

# Cerebral Blood Flow in Dystonia Due to Pantothenate Kinase-Associated Neurodegeneration (PKAN) as Measured by Arterial Spin Labeling: A Pilot Study

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## Abstract

**Background:** The rare condition of dystonia due to Pantothenate Kinase-Associated Neurodegeneration (PKAN) is characterized by a lesion of the globus pallidus, the “tiger’s eye”. Cerebral Blood Flow (CBF) has not yet been examined by magnetic resonance imaging techniques because of the high disturbance of susceptibility in this area caused by iron deposits. The present pilot study was performed to demonstrate feasibility of CBF measurement by Arterial Spin Labeling (ASL) under these conditions.

**Material and Methods:** In 4 PKAN patients and a group of 6 age-matched healthy controls, pseudo continuous ASL sequences were applied in two versions, one using gradient and one using spin echo refocusing, and T2\* time was measured as well.

**Results:** In spite of the significant differences in T2\* time of the globus pallidus between patients and controls, nearly identical CBF values were recorded by both ASL sequences, in both groups.

**Conclusion:** This pilot study showed for the first time that CBF appears to be normal in patients suffering from PKAN dystonia, including their basal ganglia, and that measurement of CBF using ASL can be applied successfully in areas of brain iron accumulation.

**Keywords:** Pantothenate Kinase-Associated Neurodegeneration, Cerebral Blood Flow, Arterial Spin Labeling

## 1. INTRODUCTION

Pantothenate Kinase-Associated Neurodegeneration (PKAN) is a genetically transmitted metabolic disorder belonging to the group of rare or orphan diseases with a general prevalence of about 1 : 1,000,000 persons [1]. In the Dominican Republic, a rather large group of these patients has been identified, which is characterized by the same missense mutation of the PANK2 gene (c.680 A>G, p.Y227C) [2] and clinically by a delayed type of onset of symptoms during late infancy or early adolescence. Imaging studies have revealed the “eye-of-the-tiger” sign in most of these patients, whereas in some cases, the typical bright spot was found to be obscured by an excessive accumulation of iron in the globus pallidus [3, 4].

Accordingly, Quantitative Susceptibility Imaging (QSM) showed high disturbances of the local magnetic field in affected areas [5, 6], which might interfere severely with dynamic

contrast perfusion studies. Thus, Cerebral Blood Flow has been measured by now only using Single Photon Emission Computed Tomography (SPECT) in two siblings affected by PKAN, who showed decreased perfusion of cortical areas and the basal ganglia [7].

However, a different technique of Magnetic Resonance Imaging (MRI) called Arterial Spin Labelling in its Pseudo Continuous variant (PCASL) is less susceptible to local field inhomogeneities and has been applied successfully in Parkinson’s disease [8,9].

The present study was carried out to proof the feasibility of recording CBF by application of PCASL in brain areas of high iron concentration as well as to accumulate more data about CBF in PKAN dystonia.

## 2. MATERIAL AND METHODS

This prospective pilot study had been approved by the CEDIMAT Ethics Committee, and

informed consent had been received from all participants.

### 2.1. Patients and Controls

Included were ASL data from 4 PKAN patients, three female and one male, of an age of 10, 11, 15 and 20 years with genetically proven homozygous mutation of the PANK 2 gene. In these patients, first symptoms had appeared between 8 and 15 years of age, and by time of MRI examination, had reached a score of 4, 8, 17 and 32 points on the Burke-Fahn-Marsden dystonia scale. Results were compared to 6 healthy volunteers, 4 female and 2 male, between 9 and 20 (mean 15.7) years old.

### 2.2. Magnetic Resonance Imaging

Imaging was carried out on a Philips 3 T Achieva scanner.

Apart from a routine T1- and T2-weighted sequence, MRI included two variations of PCASL, one using the more commonly applied gradient echo (FFE-EPI) sequence, and a second one using a spin echo (SE-EPI) sequence which due its refocusing pulse, is less susceptible to local field disturbances. The following parameters were applied in both sequences: 18 slices of a thickness of 6 mm and 6 mm spacing covering whole head, acquisition matrix 128x128, TR 4000 ms, flip angle  $90^{\circ}$ , label time 1650 msec. Post label delay was 1780 msec for FFE and 1400 msec for SE, TE was 14.0 msec for FFE and 23.6 msec for SE, and slice acquisition time was 47.7 msec for FFE and 80.0 msec for SE.

