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Presynaptic hemiparkinsonism following cerebral toxoplasmosis: case report and literature review

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Abstract

Background: Cerebral toxoplasmosis (CTx) is a CNS opportunistic infection with variable neurological manifestations. While tropism of *Toxoplasma gondii* for the basal ganglia is well known, movement disorders (MDs) represent only a small percentage of CTx-related neurological complications. CTx-associated MDs are usually hyperkinetic, whereas parkinsonism associated with evidence of presynaptic dopaminergic deficit has never been described.

Case: We report an HIV-positive patient who developed a complex MD featuring unilateral tremor combined with parkinsonism and dystonia following an acute episode of disseminated CTx. Her DaTscan documented contralateral presynaptic dopaminergic deficit. Levodopa initiation improved both tremor and parkinsonism after ineffective trials of several other medications over the years.

Literature review: A total of 64 patients presenting with CTx-related MDs have been described. The most common MD was chorea (44%), followed by ataxia (20%), parkinsonism (16%), tremor (14%), dystonia (14%), myoclonus (3%) and akathisia (2%). DaTscan was performed only in one case, of Holmes tremor, that demonstrated reduced presynaptic dopaminergic uptake. Positive response to dopaminergic treatment was reported in three cases of Holmes tremor and two of parkinsonism.

Conclusions: Presynaptic dopaminergic deficit may occur in CTx-related tremor combined with parkinsonism. Its identification should prompt initiation of levodopa, thus avoiding unnecessary trials of other drugs.

Toxoplasmosis is the most common CNS opportunistic infection, particularly in the setting of HIV co-infection, and more rarely in hematologic malignancies and organs transplantation.[1] Its neurological manifestations are variable, depending not only on the size, number and localization of the encephalitic lesions, but also on the presence of meningitis, edema, vasculitis and hemorrhage.[2] While it is well known that *Toxoplasma gondii*-associated lesions have predilection for the basal ganglia (BG), movement disorders (MDs) usually constitute a small percentage (6-7%) of the neurological manifestations.[3,4] Notwithstanding, MDs can be the presenting feature of cerebral toxoplasmosis (CTx), and early clinical suspicion can prompt initiation of specific treatment(s).[5] Hyperkinetic MDs, especially hemi-chorea/ballismus, are the most common MDs in CTx,[3] whereas hemiparkinsonism associated with evidence of presynaptic dopaminergic deficit has never been described. MDs secondary to focal brain lesions, as in the case of CTx, are usually difficult to treat, and levodopa initiation in those conditions where nigrostriatal system involvement is documented might be the best therapeutic choice.[6]

We herein report the case of an HIV-positive patient who developed a complex MD featuring unilateral tremor combined with parkinsonism, and dystonia following resolution of an acute episode of CTx. Contralateral presynaptic dopaminergic deficit was documented on DaTscan. We additionally reviewed all cases of MDs in CTx reported so far and summarized their phenomenology and natural history.

Case report

A 41-year-old Black African female presented with an acute episode of disseminated toxoplasmosis in the context of previously undiagnosed HIV infection at the age of 27 years. She was profoundly immunosuppressed, with a baseline CD4 cell count of 20/mm^3 and an RNA-HIV viral load of 2.2 million copies/ml. *T. gondii* was isolated from blood, CSF, lymph nodes, and bronchial washing, and her brain MRI at onset showed multiple infra- and supratentorial ring-enhancing lesions consistent with cerebral abscesses, two of which involving the left anterior midbrain and left thalamus. After a long ITU admission during which she was treated for toxoplasmosis and started on anti-retroviral therapy, she eventually recovered with a right spastic hemiparesis. Around five months later, she developed right sided combined rest and action tremor, which has remained stable for nine years. Trials of levetiracetam, gabapentin, clonazepam, and botulinum toxin resulted in modest or no effect. There was no history of exposure to dopamine receptor antagonists, and HIV infection was well controlled at the time of

MD onset. Her first neurological examination in the MD clinic at age 36 (**Video, segment 1**) revealed supranuclear horizontal gaze palsy to the right, right central facial palsy and right hemiparesis with brisk reflexes. She had a rest tremor in the right hand, associated with mild postural and kinetic tremor, and intermittent rest tremor in the leg. Muscle tone was increased in her right limbs due to a combination of moderate spasticity and mild cogwheel rigidity. There was decreased right side shoulder shrug and slowness of ipsilateral limbs, but true bradykinesia was difficulty to access due to the pyramidal syndrome overlap. She had an additional dystonic posture in the right hand. Her gait was mainly spastic with circumduction of the right lower limb. While right limb spasticity and dystonia dominated the clinical picture, tremor, which was associated with mild parkinsonian features and minimal response to previous treatments, was the patient's main complaint. In view of that, she underwent a DaTscan, which showed unilateral dopaminergic deficit with absent uptake on the left side and normal uptake on the right BG (**Figure 1**). Follow-up brain MRI showed partial involution of the toxoplasmosis lesions, without evidence of any active, acute process; small, round T2-hyperintensity lesions persisted in the cerebellum hemispheres and supra-tentorial compartment, namely one involving the left anterior midbrain and adjacent thalamus (**Figure 2**). She was therefore started on levodopa (**Video 1, segment 2**), with mild improvement in her tremor and slowness of movements, having developed right foot dyskinesia when daily dose was increased to 800 mg.

Literature review

To further investigate the relationship between CTx and MDs we conducted a systematic review. We searched PubMed on DATE for English language articles using the following search strategy: "cerebral toxoplasmosis" AND "chorea" (8 results), "cerebral toxoplasmosis" AND "ballismus" (1 result), "cerebral toxoplasmosis" AND "dystonia" (6 results), "cerebral toxoplasmosis" AND "myoclonus" (2 results), "cerebral toxoplasmosis" AND "tremor" (12 results), "cerebral toxoplasmosis" AND "parkinsonism" (11 results), "cerebral toxoplasmosis" AND "movement disorders" (14 results), "cerebral toxoplasmosis" AND "ataxia" (8 results) and "cerebral toxoplasmosis" AND "tics" (1 result). After result deduplication, a total of 38 articles were obtained.

