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NEUROPAREIDOLIA

Diagnostic clues apropos of visual illusions

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Abstract – Diagnosis in neuroimaging involves the recognition of specific patterns indicative of particular diseases. Pareidolia, the misperception of vague or obscure stimuli being perceived as something clear and distinct, is somewhat beneficial for the physician in the pursuit of diagnostic strategies. Animals may be pareidolically recognized in neuroimages according to the presence of specific diseases. By associating a given radiological aspect with an animal, doctors improve their diagnostic skills and reinforce mnemonic strategies in radiology practice. The most important pareidolical perceptions of animals in neuroimaging are the hummingbird sign in progressive supranuclear palsy, the panda sign in Wilson's disease, the panda sign in sarcoidosis, the butterfly sign in glioblastomas, the butterfly sign in progressive scoliosis and horizontal gaze palsy, the elephant sign in Alzheimer's disease and the eye-of-the-tiger sign in pantothenate kinase-associated neurodegenerative disease.

KEY WORDS: pareidolia, neuroimaging, progressive supranuclear palsy, Wilson's disease, sarcoidosis, glioblastomas, progressive scoliosis and horizontal gaze palsy, Alzheimer's disease, pantothenate kinase-associated neurodegenerative disease.

Neuropareidolia: pista diagnóstica a partir de uma ilusão visual

Resumo – O diagnóstico em neuroimagem envolve o reconhecimento de padrões específicos indicativos de doenças particulares. Pareidolia, é a perceção equivocada de algo claro e distinto a partir de um estímulo vago e obscuro, por vezes benéfico a quem interpreta exames de imagem na procura do diagnóstico. A este propósito, alguns animais podem pareidolicamente ser reconhecidos em neuroimagens associadas a determinadas doenças específicas, promovendo mais rapidez na habilidade diagnóstica e naturalmente reforçando estratégias mnemônicas individuais na prática do diagnóstico neuroradiológico. Alguns dos sinais de neuroimagens relacionados a percepções pareidolicas de animais são: o sinal do beja-flor na paralisia supra nuclear progressiva; o sinal do panda na doença de Wilson; o sinal do panda na sarcoisdose; o sinal da borboleta no glioblastoma; o sinal da borboleta no escoliose progressiva e paralisia do olhar horizontal; o sinal do elefante na doença de Alzheimeir; e o sinal do olho de tigre na doença degenerativa ligada a pantothenato kinase.

PALAVRAS-CHAVE: pareidolia, neuroimagem, paralisia supranuclear progressiva, doença de Wilson, sarcoidose, glioblastoma, escoliose progressiva e paralisia do olhar horizontal, doença de Alzheimer, doença neurodegenerativa associada a pantothenate kinase.

Pareidolia (from the Greek para – beside; and eidolon – image, form, shape) is a psychological phenomenon characterized by misperceptions of vague stimuli, frequently images and sounds, as meaningful and significant[1]. Examples include involuntary interpretations of clouds as faces or animals, and perceptions of hidden messages in songs played backwards.

Pareidolia may explain certain visions and holy figures apparitions such as Our Lady silhouette depicted as a shadow on a wall, Saint George riding his horse in the

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moon, or God's face rendered in the sunlight reflex on a water surface. In Brazil, Saint George is associated with the moon due to influences of African religious traditions. The divinity "Oxossi" is linked to the moon and connected with Saint George. The gray shades seen in the full moon are believed to represent Saint George holding his sword on his horse. Some psychologists even encourage the use of pareidolia to approach patients' psyche using the Rorschach examination[2].

Meshberger wrote on his neuroanatomical interpretation of the Michelangelo's oil "Creation of Adam"[3]. By comparing the image of God wrapped in a swirling cloak surrounded by cherubins depicted at the right side of the picture to a brain sagittal view, he probably provided the pareidolia example with the greatest repercussion in modern medical literature. In a pure pareidolia attempt, convinced that the left-handed master from Florence purposefully included anatomical messages in his pieces, two Brazilian authors wrote a book on putative interpretations of Michelangelo's paintings' details as organs, bones, joints, and a series of other aspects of the human anatomy[4].

