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# **PET Study of Microglial Activation in Kleine-Levin Syndrome**

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# Abstract

## Objectives:

Kleine-Levin syndrome (KLS) is a rare recurrent hypersomnolence disorder associated with cognitive and behavioral disturbances, of unknown origin, but inflammatory mechanisms could be involved. We aimed to explore in vivo microglia activation using [<sup>18</sup>F]DPA-714 PET imaging in patients with KLS compared with controls, and during symptomatic vs asymptomatic periods.

## Methods:

Patients with KLS and controls underwent a standardized clinical evaluation and PET imaging, using a radiolabeled ligand specific to the 18 kDa translocator protein. Images were processed on the PMOD (peripheral module) interface using a standard uptake value (SUV). Five regions of interest (ROIs) were analyzed: hypothalamus, thalamus, frontal area, cerebellum, and whole brain. SUV ratios (SUVr) were calculated by normalizing SUV with cerebellum uptake.

## Results:

Images of 17 consecutive patients with KLS (7 during episodes, 10 out of episodes) and 14 controls were analyzed. We found no SUV/SUVr difference between KLS and controls, between patients in and out episodes in all ROIs, and no correlation between SUVr and episode duration at the time of PET scan. No association was found between SUVr and sex, disease duration, or orexin levels.

## Discussion:

Our findings do not support the presence of neuroinflammation in KLS. Further research is needed to identify relevant biomarkers in KLS.

# Introduction

Kleine-Levin syndrome (KLS) is a rare disease characterized by recurrent-remittent episodes of hypersomnia associated with behavioral disturbances, cognitive abnormalities, eating disorder, and hypersexuality.<sup>1</sup> The diagnosis relies on clinical symptoms only, and the underlying pathophysiology remains unknown. Some authors suggested a recurrent primary hypothalamic dysfunction, mediated by inflammatory mechanisms.<sup>2</sup> The hypothalamus plays critical roles in wakefulness maintenance, feeding behavior, neuroendocrine, and autonomic functions.<sup>3</sup> Postmortem studies are scarce, with signs of encephalitis in thalamic/hypothalamic regions detected in 2 patients.<sup>2</sup> Microglial activation is often associated with neuroinflammation, as reported in multiple sclerosis (MS).<sup>4</sup> Mitochondrial 18 kDa translocator protein (TSPO) is one of the few available biomarkers of neuroinflammation for which there are clinically available PET imaging agents.<sup>5</sup> TSPO is highly expressed in the mitochondria of microglia and astrocytes, and neuroinflammation is associated with increased levels of TSPO and binding sites for TSPO ligands.<sup>5,6</sup> [<sup>18</sup>F]DPA-714 is a ligand used for in vivo imaging PET scan, often used in brain disorders, as a sensitive target for imaging microglial/macrophage cell density.<sup>4,6</sup>

We hypothesized that microglial activation is increased in KLS compared with controls and greater in patients during symptomatic than asymptomatic periods. We explored microglia density using brain [<sup>18</sup>F]DPA-714 PET in patients with KLS compared with controls and studied the links between microglia density in regions of interest (ROIs) and clinical characteristics of KLS.

## Methods

### Participants, Design

Seventeen consecutive drug-free patients with KLS, diagnosed according to ICSD-3 criteria<sup>1</sup> at a National Reference Center for Rare Hypersomnias in Montpellier-France, were included from January 2020 to November 2021. Seven patients were included during an episode (10[4–28] days since episode onset) and 10 outside (361.5[49–1,518] days postepisode). They were hospitalized for clinical assessment, blood testing, video-polysomnography, and PET imaging. Eight patients had a lumbar puncture to measure CSF orexin-A levels. Seventeen controls with normal neurologic examination, no history of inflammation, neurologic, or psychiatric disorder were recruited during the same period, with blood testing and PET imaging. None of participants took immunomodulatory, anti-inflammatory, or any CNS drug.

### Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by French ethics committees (EudraCT 2018-001584-23 CPP18032). Each subject provided written informed consent, and both parents for minors.