All articles were screened by reviewing the title and/or abstract, and we performed full-text review of all case reports or studies describing MDs in patients with CTx. Seven articles were excluded due to lack of relevance (not related with CTx, not describing patients with MDs and CTx, or MD best attributed to neuroleptic treatment). Additionally, seven articles were included via screening of the references of articles. Clinical cases were reported in 38 articles, for a total of 64 patients presenting with CTx-related MDs.

Results are presented in **Table 1**. Chorea was the most common MD in CTx, affecting 28 (44%) patients; in most cases, chorea involved one hemibody and was associated with ballistic movements, in the presence of contralateral subthalamic nucleus lesion. Other MDs observed were ataxia (n=13, 20%), parkinsonism (n=10, 16%), tremor (n=9, 14%), dystonia (n=9, 14%), myoclonus (n=2, 3%) and akathisia (n=1, 2%). Ataxia was more frequently axial, and appendicular dysmetria was identified in four patients. Unilateral Holmes tremor (HT) was the predominant form of tremor (n=5/9) and was related to midbrain lesions, ipsi- (n=2/5) or contralaterally (n=3/5) to the tremor side. Parkinsonism was poorly detailed, being generally correlated with bilateral BG lesions. Dystonia affected one hemibody in six patients, the cervical region in one case, and was focal to a limb in three patients (concurrent with chorea in two). MDs were rarely observed as isolated neurological manifestations since the majority of cases had a complex neurologic syndrome comprising other MDs, lethargy, cognitive deterioration, cranial nerve palsy and/or pyramidal syndrome, which is in accordance with the diffuse supra- and infratentorial involvement verified in CTx. MD presentation can be acute or subacute, emerging simultaneously with other clinical manifestations of CTx (mainly in the cases of chorea-ballismus and ataxia) or afterwards, with a time interval varying between few days and six months. As for treatment response, HT was reported to improve with different types of symptomatic medication (clonazepam, trihexyphenidyl, primidone, levodopa, pramipexol, isoniazid) and to various degrees (complete resolution in only two cases). The response to levodopa was only mentioned in 3/10 patients with parkinsonism (mild in two and absent in one), and in two cases, improvement was linked to initiation of specific therapy for CTx. Chorea was the MD with the best prognosis, as almost all cases had significant improvement, which was attributed to initiation of CTx therapy and successful infection control. Notably, radiological improvement was frequent, but did not correlate with the evolution of the MD, since the latter could persist, despite size reduction of the brain lesions. In one case of CTx with acute ataxia, follow-up MRI showed bilateral T2-hyperintensity at the level of the ventral medulla, compatible with hypertrophic olivary degeneration.[7] DaTscan was performed only in one case of HT, that demonstrated reduced presynaptic dopaminergic uptake in the putamen contralateral to the side of the tremor.[8] CTx was associated with HIV infection in the majority of cases (n=58, 91%); other immunosuppressive conditions (n=4) were observed in HIV-negative patients, including liver transplantation (due to Wilson disease, in a patient without neurological manifestations prior to the transplantation),[9] diffuse large B cell lymphoma,[10] stem cell transplantation,[11] and X-linked hyper IgM syndrome.[12]

Discussion

We reported a case of HIV-related CTx in which (1) three types of MDs developed subacutely after successful infection control (i.e., right upper limb tremor combined with right sided

hemiparkinsonism, and right hand dystonia), (2) the strictly unilateral MDs were topographically related to the sequelae of CTx brain MRI lesions [i.e., contralateral (left) anterior midbrain, involving the substantia nigra (SN), and contralateral (left) thalamus], (3) DaTscan demonstrated absent dopaminergic uptake in the left BG (a finding at times observed in presence of ipsilateral midbrain lesions),[6] and (4) the introduction of levodopa mildly improved tremor combined with parkinsonism and led to development of dyskinesia, in accordance with documentation of presynaptic dopaminergic deficit.

Although MDs in CTx are more frequently of the choreic type, other forms have been described and the clinical picture of our patient is in line with those reports. Reduced putaminal uptake in the DaTscan was previously reported in one case of HT[8] and none of parkinsonism, and L-dopa efficacy was shown in three cases of HT[8,9,13] and two of parkinsonism.[1,14]

While one could consider call the patient's tremor HT, we think that according to the consensus statement on the classification of tremors of the Movement Disorder Society,[15] "tremor combined with parkinsonism" is the most accurate syndromic classification, because (i) both postural and kinetic tremor may coexist with rest tremor in patients with parkinsonism, (ii) although the frequency of the tremor was not confirmed by EMG, in naked-eye observation it was superior to the 5 Hz cutoff set for HT, and (iii) the anterior midbrain lesion in MRI did not involve the red nucleus (RN). Moreover, the MRI of the patient exhibits multiple CTx lesions in the bilateral hemispheres of the cerebellum, and albeit mild cerebellar features, such as limb dysmetria and intentional tremor, cannot be completely excluded, due to spasticity and dystonia overlaps, we do not think that these lesions are causing the tremor, as they not involve the nuclei or pedunculi. HT is a clinical syndrome, but pathophysiology heterogenous, requiring the disruption of at least two of the following systems: cerebello-thalamo-cortical, dentate-rubro-olivary and dopaminergic nigrostriatal.[16] In this last one, the proximity of the RN and SN in midbrain may explain the improvement observed with L-dopa in three reported cases of CTx-related HT. [8,9,13]

Regarding the pathophysiology of CTx-related parkinsonism, the first report, from Carrazana et al.[17] postulated that parkinsonism can be caused by direct (by toxoplasma abscesses) or indirect (through edematous mechanical pressure) destruction of the pre- or post-synaptic dopaminergic cells, at the level of the SN or striatum, respectively; interruption of the nigrostriatal dopaminergic pathways travelling through the internal capsule; and transient vascular disturbances of the anterior choroidal artery. Later on, other studies provided additional evidence on the interplay between *T. gondii* and parkinsonism, although this probably accounts for the perpetuation of MD rather than its emergence in the setting of acute CTx: (1) one study of animal models infected with *T. gondii* discovered tyrosine hydroxylase, the rate limiting enzyme for dopamine synthesis, in intracellular tissue of brain cysts, and increased dopamine metabolism in neuronal cells,[18] and

(2) higher prevalence of toxoplasmosis seropositivity was demonstrated in Parkinson's disease patients, but this was an inconsistent finding across studies.[19]

In view of that, our study reinforces that CTx-related parkinsonism can be cause by direct SN damage, rather than BG (which would cause a post-synaptic dopaminergic deficit), as it was demonstrated by brain MRI (T2 hyperintensity of left midbrain, involving partially the SN) and DaTscan (absent dopaminergic uptake in left BG). Of note, we cannot exclude that a previously involuted toxoplasmosis abscess, or even residual tissue necrosis at the level of left caudate or putamen might contribute to the absence of tracer uptake in the left BG.