Macroscopic as well as microscopic aspects of several diseases have been traditionally compared with letters[5], inverted letters[6], comestibles such as orange[7], mango[8], rice grain[9], onion-bulb[10], pear[11], tomato[12], strawberry jam[13], grapes cluster[14], honeycomb[14], and Swiss cheese[15]; or objects such as a pencil[16], corkscrew[17], and candle flame[18], or botanic aspects such as leaves[19] and bamboo[20]; or a tooth[21].

New and powerful medical imaging techniques have not only significantly expanded our general diagnosis capability, but also inevitably increased pareidolical interpretations of particular visual aspects related to a multitude of nervous system diseases. Recognized as diseases' fingerprints, pictures carrying wildlife resemblance emerge paralleling the imaging technology development. The physician's creativity is the sole limit for medical pareidolia.

We review some of the most interesting illusions characterized by visual resemblance with animals perceived in the neuroimaging field indicative of several central nervous system ailments.

HUMMINGBIRD SIGN

Progressive supranuclear palsy (PSP) is a degenerative disease of the Tau protein pathologies group described in 1964 as "*heterogeneous system degeneration*" by the neurologist J. Clifford Richardson in collaboration with neuropathologist Jerzy (George) Olszewski and the medical resident John Steele[22]. PSP is characterized by postural instability with early and frequent falls, axial rigidity-in-extension, supranuclear vertical gaze palsy, as well as pseudobulbar and frontal syndromes. It usually starts at middle age and progresses until decease around six years later, with very poor Levodopa response[23].

The brain sagital magnetic resonance (MR) scan may be suggestive of PSP when a pareidolic aspect of either a hummingbird or a king penguin is seen as the result of a mesencephalic tegmentum atrophy with a relatively spared pons (Fig 1).

THE PANDA SIGN IN WILSON'S DISEASE

Reviewing data hitherto available and adding four new cases, Kinnier Wilson wrote his graduation monograph in 1912, a work ever since considered a cornerstone in the literature on the disease named after him[24]. Wilson's disease is a relatively rare autosomal recessive enzymopathy related with copper metabolism that affects between

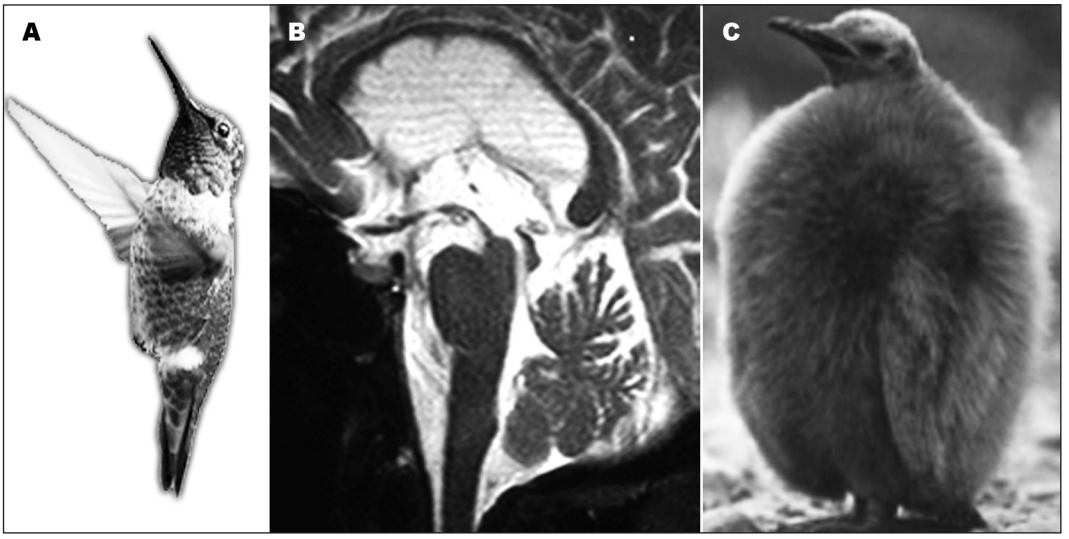

Fig 1. Brain T2-weighted sagital MR scan from a PSP patient [B]. Notice the relative atrophy of the mesencephalon as compared with the pons. The brain stem in this case resembles a hummingbird [A] or a king penguin [C].

