hole.

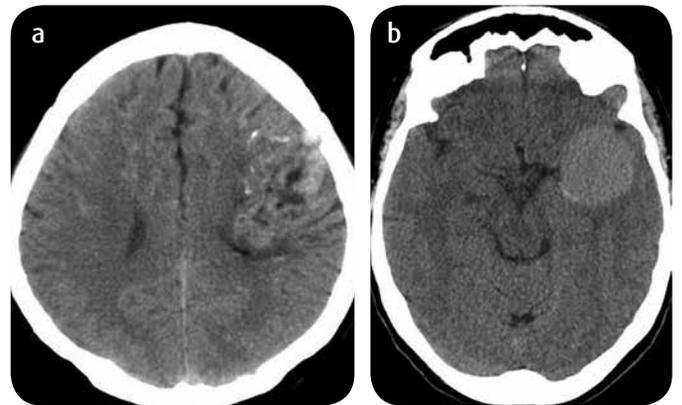


Figure 12. Axial CT cuts of the single skull: a) Left frontal cerebral arteriovenous malformation: calcifications with serpentine distribution along the vessels. b) Aneurysm of the middle cerebral artery located in the silviano valley and with fine posterointernal mural calcifications.

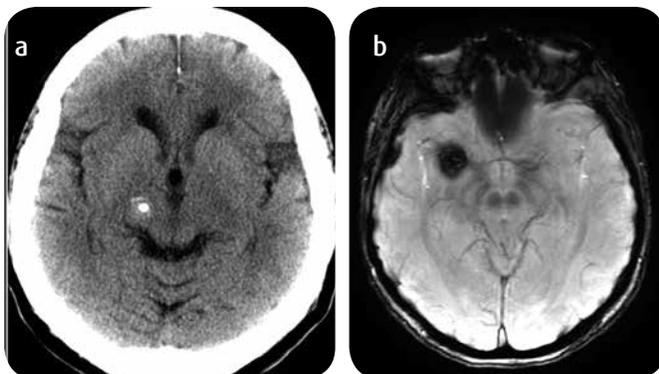


Figure 13. Axial CT scan of single skull. a) Gross localized calcification in the right cerebral peduncle in a patient with a diagnosis of cavernomatous malformation. b) MRI: axial sequence of magnetic susceptibility: The typical morphology in "popcorn" is visualized in a cavernomatous malformation.

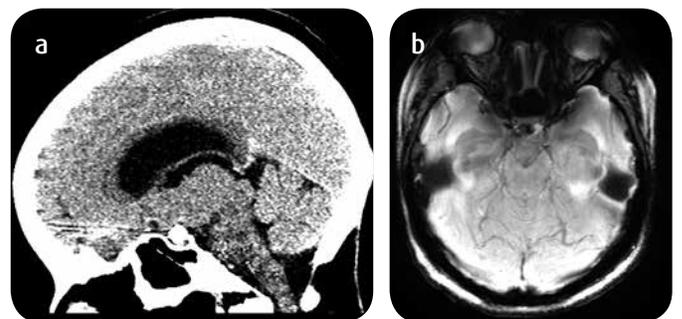


Figure 14. a) Sagittal reconstruction in CT of the skull in a patient with craniopharyngioma of suprasellar location, with amorphous and lobulated calcifications. b) MRI axial sequence of magnetic susceptibility where the calcification of suprasellar location.

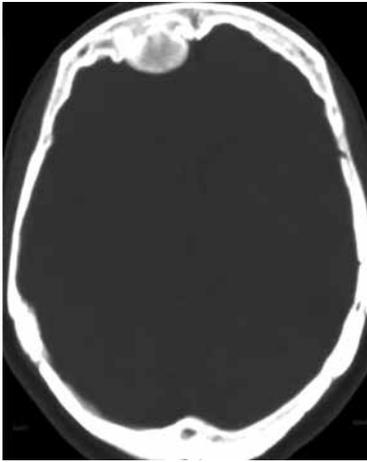


Figure 15. Axial CT scan of skull in a bone window: right frontal calcification associated with a focal thickening of the bones of the skull in a patient diagnosed with meningioma.

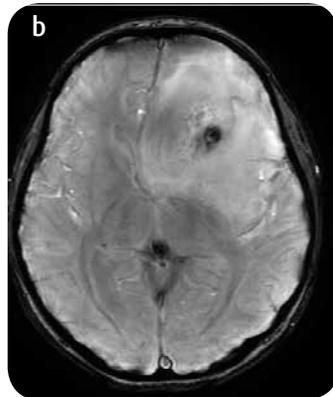
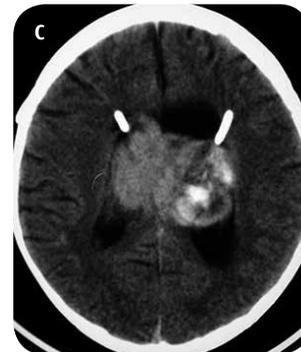
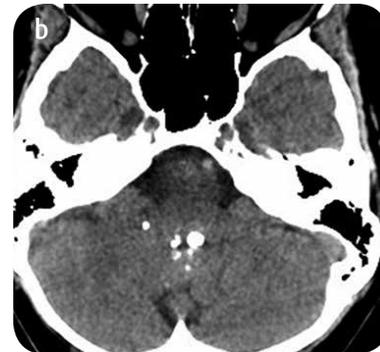


Figure 16. a and b) Axial cranial CT scan of the skull: right frontal intraaxial lesion with associated vasogenic edema and central calcifications also observed in MRI (b) as low-signal grouped images, this finding is characteristic of oligodendrogliomas.