Notably, not all patients with parkinsonism and HT have improved with levodopa (two cases),[17,20] and other therapeutic options have been effective (treatment of the CTx itself, and for Holmes tremor, clonazepam, trihexyphenidyl, primidone, and isoniazid),[9,13,17,20–22] emphasizing that other mechanisms also interfere in the pathophysiology of these MDs (as stated above by Carrazana et al).[17]

Similarly to CTx, cysticercosis, tuberculosis and cryptococcosis have also been associated with parkinsonism either as a consequence of lesions (granulomas or abscesses) involving the BG or SN, or secondarily to direct pressure of SN from ventriculitis and obstructive hydrocephalus. Although positive response to levodopa and *post mortem* neuropathological evidence of nigrostriatal damage were described in some cases, findings from presynaptic dopaminergic imaging have never been reported.[23–25]

The persistence or appearance of a MD, despite improvement of MRI/CT lesions, as in our case and others in the literature, does not mean toxoplasmosis treatment failure, but it is probably due to residual injury from coagulative necrosis.[26] Alternatively, HIV co-infection may contribute to perpetuate the MD.[5] Neuropathological studies have shown damage to the BG and reduce levels of dopamine in HIV encephalopathy, which, in turn, is clinically supported by the observations of greater neuroleptic sensitivity in HIV patients and higher proportion of MDs in patients with CTx/HIV co-infections, than in patients with CTx without HIV.[27] Moreover, in one study of simian immunodeficiency virus (SIV)-infected monkeys, dopamine was reduced by 44% at two months of infection,[28] and another one demonstrated 25% of nigral neuronal loss in HIV-positive patients, even if asymptomatic.[29] Importantly, HIV-induced parkinsonism was shown to be successfully treat with levodopa.[30]

In conclusion, our case provides evidence that SN damage and hence presynaptic dopaminergic deficit may occur in CTx-related parkinsonism. Its presence should be search in MDs (specially in "tremor combined parkinsonism" syndromes) related to CTx or to other causes of structural

lesions affecting the midbrain, allowing prompt initiation of levodopa, and thus avoiding unnecessary trials of other drugs. Practically all types of MD can be observed in CTx and although the latter is expected to decrease in the era of HIV anti-retroviral therapies, it remains an important cause of acquired MDs.

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Author Roles

1. Research project: A. Conception, B. Organization, C. Execution;
2. Data Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

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Ethical Compliance Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The authors confirm that the approvoal of an institutional review board was not required for this work. Patient consent was obtained for video recording and publication.