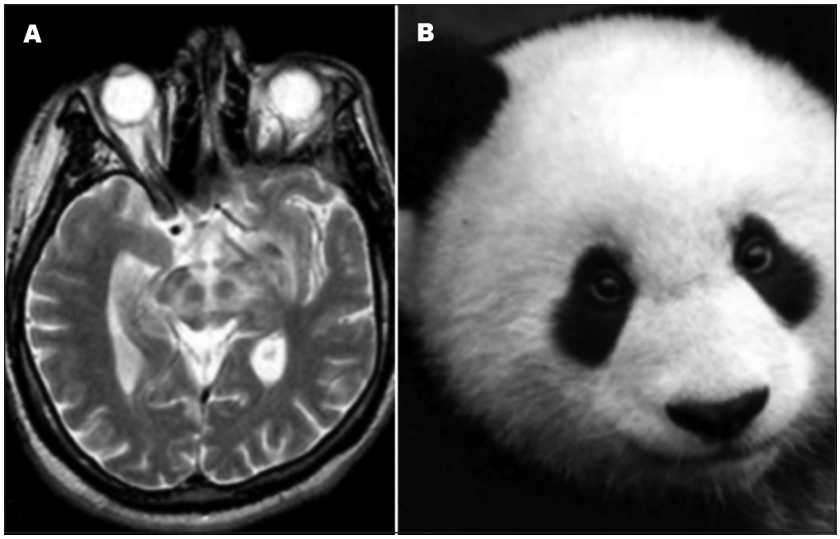

Fig 2. Midbrian aspect in a T2 weigthed RM scan as a result of to [?] normal signal at the red nuclei (eyes) and lateral aspects of the substantia nigra (ears), high signal at the tegmentum and hypointense superior colliculi [A]. Notice the resemblance to a panda [B].

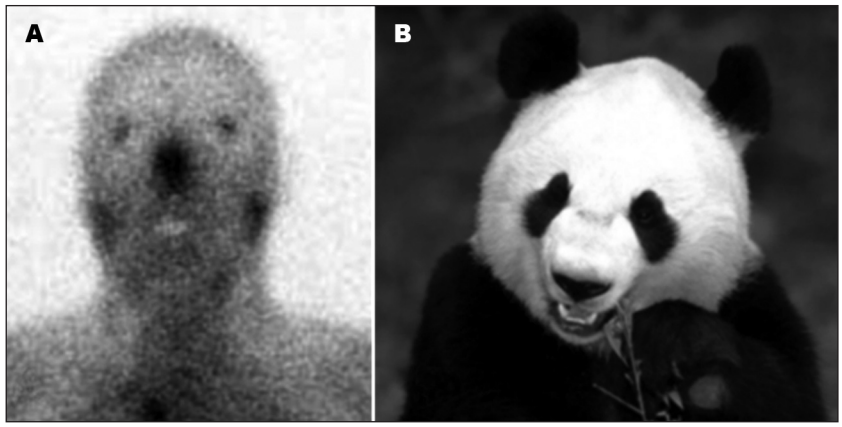

Fig 3. Galium-67 scintigraphy. Panda's sign due to simectirc galium uptake in the parotid and lachrymal glands [A]. The pareidolic image resembles a panda bear [B].

1:30,000 and 1:100,000 people[25]. Symptoms usually start during the second / third decades of life, at first secondary to hepatic copper accumulation. The clinical picture is pleomorphic and includes neurologic, psychiatric, and hepatic signs and symptoms[26]. In more advanced phases patients may present recurrent hepatitis, cirrhosis, hepatic insufficiency, asterixis, rigidity, tremor, dystonia (with the fixed and rigid wilsonian smile) acatisia; depression, psychosis, phobias, and anti-social behaviour, and the so-called Kayser-Fleischer sign, a copper deposit at the Descement membrane.