## TSPO Genotyping, Brain Imaging

The affinity for TSPO is determined by the rs6971 single-nucleotide variant in the TSPO gene.<sup>7</sup> Thus, its genotyping was performed by the PCR reaction followed by DNA sequencing (3130xl, Thermo Fisher Scientific). Individuals were categorized as TSPO high-affinity (HAB; C/C genotype), mixed-affinity (MAB; C/T), or low-affinity (LAB; T/T) binders. LAB participants were further excluded.

The methods of image processing and analyses have been described in detail elsewhere.<sup>8</sup> The PET scan was performed after 3.5MBq/kg IV injection of [<sup>18</sup>F]DPA-714. Five ROIs were analyzed: hypothalamus, thalamus, frontal areas, cerebellum, and whole brain. The standard uptake value (SUV) ratio (SUVR) is the SUV of interest divided per the cerebellum SUV, in line with studies using the cerebellum as a pseudoreference region.<sup>2</sup> Sixteen patients and 9 controls also underwent brain MRI. Data imaging analysis was performed twice, using PMOD (Technologies Ltd) and transformed in the Montreal Neurologic Institute space, by 2 investigators blinded of the diagnosis, to confirm the concordance of the results.

## Statistics

Categorical variables were described by numbers/percentages, continuous variables by means/SD. The Mann-Whitney test compared continuous variables, Chi-square or Fisher exact test categorical data between controls and KLS. False discovery rate (FDR) correction was applied for multiple comparisons of SUVs and SUVRs. Spearman rank order correlations determined associations between continuous variables. Analyses were conducted using SAS (9.4), with a significant level at  $p < 0.05$ .

## Data Availability

Anonymized data will be shared by reasonable request from any qualified investigator.

## Results

The brain imaging [<sup>18</sup>F]DPA-714 PET data of all 17 patients ( $20.3 \pm 3.4$  yo, 10-HAB/7-MAB) and 14 controls ( $23.4 \pm 0.2$  yo, 6-HAB/8-MAB) were finally analyzed. Three controls were excluded: 1 TSPO-LAB and 2 because of technical imaging issues. Sex, BMI, and proportion of HAB participants did not differ between patients and controls, but patients were younger ( $p = 0.03$ ). Age, sex, and BMI were not different among HAB (10 KLS vs 6 controls) and MAB (7 KLS vs 8 controls) participants. KLS and severity are described in [Table 1](#).

**Table 1** Characteristics of Patients With Kleine-Levin Syndrome (KLS) and Controls With PET Imaging

	Patients with KLS N = 17		KLS with PET during a symptomatic episode N = 7		KLS with PET during an asymptomatic period N = 10		Controls N = 14	
	n	%	n	%	n	%	n	%
<b>Sex, female</b>	7	41.18	2	28.57	5	50.00	7	50.00
<b>Age, y<sup>a</sup></b>	20.34 ( $\pm$ 3.43)		20.33 ( $\pm$ 2.95)		20.34 ( $\pm$ 3.89)		23.38 $\pm$ 4.21	
<b>BMI, kg/m<sup>2a</sup></b>	23.48 ( $\pm$ 4.67)		20.82 ( $\pm$ 3.17)		25.35 ( $\pm$ 4.76)		22.58 $\pm$ 2.47	
<b>TSPO binding</b>								
<b>High (HAB)</b>	10	58.82	5	71.43	5	50.00	6	42.86
<b>Mixed (MAB)</b>	7	41.18	2	28.57	5	50.00	8	57.14
<b>Disease symptoms and severity</b>								
<b>Age at first episode of KLS, y.o.</b>	15.82 ( $\pm$ 2.81)		15.57 ( $\pm$ 1.62)		16.00 ( $\pm$ 3.50)			
<b>Age at diagnosis, y.o.</b>	17.68 ( $\pm$ 3.95)		17.14 ( $\pm$ 3.13)		18.05 ( $\pm$ 4.56)			
<b>Duration of evolution of KLS at the time of PET, y</b>	4.51 ( $\pm$ 2.45)		4.76 ( $\pm$ 2.96)		4.34 ( $\pm$ 2.18)			
<b>Number of KLS episodes before the PET scan (lifetime)</b>	10.82 ( $\pm$ 8.86)		12.71 ( $\pm$ 10.63)		9.50 ( $\pm$ 7.72)			
<b>Mean duration of KLS episodes, d</b>	14.56 ( $\pm$ 10.03)		12.83 ( $\pm$ 10.24)		15.77 ( $\pm$ 10.25)			
<b>Ratio KLS episodes/year</b>	2.94 ( $\pm$ 1.90)		3.27 ( $\pm$ 1.68)		2.70 ( $\pm$ 2.10)			
<b>Symptomatology during most episodes<sup>b</sup></b>								
<b>Cognitive dysfunction, yes</b>	16	94.12	6	85.71	10	100.00		
<b>Altered perception, yes</b>	13	76.47	6	85.71	7	70.00		
<b>Eating disorder, yes</b>	13	76.47	6	85.71	7	70.00		
<b>Disinhibited behavior, yes</b>	5	29.41	2	28.57	3	30.00		
<b>CSF orexin levels, pg/mL</b>								
<b>During an episode</b>	7; 213.57 ( $\pm$ 62.87)		4; 195.75 ( $\pm$ 33.19)		3; 237.33 ( $\pm$ 93.4)			
<b>Out of an episode</b>	3; 292.37 ( $\pm$ 67.45)		1; 292		2; 292.55 ( $\pm$ 95.39)			