To measure T2\* time, we used a 3D FFE sequence: 10 slices of 4 mm thickness covering the basal ganglia: TR 329 ms, TE 2.1 ms, flip angle  $12^{\circ}$ , 10 echoes with 3.2 ms spacing. Here, pixel size was 1.3 x 1.3 mm.

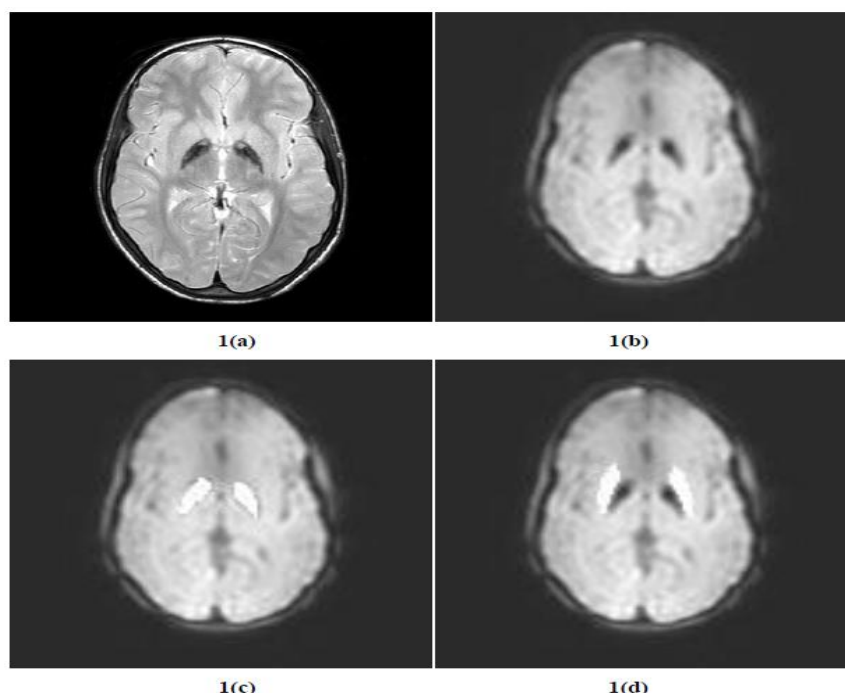
### 2.3. Postprocessing of Data

Images were realigned with Statistical Parametric Mapping (SPM) 10 running under MATLAB and CBF was calculated using the ASL Data Processing Toolbox [10] which principally performs the subtraction of the labeled from the non-labeled control image and calculates CBF values according to the general kinetic model for quantitative perfusion [11]. Label efficiency was set to 0.85.

T2\* maps were calculated with in-house software developed in Python ([www.python.org](http://www.python.org)). Data were fitted to a mono-exponential decay model using the Levenberg-Marquardt algorithm from the Scipy scientific libraries ([www.scipy.org](http://www.scipy.org)).

To measure CBF and T2\* time, Regions of Interest (ROIs) were drawn individually on the means from the control images, covering the globus pallidus and putamen (Fig. 1). For grey matter measurements, ROIs were taken from the segmented means of the control images.

Results were compared between patients and controls by 2-tailed ttest and CBF of basal ganglia was correlated to T2\* time measured in these areas.



**Fig1:** MRI of 11-year-old girl suffering from PKAN dystonia since 2 years, Burke-Fahn-Marsden scaling of 32 points. T2weighted image showing the typical “tiger’s eye” and mean CBF images (b) with ROIs covering the globus pallidus(c) and the putamen (d)

**3. RESULTS**

Whereas CBF maps could be calculated in controls from FFE and SE sequences in all six cases, this was possible in the patient group only in two cases, whereas in one patient, data from the FFE sequence and in the other one, data from the SE sequence had to be discarded because of movement artifacts. Thus, patients' data were calculated from three different data sets only.

Comparison of CBF maps did not show any significant difference between patients and controls, neither from FFE nor from SE sequences:  $p > 0.3$  in all cases (see table 1).