The *ATP7B* gene related to this condition, located to the short arm of chromosome 13, encodes the transmembrane ATPase ATP7B protein that not only plays a role in the copper transport through the Golgi organelle membrane but also helps copper absorption by ceruloplasmine and biliary excretion. More than 300 mutations have been described in the ATP7B gene leading to abnormal copper deposit[25].

The diagnosis is based on the clinical picture along with abnormal levels of ceruloplasmine (serum) and copper (serum and urine). The brain MR depicts widespread lesions involving the putamen, globus pallidus, caudate nucleus, thalamus, midbrain, and pons. There may be cortical atrophy and scattered white mater abnormalities as well.

The progressive midbrain involvement leads to the typical pareidolic sign in Wilson's disease: The Mesencephalic Panda Sign[27,28] (Fig 2). This sign occurs when the MR signal is preserved at the red nucleus, lateral portion of the substantia nigra pars reticulata; is increased at the mesencephalic tegmentum; and decreased at the superior colliculi.[28] Treatment is based on anti-copper agents such as D-penicilamine and Trientine, aimed at quelling copper toxicity. Zinc may be of help as it interferes with copper absorption at the gastro-intestinal tract and therefore reduces its uptake[26].

PANDA SIGN IN SARCOIDOSIS

Sarcoidosis is a granulomatous inflammatory multi-systemic disease. Heerfordt, a Danish ophthalmologist, first reported on the neurologic manifestations of sarcoidosis in 1909[29]. The disease affects slightly more females than males, mostly during the third and fourth decades of life,

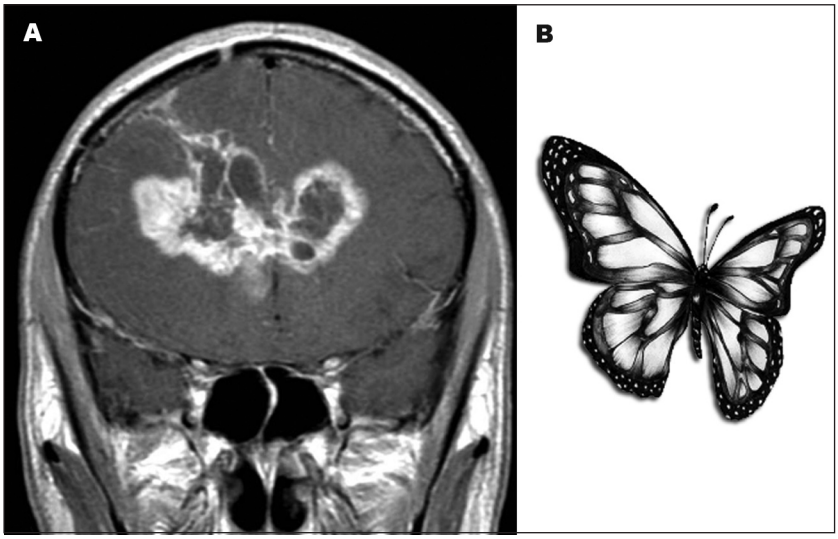

Fig 4. T1-weighted contrast enhanced coronal MR imaging showing an irregular lesion hypointense at the centre with hyperintense margins invading the frontal lobes [A]. The pareidolic aspect of a butterfly is remarkable [B].

with a prevalence of approximately 10–40:100,000[29,30]. Although sarcoidosis strictly restricted to the nervous system is unusual, neurologic involvement is relatively common and may represent a diagnostic challenge. The most frequent presentation of neurosarcoidosis is cranial nerve neuropathy, mostly facial and optic. Seizures (15%), chronic meningitis (26%), mental disorders (20%), and intracranial hypertension may also occur[29].