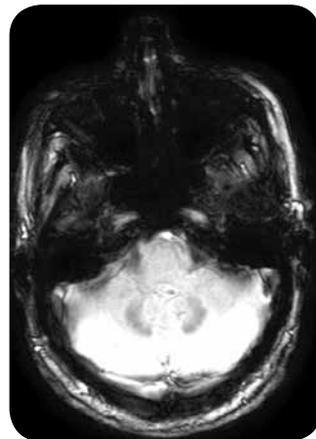
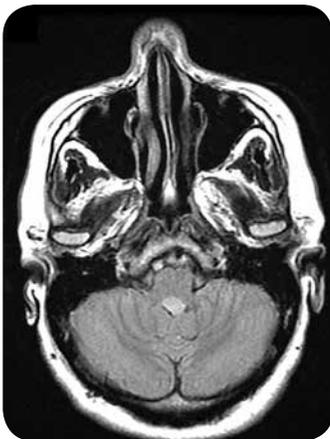


Figure 17. MRI Axial sequences of FLAIR and magnetic susceptibility where high signal lesion is visualized in the fourth ventricle with calcifications in its interior in a patient diagnosed with ependymoma.

Figure 18. Axial cus toms of simple cranial tomography in patients diagnosed with a) astrocytoma, b) subependimoma and c) PNET, where both peripheral and central calcifications are visualized as well as thick intratumoral localization.

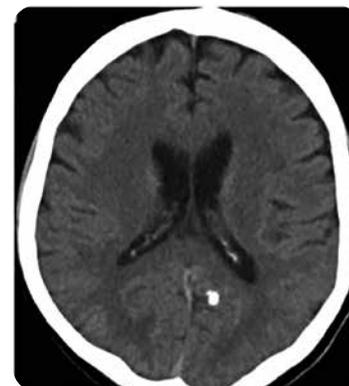


Figure 19. Axial CT scan of the single skull: small left occipital intraaxial calcification after trauma cranioccephalic.

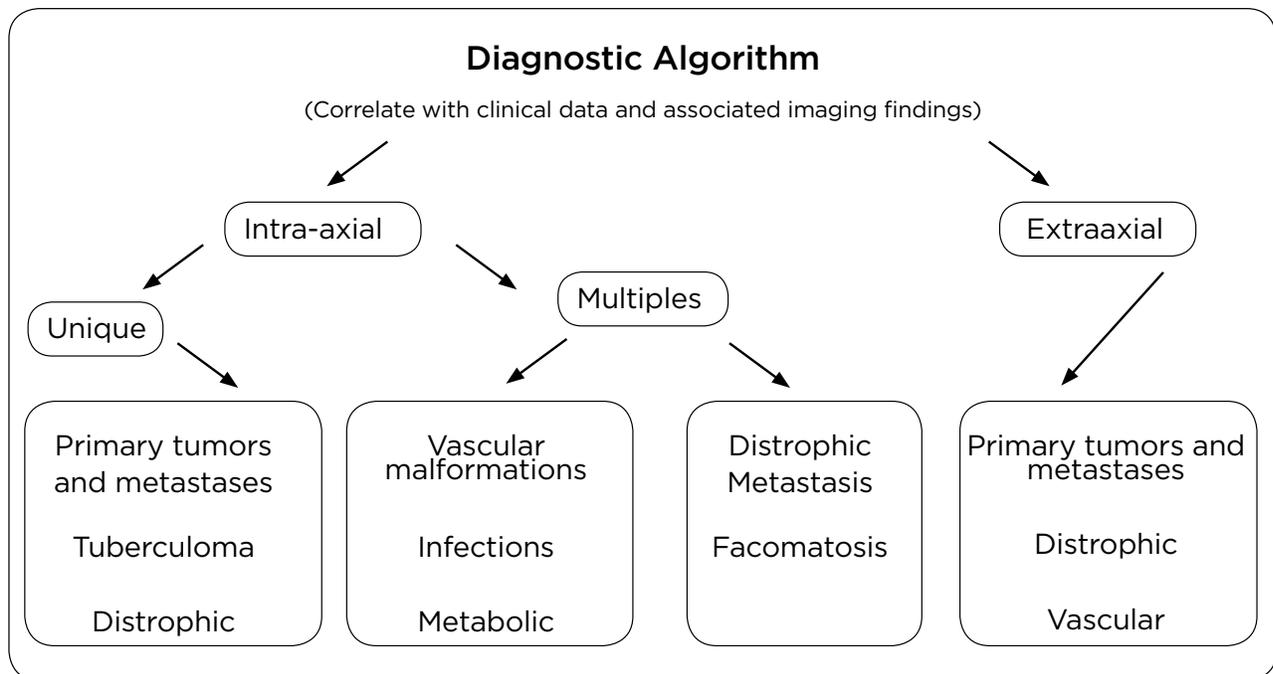


Figure 20. Diagnostic Algorithm

Conclusion

For a correct approach of the intracranial calcifications it is necessary to define, in the first instance, if they are physiological or pathological; then, together with their location, pattern and morphology, clinical information and other findings in images, to approach possible differential diagnoses, in order to reduce the amount of them.

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Received for evaluation: April 28, 2017
 Accepted for publication: June 27, 2017