Table 1. Literature review

Author, year	Nr of patients, gender	Type of MD	Other neurological manifestations	Age in the article (years, y)	Latency between CTx onset and MD[#]	Related CTx cause (other CNS infections)	Brain MRI/CT	Evolution of the MD[$]	Radiological improvement
Tremor									
Koppel BS, 1990[20]	1 pt, M	Holmes tremor (L hemibody)	Lethargy, dysarthria, L Weber syndrome	35y	0	Drug user	CT: Ring-enhancing mass lesions in L frontal lobe and L midbrain	Tremor progressed to involve the jaw in 1 month; no response to clonazepam, levodopa or primidone; mild improvement with trihexyphenidyl and isoniazid (died)	Partial resolution (3 weeks)
Coelho JCU, 1996[9]	1 pt, M	Intentional and rest tremor, 4 limbs rigidity	Dysarthria, dysphagia, spasticity	16y	0	Liver transplantation in Wilson Disease* (CMV)	CT: Hypodensity of the thalamus, BG, and external capsule	Moderate improvement with levodopa and trihexyphenidyl (died)	NA
Micheli F, 1997[26]	1 pt, M	Action and postural tremor (4 Hz, R hemibody)	R hemi-sensory motor syndrome	39y	1 month	HIV	MRI: Enhancing lesions in L posterior thalamus and posterior arm of internal capsule	Unchanged at 2 months, residual at 11 months follow-up; medication not specified	Marked improvement (2 weeks)
Pezzini A, 2002[13]	1 pt, M	Holmes tremor (L UL)	L hemiparesis	46y	4 months	HIV	CT: Multiple supratentorial nodular lesions, including R thalamus and R midbrain with edema and homogenous enhancement	Rest tremor improved with levodopa; postural/kinetic component improved with isoniazid; no response to clonazepam and trihexyphenidyl	Reduction in size (2 weeks)
Mattos JP, [illegible]	1 pt, M	Holmes tremor (L UL)	HIC	36y	NA	HIV (cerebral TB)	CT: Lesions in L midbrain and L cerebellar hemisphere	Disappeared with anti-TxT	Disappeared
[illegible]recker K 2007[8]	1 pt, M	Holmes tremor (R UL)	L Weber syndrome	51y	5 months	HIV	MRI: Ring-enhancing lesion in midbrain (L red nucleus and CP); DaTSCAN: Reduce uptake in L putamen	Tremor slowly evolved during 5 months; significant improvement after introduction of pramipexole	NA
Lekoubou A, [illegible][21]	1 pt, M	Holmes tremor (L hemibody)	Confusion, cerebellar dysarthria, L hemi-sensory motor syndrome	35y	18 days	HIV	CT: Ring-enhancing lesion in R internal capsule, R thalamus, with edema extending to upper midbrain	Improvement with anti-TxT, clonazepam and trihexyphenidyl; resolution in 8 days	NA
Dystonia									
[illegible] 1991[illegible]	1 pt, M	L UL dystonia, intentional tremor	-	29y	0	HIV	MRI: Enhancing lesions in R thalamus, R LN and L temporal lobe, with edema	Persisted at 6 months follow-up; medication not specified	Marked improvement
[illegible]inazasoro G, 1994[32]	3 pts (2M, 1F)	R hemi-dystonia	NA	25/25/27y	NA	HIV	CT: Lesions in GPi, thalamus and STN	NA	NA
Micheli R, 1994[33]	1 pt, F	R hemi-dystonia, R hemi-chorea-balllismus	-	11y	0	-	CT and MRI normal	No response to trihexyphenidyl; improvement with anti-TxT; complete resolution at 2 months follow-up	-
[illegible]attos JP, 2002[22]	1 pt, M	R hemi-dystonia	NA	28y	NA	HIV	CT: Hypodense lesion in L BG	No improvement; medication not specified	Improvement
Factor SA, 2003[2]	1 pt, M	R torcicollis, R hemi-dystonia, head and UL rest tremor, myoclonus	Stupor, R NCIII palsy, papilledema, increased muscle tonus, bilateral Babinski sign, R hemiparesis	44y	14 days	HIV	CT: Non-enhancing mass lesions in R caudate, L thalamus, L frontal lobe, with midline shift	No improvement with anti-TxT	NA
Ataxia									
Navia B [illegible]	6 pts, NA	6 ataxia (2 w/ limb dysmetria)	Headache, lethargy, NCVI palsy, aphasia, HH	NA	3 days – 3 weeks	HIV	CT: Single to multiple enhanced cortical lesions (1 cerebellum involvement)	Improvement mentioned in 3, death in 1	NA
[illegible]erod LD, 1996[34]	1 pt, M	Ataxia	Seizures, dysarthria, L hemiparesis, HH, cognitive declaine, nystagmus	42y	NA	HIV	MRI: Lesions in R frontal and bilateral parietal lobes	NA	NA
[illegible] 2002[35]	1 pt, M	Ataxia	Headache, nausea	26y	0	HIV	MRI: Multiple ring-enhancing lesions in the cerebellum. BG and L occipital lobe	Clinically well at 1 year follow-up	Marked improvement (2 weeks); resolution (1 year)
Pott H, 2013[36]	1 pt, M	Ataxia, limbs dysmetria	Headache, confusion	50y	0	HIV	MRI: Ring-enhancing lesion in R cerebellar hemisphere	Resolution after 2 weeks of anti-TxT	Reduction (2 weeks)
Savsek L, 2016[10]	1 pt, F	Ataxia, limbs dysmetria	Cognitive decline, HH, R UL paresis	62y	0	Diffuse large B cell lymphoma	MRI: Ring-enhancing lesions in cortical and cerebellar hemispheres	Improvement with anti-TxT	Reduction, with hemorrhagic inclusions in some lesions (6 weeks)
Liu 2017[10,12]	1 pt, M	Ataxia	Lethargy	2y	0	Primary immunodeficiency disease (XHIGM)	MRI: Ring-enhancing lesions in bilateral cerebral hemispheres, BG and thalamus	Died	NA
Belizadi [illegible]	1 pt, F	Ataxia	Headache	54y	0	HIV	MRI: Ring-enhancing lesions in R caudate, R thalamus, bilateral SCP	NA	Improvement, bilateral HOD (6 weeks)
Myoclonus									
De Ma[illegible]	1 pt, M	Myoclonus	NA	NA	NA	HIV	NA	NA	NA
Akathisisa									
[illegible] 1989	1 pt,M	R akathisia	R hyperreflexia	54y	0	HIV	CT: Enhancing nodular lesions in L STN, L LN, L parietal lobe, with edema	Worsened with haloperidol (died)	NA
Parkinsonism									
[illegible]anzana, 1989[17]	1 pt, F	Bilateral parkinsonism, w/ severe dysarthria	Lethargia, R hyperreflexia, spastic tetraparesis	66y	0	HIV	CT: Enhancing lesions in bilateral internal capsules with edema	No response to levodopa (died)	NA
Noel, 1992[7]	1 pt, M	R parkinsonism	R pyramidal syndrome	28y	NA	HIV	CT: Enhancing lesion in L LN	NA	NA
Linazasoro G, 1994[32]	1pt, M	Parkinsonism (postural and rest tremor)	NA	30y	NA	HIV	CT: Bilateral BG lesions	NA	NA
Maggi P, 2000	1 pt, M	Bilateral parkinsonism, w/ moderate dysarthria	Abulia, R NCVII palsy	31y	30 days	HIV (cerebral TB)	MRI: Abscesses involving L LN and R BG	Died	Slight regression (2 months)
Murakami T, 2000[14]	1 pt, M	Asymmetrical L>R parkinsonism, w/ pill rolling tremor	Confusion, downward and horizontal gaze palsy, LL hyperreflexia	49y	MD 3 months before CTx diagnosis	HIV	MRI: Multiple lesions with edema in subcortical WH of bilateral parietal lobes and R LN, some with ring-enhancement	Partially improvement with anti-TxT and levodopa (300mg/day); resolution of downward gaze limitation	Reduction (2 months)
De Mattos J, 2002[22]	2 pts, NA	Parkinsonism	-/Benedikt syndrome	NA	NA	HIV	CT: Hypodense mass in R BG/ MRI: Enhanced lesion in midbrain	NA/ Improvement with anti-TxT	NA
Arbune AA, 2016[1]	1 pt, F	Parkinsonism, choreoathetosis	Coma, R convergent strabismus, tetraparesis	58y	6 months	HIV	MRI: Multiple nodular enhancing lesions in frontoparietal region, cerebellum and BG	Mild improvement with levodopa and clonazepam	Improvement (1 year)