The definite diagnosis is based on the clinical picture and histopathological examinations after other afflictions had been excluded. Blood and cerebral fluid tests point to inflammation within the nervous system. Magnetic resonance imaging is required in case of meningitis regardless the presence of sarcomatous parenchymal lesions. Whole-body Galium-67 scintigraphy may show symmetric radiotracer uptake at the lachrymal and parotid glands unveiling the "panda's face" pareidolic aspect (Fig 3). This appearance is not specific and may be found in malignant and inflammatory diseases such as tuberculosis, lymphoma (following irradiation), Sjögren syndrome, and AIDS[29] .

Steroids, usually associated with immunosupression, remain as the leading treatment for sarcoidosis.

THE BUTERFLY SIGN IN GLIOBLASTOMA

Glioblastoma (GB), the most malignant central nervous system tumour of the astrocytic cell line, is relatively rare, representing 25% of all malignant tumours, with an annual incidence of 2–3:100,000[31]. Histopathology shows cellular polymorphisms, nuclear atypia, exuberant mitotic activity, thrombosis with microvascular proliferation, and necrosis, the last two being required provisos for the diagnosis[32]. Symptoms include motor / cognitive impairment, seizures, and/or headache. Neuroimaging is mandatory. MR spectroscopy may reveal low N-acetyl-aspartate and creatine; high choline and lactate levels. GB appears as hypointense nodules irregularly enhanced by gadolinium in T1-weighed MR images, hyperintense in T2 and FLAIR.

GB tumours that extend from one hemisphere to the other through the corpus callosum may present as an image suggestive of a butterfly ("butterfly wings tumour", Fig 4). Due to its invasive nature, GB can hardly be completely removed, resulting in high post-operative relapsing percentages. One, three, and five years after the diagnosis survival rates remain respectively around 30%, 5% and 3%. Chemo-radiotherapy right after surgery is recommended. Temozolamide has been used as a valid alternative.

PROGRESSIVE SCOLIOSIS AND HORIZONTAL GAZE PALSY

Horizontal gaze palsy secondary to progressive scoliosis is a rare autosomal recessive disorder characterized by two main features: (1) Complete or almost complete horizontal gaze palsy with normal convergence and vertical ocular movements; (2) Progressive scoliosis during childhood and adolescence. Asymmetric intermittent blinking and nystagmus may be present[33-36]. The pathophysiology of this interesting association between distinct neuro-ophthalmological and bone structural abnormalities remained obscure until 2004, when Jen at al. linked the picture to a mutation in the ROBO3 gene located to the long arm of chromosome 11 (11q23–25). The guidance receptor Robo3/Rig1 belongs to a transmembrane receptor family that expresses in growing axons and are indispensable for controlling axons grow, leading them to accomplish their task[36]. Since ROBO3 protein is required for hindbrain axon midline crossing, its dysfunction causes malformations in brainstem structures as well as non-crossing of corticospinal and posterior spinal tracts. Although the pathophysiology behind progressive scoliosis development remain partially unknown, it has been suggested that the lack of