**Table 1:** Global CBF of basal ganglia and cortex (in ml/sec/100 g) in patients and controls, as measured by PCASL FFE and SE sequences, and T2\* time of globus pallidus and putamen (in msec)

	Age (years)	CBF Global PCASL FFE	CBF Pallid. PCASL FFE	CBF Put. PCASL FFE	CBF Cortex PCASL FFE	CBF Global PCASL SE	CBF Pallid. PCASL SE	CBF Put. PCASL SE	CBF Cortex PCASL SE	T2* time Pallidum	T2* time Putamen
Patients N=4	14.0 ± 4.55	46.44 ± 5.11	29.56 ± 7.01	60.73 ± 9.32	81.11 ± 14.90	45.00 ± 3.56	32.65 ± 13.81	58.02 ± 13.99	84.39 ± 16.17	18.74 ± 3.36	55.43 ± 3.38
Controls N=6	15.7 ± 4.50	42.26 ± 6.77	33.16 ± 8.18	62.55 ± 11.52	82.47 ± 15.30	40.53 ± 8.81	33.83 ± 9.85	61.60 ± 11.54	87.38 ± 19.33	34.95 ± 6.08	52.45 ± 5.09

We did not see any significant difference between the CBF results obtained from measurements with FFE and from measurements with SE sequences over all participants, which applied to global flow (43.65 vs. 42.02 ml/sec/100g as measured by FFE and SE) as well as to CBF of globus pallidus (31.96 vs. 33.43 ml/sec/100g,  $p > 0.4$ ), and there was no close correlation between CBF of globus pallidus and its T2\* time (Pearson's  $CC = 0.166$  in CBF measured from FFE sequence and  $CC = -0.269$  measured from SE sequence).

**4. DISCUSSION**

The most important result of the present study as seen from the patients' view is that they clearly showed a normal CBF in all measured areas, most notably also in their globus pallidus, as has been measured recently by Hetzer (2018) [12] in 14 normal male volunteers using as well PCASL. In PKAN, globus pallidus is severely affected, being the site of the primary lesion, and later by progressing accumulation of iron deposits. This combination of lesions has been described originally by Hallervorden and Spatz (1922) [13] and later confirmed by pathological and imaging studies [14-16].

Our finding is in contrast to the above-mentioned SPECT study from Doi et al. (2010) [7], who reported decreased CBF "in the bilateral frontoparietal lobes, the globus

This applied as well to CBF of globus pallidus, which amounted to 29.56 (as measured by FFE) resp. 32.65 ml/sec/100g (as measured by SE) in patients and to 33.16 resp. 33.83 ml/sec/100g in volunteers, in spite of the significantly different T2\* time, which -in correspondence to the presence of the "tiger's eye" in all PKAN cases- was 18.74 ± 3.36 msec in patients and 34.95 ± 6.08 msec in healthy controls ( $p < 0.01$ ). The relation of CBF measured from globus pallidus and from putamen was similar as well: 48.3% in patients vs. 53.5% in controls (FFE) and 54.63% in patients vs. 54.16% in controls (SE).

pallidus, the striatum, and around the ventriculus quartus" in two siblings with a novel mutation of the PANK2 gene (Ile346Ser). Because of the different type of mutation and a different clinical course (adult onset and slow progression), the PanK2, the specific isoform of pantothenate kinase involved in PKAN and being localized to mitochondria, might have been affected in a different way in these siblings, with resulting different affection of the globus pallidus. This hypothesis however remains highly speculative because of the lack of further data concerning CBF in PKAN.

The other important finding of our study is the fact that PCASL clearly works in areas of iron accumulation and this technique is not influenced so much by the inhomogeneity of a local magnetic field, neither in its FFE nor in its SE version. Very similar CBF values were recorded from the globus pallidus in spite of the significant difference in T2\* relaxation between patients and controls. This is due to the fact that the CBF calculation is mainly based on the effect of the label pulse [17, 18]. Considering that the label and control images are affected equally by susceptibility provided sufficiently high signal-to-noise ratio, the subtraction of both images cancels the susceptibility effects.

The SE-EPI variant of the PCASL pulse sequence potentially is more robust with respect to artifacts in regions with high susceptibility

which is an important consideration [19] for the choice of the most adequate acquisition technique.

## 5. CONCLUSION

This pilot study showed for the first time that CBF appears to be normal in patients suffering from PKAN dystonia, including their basal ganglia, and that measurement of CBF using PCASL can be applied successfully in areas of brain iron accumulation. Our results have to be confirmed by a prospective project including more patients and volunteers.

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