Author, year	Nr of patients, gender	Type of MD	Other neurological manifestations	Age in the article (years, y)	Latency between CTx onset and MD[#]	Related CTx cause (other CNS infections)	Brain MRI/CT	Evolution of the MD[$]	Radiological improvement
Tateno T, 2017[11]	1 pt, M	Parkinsonism	Seizure	53y	0	Stem cell transplantation	MRI: Diffuse T2-hyperintensities in bilateral BG, without ring enhancement	Died	NA
De Almondes K, 2020[38]	1 pt, M	Parkinsonism	Seizure, aphasia, R hemiparesis	63y	NA	HIV	MRI: Bilateral BG and cortico-subcortical frontal lesions with edema	NA	NA
Chorea									
Navia B, 1986[4]	2 pts, NA	Chorea, rigidity/ Choreoathetosis	Lethargy/ Headache, hemiparesis	NA	4-5 weeks	HIV	CT: Hypodense lesions in bilateral BG/ Ring-enhancing lesion in L internal capsule, R occipital lobe	No response (died)	NA
Nath A, 1987[39]	3 pts, F/M/M	3 R hemi-chorea-ballismus	1 Headache/ -/ -	26/56/47y	NA	HIV (1 cryptococcal meningitis)	CT: Contrast-enhancing lesions in L frontal lobe and L BG/ L STN abscess/ multiple abscesses, 1 L BG	Improvement with anti-TxT/ NA/ NA	NA
Sanchez-Ramos J, 1989[40]	1 pt, F	L hemi-chorea-ballismus	Headache, nausea	33y	0	HIV	CT: Ring-enhancing lesions in L caudate, R thalamus, R STN, R cerebellum, with edema	Dramatic improvement after 4 days of anti-TxT, with resolution in day 20	Marked improvement (2 weeks)
Piccol[illegible]	2 pts, M	R hemi-ballismus/ Generalized chorea, ataxia	-/L hemiparesis	27y/ 35y	0	HIV	MRI: Ring-enhancing lesions in L STN/ MRI: TR-hyperintensities in midbrain, R CP, R BG, L thalamus-capsule, L frontal operculum, L occipital lobe, with contrast enhancement	Resolution in 2 months after initiation of anti-TxT /Chorea present till death	Resolution (1 month)/ NA
Nath A, 1993[5]	1 pt, M	L hemi-chorea-ballismus, involving the hemi-face	L brisk reflexes	32y	MD (hemi-facial chorea) 1 month before CTx diagnosis	HIV	CT: Ring-enhancing lesion in R GPi, R parietotemporal and L temporal regions	Some response to TxT and haloperidol	Considerable improvement (10 days)
[illegible] J, 1993[42]	1 pt, M	R hemic-chorea-ballismus	Disinhibited behaviour	65y	0	HIV	MRI: Ring-enhancing mass in L STN	Resolution within few weeks after initiation of anti-TxT	Reduction
[illegible], 1994[32]	2 pts, M/F	2 R hemi-chorea-ballismus	NA	25y/25y	NA	HIV	CT: lesions in LN and STN	NA	NA
[illegible] 1995[illegible]	1 pt, M	R hemi-ballismus	NA	32y	NA	HIV	MRI: Enhancing lesions with edema, one in L STN	No response to pharmacological therapy; resolution with chordotomy	NA
Manji H, 1995[44]	1 pt,	R choreoathetosis, R hand dystonia	Headache, R hemiparesis, R brisk reflexes, dysphagia	28y	0 (dystonia 5 months)	HIV	CT: Low density lesions in bilateral thalamus, LN, R frontal and L parietal lobes	Significant improvement 5 weeks after initiation of anti-TxT	Almost complete resolution
Maggi P, 1996[3]	3 pts, M	L hemi-coreoathetosis	Aphasia, R hemiparesis/ -/ confusion	27y/ 31y/ 32y	0	HIV	MRI: Multiple supratentorial lesions, including R STN	Resolution within 10-30 days of anti-TxT	NA/Reduction (4 months/Resolution (3 months)
[illegible] J, 2002[22]	6 pts, M	6 hemi-chorea-ballismus	2 HIC	27-40y	NA	HIV	CT: Ring-enhancing lesions in BG and frontal lobe	NA	NA
Rabbi S, 201[illegible]1	1 pt, F	L hemi-chorea-ballismus	Headache, nausea, L hemiparesis	59y	0	HIV	MRI: Ring-enhancing lesion in R capsule-thalamus with edema	Resolution within 2 weeks of anti-TxT	Resolution
Reyes AJ, 2016[46]	1 pt, M	R hemi-coreoathetosis, R foot dystonia	Cognitive decline	22y	0	HIV	MRI: T2-hyperintensities in bilateral BG, thalamus and frontal lobe, R parietal and temporal lobes	Resolution 10 days after initiation of anti-TxT and haloperidol	Improvement (2 months
Dimal NP, 2021[47]	1 pt, M	L hemi-chorea-ballismus	L hemiparesis	24y	0	HIV (cerebral TB)	MRI: T2-hyperintensities in R STN, R CP and ring-enhancing lesion in L frontal lobe	Dramatic improvement with anti-TxT and risperidone; almost complete resolution at 9 months follow-up	Resolution (4 months)

0 means MD was simultaneous with other CTx-related manifestations;

[#] death is indicated, when it happens as a direct result of the acute CTx infection;

[$] Neurological manifestations prior to the transplantation.

Anti-TxT, anti-toxoplasmosis treatment; BG, basal ganglia; CMV, cytomegalovirus; CP, cerebellar peduncles; CTx, cerebral toxoplasmosis; F, female; GPi, globus pallidus internus; HH, homonymous hemianopsia; HIC, intracranial hypertension; HOD, hypertrophic olivary degeneration; L, left; LL, lower limbs; LN, lenticular nucleus; M, male; MD, movement disorder; R, right; SPC, superior cerebellar peduncles; STN, subthalamic nucleus; TB, tuberculosis; UL upper limb; XHIGM, X-linked hyper IgM syndrome.

Legends

Figure 1. DaTscan performed in 2016, 9 years after the episode of CTx, showing complete absent tracer uptake in the left basal ganglia, and normal tracer activity in the right basal ganglia.

Figure 2. Brain MRI performed in 2018, showing T2-hyperintensity in cerebellum hemispheres (upper left panel), and in anterior left midbrain (upper middle panel, arrow), extending superiorly towards the medial left thalamus (upper right panel, arrow). Caudate or putaminal lesions were not observed in T1, T2 and gadolinium-enhanced sequences at the striatum level (lower panels).

Video. Segment 1. Patient at first neurological observation (2016, 36 years old). She has right sided rest, postural and kinetic tremor. Evaluation of the intentional component is limited by the ipsilateral hemiparesis. There is slowness of movements on the right limbs and ipsilateral hand dystonia. Gait is spastic with circumduction of the right lower limb. **Segment 2.** Patient observed 6 weeks later, on 300 mg of levodopa. She reported a slight improvement of the rest tremor and the gait.