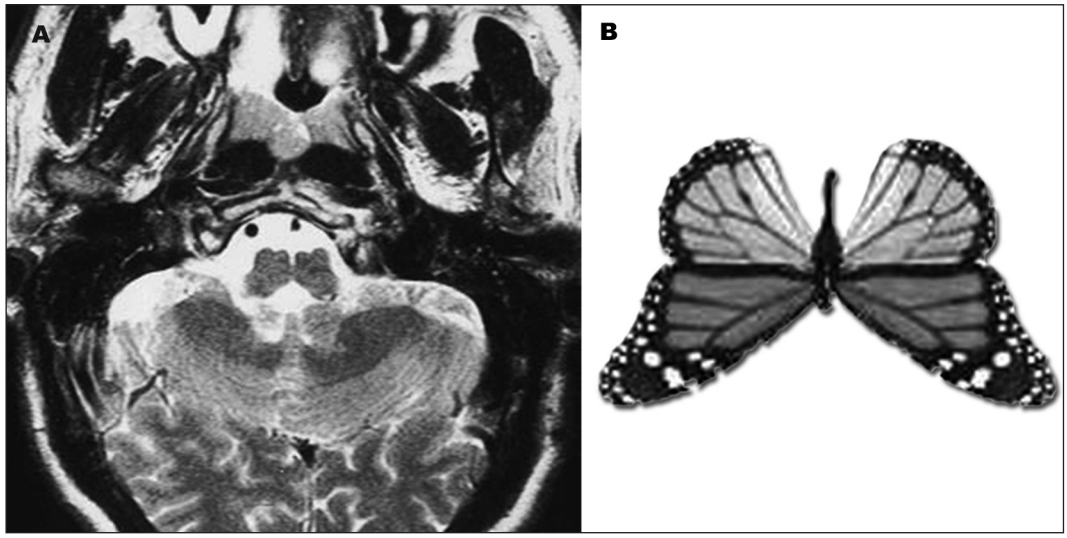

Fig 5. T2-weigthed brain MRI, axial view. Dysplasic and athrophic medulla with a particularly pronounced ventral sulcus [A]. The olives are prominent as compared to the pyramides, giving a pareidolic aspect of a butterfly to the brainstem [B].

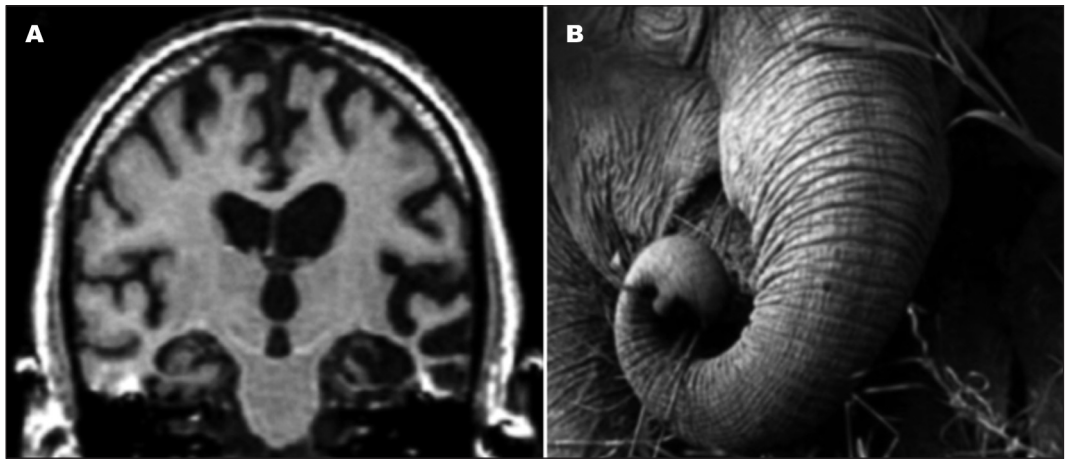

Fig 6. T1-weigthed coronal brain MRI showing atrophy at the medial aspects of the temporal lobes and hippocampi. Notice the sulcal exaggeration [A]. The pareidolic aspect of an elephant trunk has been referred to as the elephant sign [B].

tracts crossing may contribute to bad regulation of the paraspinal muscles tonus and provoke scoliosis[36].

The brain MR imaging depicts typical changes, especially in the brainstem. Because the olives are seen more prominent than the pyramids the insinuate aspect of a butterfly[37] (Fig 5).

THE ELEPHANT SIGN

Alzheimer's disease (AD) was described by Alois Alzheimer in 1907 apropos of a 55 year-old patient who presented as first symptom of her ailment extreme jealousy towards her husband. AD is considered today the most frequent dementia[38]. Initial symptoms typically present as subtle memory deficits, followed by other cognitive impairments[39]. The definite diagnosis depends on the histopathological finding of extracelullar amyloid plaques and intracellular neurofibrillary tangles originating from abnormal tau protein. Neuronal death progressively leads to atrophy seen on neuroimaging studies.

Medial aspects of the temporal lobes, including the entorhinal cortex and hippocampus are initially affected[39], causing the pareidolic aspect of an elephant trunk. – The elephant sign[40] (Fig 6). Although hippocampal atrophy has been considered as a biomarker of Alzheimer's disease[41]. Such findings must be regarded with caution, as other dementias may present medial temporal lobe atrophy. Besides, lack of atrophy does not necessarily rule out Alzheimer's disease[42].