Table 1. Literature review.

References

1. Arbune AA, Arbune M, Stefanescu V. Parkinsonian Syndrome and Toxoplasmic Encephalitis. *The Journal of Critical Care Medicine*. 2016;2(2):89-92. doi:10.1515/jccm-2016-0009
2. Factor SA, Troche-Panetto M, Weaver SA. Dystonia in AIDS: Report of four cases. *Movement Disorders*. 2003;18(12):1492-1498. doi:10.1002/mds.10602
3. Maggi P, de Mari M, de Blasi tR, et al. Choreoathetosis in Acquired Immune Deficiency Syndrome Patients with Cerebral Toxoplasmosis. *Movement Disorders VoI* . 1996;11(4):434-436. doi:10.1002/mds.870110414
4. Navia BA, Petito CK, Gold JWM, Cho E -S, Jordan BD, Price RW. Cerebral toxoplasmosis complicating the acquired immune deficiency syndrome: Clinical and neuropathological findings in 27 patients. *Ann Neurol*. 1986;19(3):224-238. doi:10.1002/ana.410190303
5. Nath T, Hobson DE, Russell A. Movement Disorders with Cerebral Toxoplasmosis and AIDS. *Mov Disord*. 1993;8(1):107-112. doi:10.1002/mds.870080119
6. Tuma Santos CA, Wallace WD, Kim S, Vijayakumar V. Pitfalls and artifacts of 123i-ioflupane SPECT in parkinsonian syndromes: A quality improvement teaching tool. *J Nucl Med Technol*. 2021;49(2):114-119. doi:10.2967/jnmt.120.258491
7. Behzadi F, Fiester PJ, Rao D. Bilateral Hypertrophic Olivary Degeneration Following Brainstem Insult: A Retrospective Review and Examination of Causative Pathology. *Neurosci Insights*. 2021;16. doi:10.1177/26331055211007445
8. Strecker K, Schneider JP, Sabri O, et al. Responsiveness to a dopamine agent in Holmes tremor - Case report. *Eur J Neurol*. 2007;14(4). doi:10.1111/j.1468-1331.2006.01665.x
9. Coelho J, Wiederkehr J, Cat R, et al. ExtrapyramidaJ Disorder Secondary to Cytomegalovirus Infection and Toxoplasmosis After Liver Transplantation. *Eur J Pediatr Surg*. 1996;6(2):110-111. doi:10.1055/s-2008-1066485

10. Savsek L, Opaskar TR. Cerebral Toxoplasmosis in a Diffuse Large B Cell Lymphoma Patient. *Radiol Oncol*. 2014;0(0). doi:10.2478/raon-2014-0042

11. Tateno T, Onozawa M, Hashiguchi J, et al. Disseminated toxoplasmosis after hematopoietic stem cell transplantation showing unusual magnetic resonance images. *Transplant Infectious Disease*. 2017;19(4). doi:10.1111/tid.12720

12. Liu X, Zhou K, Yu D, et al. A delayed diagnosis of X-linked hyper IgM syndrome complicated with toxoplasmic encephalitis in a child: A case report and literature review. *Medicine (United States)*. 2017;96(49). doi:10.1097/MD.0000000000008989

13. Pezzini A, Zavarise P, Palvarini L, Viale P, Oladeji O, Padovani A. Holmes' tremor following midbrain Toxoplasma abscess: clinical features and treatment of a case. *Parkinsonism Relat Disord*. 2002;8(3):177-180. doi:10.1016/s1353-8020(01)00013-x

14. Murakami T, Nakajima M, Nakamura T, et al. Parkinsonian Symptomsas an Initial Manifestation in a Japanese Patient with Acquired Immunodeficiency Syndrome and Toxoplasma Infection. *Internal Medicine*. 2000;39(12):1111-1114. doi:10.2169/internalmedicine.39.1111

15. Bhatia KP, Bain P, Bajaj N, et al. Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. *Movement Disorders*. 2018;33(1):75-87. doi:10.1002/mds.27121

16. Raina GB, Cersosimo MG, Folgar SS, et al. Holmes tremor: Clinical description, lesion localization, and treatment in a series of 29 cases. *Neurology*. 2016;86(10):931-938. doi:10.1212/WNL.0000000000002440

17. Carrazana E, Rossitch EJ, Samuels M. Parkinsonian symptoms in a patient with AIDS and cerebral toxoplasmosis. *Neurol Neurosurg Psychiatry*. 1984;52(12):1445-1447. doi:10.1136/jnnp.52.12.1445-a

18. Prandovszky E, Gaskell E, Martin H, Dubey JP, Webster JP, McConkey GA. The neurotropic parasite toxoplasma gondii increases dopamine metabolism. *PLoS One*. 2011;6(9). doi:10.1371/journal.pone.0023866

19. Virus MA, Ehrhorn EG, Lui LAM, Davis PH. Neurological and Neurobehavioral Disorders Associated with Toxoplasma gondii Infection in Humans. *J Parasitol Res*. 2021;2021. doi:10.1155/2021/6634807

20. Koppel B, Daras M. "Rubral" tremor due to midbrain Toxoplasma abscess. *Movement Disorders*. 1990;5(3):254-256. doi:10.1002/mds.870050314

21. Lekoubou A, Njouoguep R, Kuate C, Kengne AP. Cerebral toxoplasmosis in Acquired Immunodeficiency Syndrome (AIDS) patients also provides unifying pathophysiologic hypotheses for Holmes tremor. *BMC Neurol*. 2010;10. doi:10.1186/1471-2377-10-37

22. Pitágoras De Mattos J, Lúcia A, de Rosso Z, Corrêa RB, Novis SAP. Movement disorders in 28 HIV-infected patients. *Arq Neuropsiquiatr*. 2002;60(A):525-530.

23. Rissardo J, Caprara AF, Durante Í. Neurocysticercosis and movement disorders: A literature review. *Brain Circ*. 2020;6(4):225. doi:10.4103/bc.bc_48_20

24. Wszolek Z, Monsour H, Smith P, Pfeiffer R. Cryptococcal meningoencephalitis with parkinsonian features. *Mov Disord.* 1988;3(3):271-3. doi: 10.1002/mds.870030312

25. Parent M, Parent A. Substantia nigra and Parkinson's disease: a brief history of their long and intimate relationship. *Can J Neurol Sci*. 2010 May;37(3):313-9. doi: 10.1017/s0317167100010209

26. Micheli F, Granana N, Scorticati MC, Giannaula RJ, Reboredo G. Unilateral postural and action tremor resulting from thalamic toxoplasmosis in a patient with acquired immunodeficiency syndrome. *Movement Disorders*. 1997;12(6):1096-1098. doi:10.1002/mds.870120647

27. Cardoso F. HIV-related movement disorders: epidemiology, pathogenesis and management. *CNS Drugs*. 2002;16(10):663-668. doi:10.2165/00023210-200216100-00002

28. Koutsilieri E, Sopper S, Scheller C, ter Meulen V, Riederer P. Parkinsonism in HIV dementia. *J Neural Transm (Vienna).* 2002 May;109(5-6):767-75. doi: 10.1007/s007020200063

29. DeVaughn S, Müller-Oehring EM, Markey B, Brontë-Stewart HM, Schulte T. Aging with HIV-1 Infection: Motor Functions, Cognition, and Attention – A Comparison with

Parkinson's Disease. *Neuropsychol Rev*. 2015;25(4):424-438. doi:10.1007/s11065-015-9305-x

30. Almajali M, Almajali F, Kafaie J, Chand P. Successful Utilization of Levodopa in HIV-Induced Parkinsonism. *Cureus*. 2020 Dec 1;12(12):e11825. doi: 10.7759/cureus.11825

31. Tolge CF, Factor SA. Focal dystonia secondary to cerebral toxoplasmosis in a patient with acquired immune deficiency syndrome. *Movement Disorders*. 1991;6(1):69-72. doi:10.1002/mds.870060113

32. Linazasoro G. Movement disorders with cerebral toxoplasmosis and AIDS. *Movement Disorders*. 1994;9(2):244-245. doi:10.1002/mds.870090227

33. Micheli R, Perini A, Duse M. Hemidystonia secondary to acquired toxoplasmosis in a non-immunodeficient patient. *Eur J Pediatr*. 1994 Oct;153(10):731-3. doi: 10.1007/BF01954489

34. Ormerod LD, Rhodes RH, Gross SA, Crane LR, Houchin KW. Ophthalmologic manifestations of acquired immune deficiency syndrome- associated progressive multifocal leukoencephalopathy. *Ophthalmology*. 1996;103(6):899-906. doi:10.1016/S0161-6420(96)30589-7

35. Tsai HC, Lee SSJ, Lin HH, et al. Treatment of Toxoplasma brain abscess with clindamycin and sulfadiazine in an AIDS patient with concurrent atypical Pneumocystis carinii pneumonia. *J Formos Med Assoc*. 2021;101(9):646-655.

36. Pott H, Castelo A. Isolated cerebellar toxoplasmosis as a complication of HIV infection. *Int J STD AIDS*. 2013;24(1):70-72. doi:10.1258/ijsa.2012.012189

37. Noël S, Guillaume MP, Telerman-Toppet N, Cogan E. Movement disorders due to cerebral Toxoplasma gondii infection in patients with the acquired immunodeficiency syndrome (AIDS). *Acta Neurol Belg*. 1992;92(3):148-156.

38. de Almondes KM, Lima NC. Cerebral toxoplasmosis and alcohol abuse in AIDS: Dementia with multiple etiologies. *Dementia e Neuropsychologia*. 2020;14(4):422-429. doi:10.1590/1980-57642020dn14-040014

39. Nath A, Jankovic J, Pettigrew LC. Movement disorders and AIDS. *Neurology*. 1987;37(1):37-41. doi:10.1212/wnl.37.1.37

40. Sanchez-Ramos JR, Factor SA, Weiner WJ, Marquez J. Hemichorea-hemiballismus associated with acquired immune deficiency syndrome and cerebral toxoplasmosis. *Movement Disorders*. 1989;4(3):266-213. doi:10.1002/mds.870040308

41. Piccolo I, Causarano R, Sterzi R, et al. chorea in patients with AIDS. *Acta Neurol Scand*. 1999;100(5):332-336. doi:10.1111/j.1600-0404.1999.tb00406.x

42. Provenzale JM, Schwarzschild MA. Radiologic-Clinical Correlation Hemiballismus. *A J NR*. 1994;15:1377-1382.

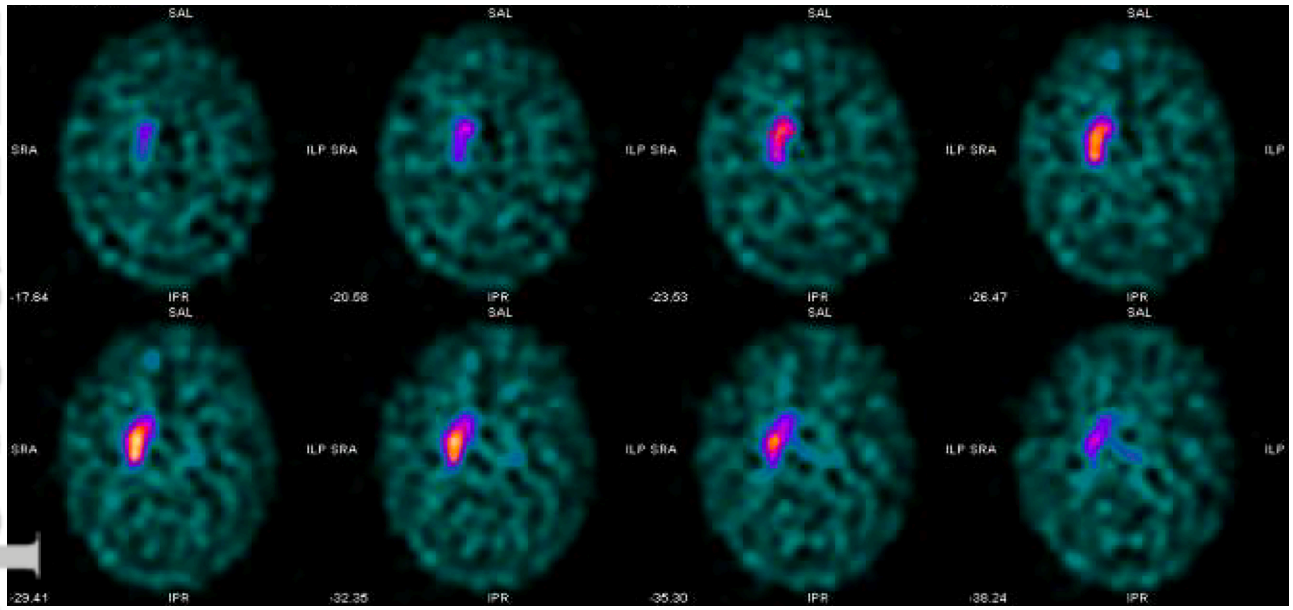
43. Krauss JK, Borremans JJ, Nobbe F, Mundingeq F, Krauss JK. Ballism Not Related to Vascular Disease: A Report of 16 Patients and Review of the Literature. *Parkinsonism Relat Disord*. 1996;2(1):35-45. doi:10.1016/1353-8020(95)00018-6