THE EYE-OF-THE-TIGER SIGN

Mutations in the genes encoding the pantothenate kinase 2 (PANK2), an enzyme responsible for the biosyn-

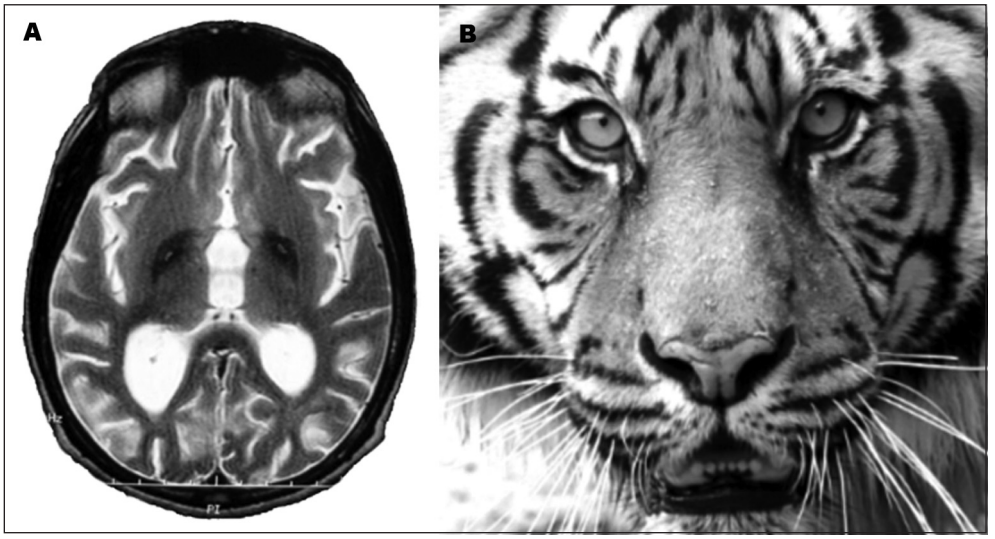

Fig 7. T2-weigthed axial brain RMI showing hyperintense signal (necrosis) surrounded by hyperintense (iron accumulation) at the medial aspects of the globus pallidus [A]. The image resembles tiger eyes - "Eye-of-the-tiger-sign" [B].

thesis of coenzyme A, are associated with a phenotype known as pantothenate kinase-associated neurodegenerative disease (PKAN)[43]. PKAN typically starts during childhood, presenting progressive gait disturbances, spasticity, hyperreflexia, Babinski sign and cognitive impairment that may evolve to dementia associated with marked extrapyramidal abnormalities such as rigidity, dysarthria, dystonia and chorea[43,44]. Retinopathy and less frequently optic nerve atrophy may occur. The development is not necessarily constant, sometimes with marked deteriorations lasting two months separated by long periods of relative stability. More than 80% of the patients cannot walk 15 years after the disease onset[43].

A correlation exists between the PANK2 gene mutation and the corresponded neuroimaging aspect, showing a hyperintense signal surrounded by a hypointense area at the medial aspects of the globus pailidus, configuring the so-called eye-of-the-tiger sign[43] (Fig 7).

Because of ethical reasons, the eponymous term "Hallervorden-Spatz syndrome" has been replaced by the well-accepted denomination "pantothenate kinase-associated neurodegenerative disease" for patients having the PANK2 mutation and "Neurodegeneration with Brain Iron Accumulation (NBIAs)" for those with the phenotype but no demonstrable mutation[43,45,46].

CONCLUSION

Various imaging techniques have developed largely as useful diagnostic tools in modern medicine. Facing a multitude of contrasts and forms, our brains naturally react trying to find familiar patterns matching typical aspects of a certain disorder. This process is similar to finding visual patterns in shadows and clouds, i.e. pareidolia. In terms of neuroimaging, some disorders may present aspects that evoke animals and suggest pareidolic denominations. Such visual illusions help memorization and improve general diagnostic skills.

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