44. Manji H, Sweeney B, Connolly " S, Hughes A, Miller RF, Harrison MJG. Movement disorders in AIDS: Infective, neoplastic and iatrogenic causes. *Parkinsonism Relat Disord*. 1995;1(1):13-19. doi:10.1016/1353-8020(95)00005-q

45. Rabhi S, Amrani K, Maaroufi M, et al. Hemichorea-hemiballismus as an initial manifestation in a Moroccan patient with acquired immunodeficiency syndrome and toxoplasma infection: a case report and review of the literature. *Pan African Medical Journal-ISSN*. 2011;10(9):1937-8688. doi:10.4314/pamj.v10i0.72216

46. Reyes AJ, Ramcharan K, Aboh S, Duke N. Reversible movement disorders due to toxoplasmosis as initial manifestation of HIV-AIDS, with sequential MR and video imaging. *BMJ Case Rep*. 2016;2016. doi:10.1136/bcr-2016-215676

47. Dimal NPM, Santos NJC, Reyes NGD, Astejada MN, Jamora RDG. Hemichorea-Hemiballismus as a Presentation of Cerebritis from Intracranial Toxoplasmosis and Tuberculosis. *Tremor Other Hyperkinet Mov (N Y)*. 2021 Jan 20;11:2. doi: 10.5334/tohm.576



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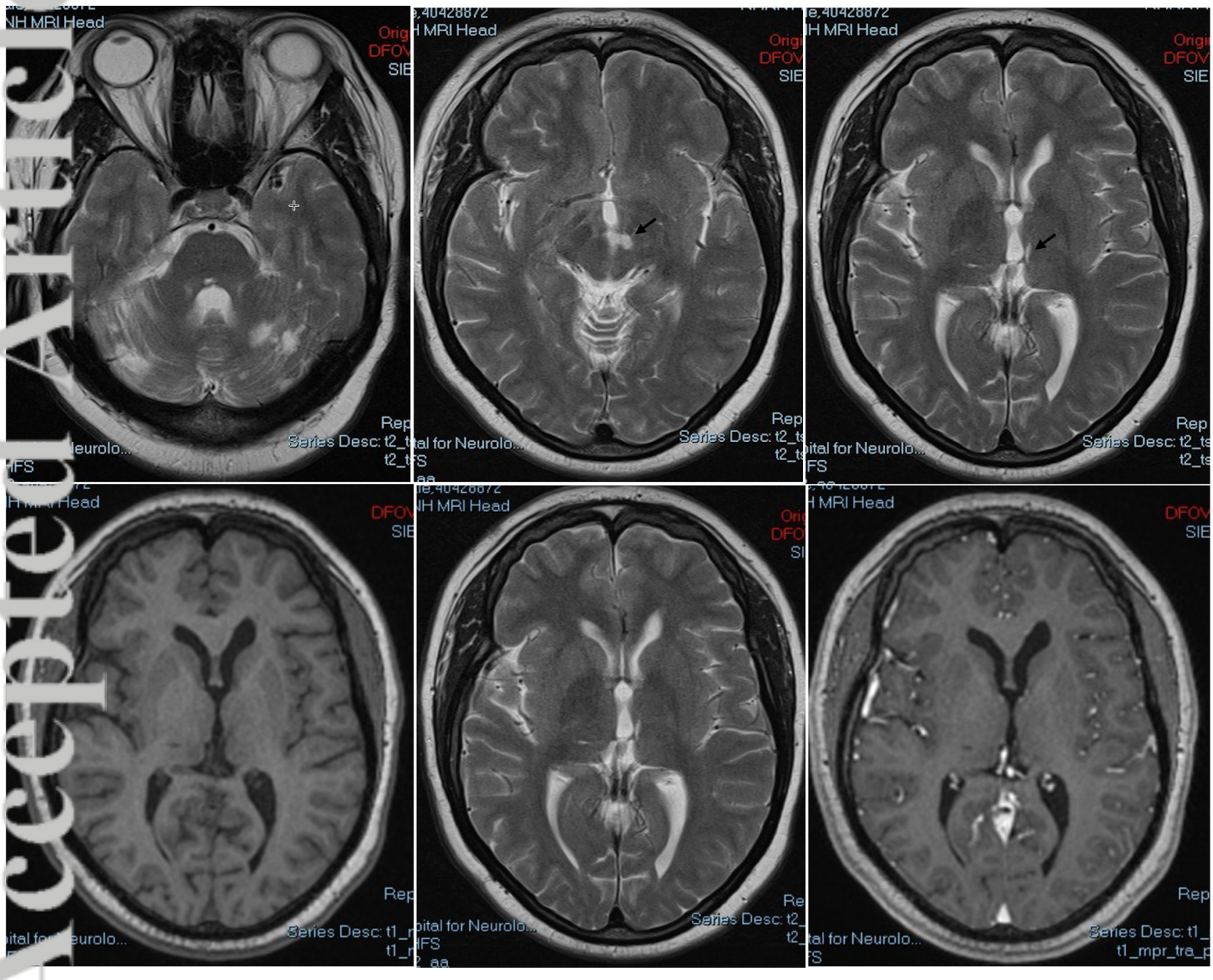

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