Abbreviations: BMI = body mass index; KLS = Kleine-Levin syndrome; TSPO = 18 kDa Translocator Protein.

<sup>a</sup> Continuous variables are expressed as means ( $\pm$ SD).

<sup>b</sup> Assessed by medical interview, according to ICSD-3 criteria.

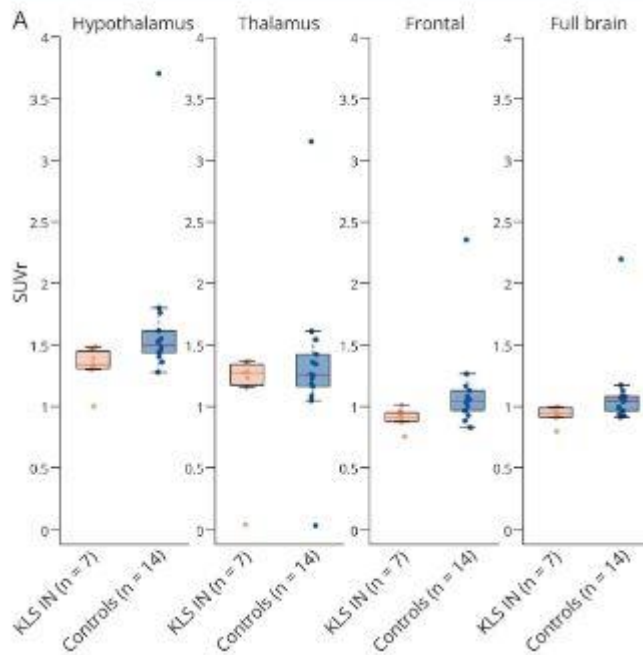
[<sup>18</sup>F]DPA-714 binding (SUV/SUVr) in the hypothalamus and thalamus did not significantly differ between KLS and controls, nor in other ROIs (Table 2). Based on TSPO binding affinity, no SUV/SUVr differences were found in any ROIs, between HAB or MAB KLS patients and controls, independently. We compared 7 patients with KLS during symptomatic episodes and controls, with no SUV/SUVr differences in none of ROIs (Figure, A). No correlation was found between SUV/SUVr in the different ROIs and duration of the episode at the time of PET scan in symptomatic patients. We also compared asymptomatic patients with KLS (n = 10) vs controls (n = 14), asymptomatic (n = 10) vs symptomatic patients (n = 7), and found no SUV/SUVr differences in the hypothalamus, thalamus, or other ROIs (Figure, B). We further analyzed the subsample of HAB patients during asymptomatic and symptomatic periods (5 vs 5) and confirmed the absence of difference. Finally, no association was found between SUVr and sex, age at disease onset, disease duration, or orexin levels in the different ROIs in patients with KLS.

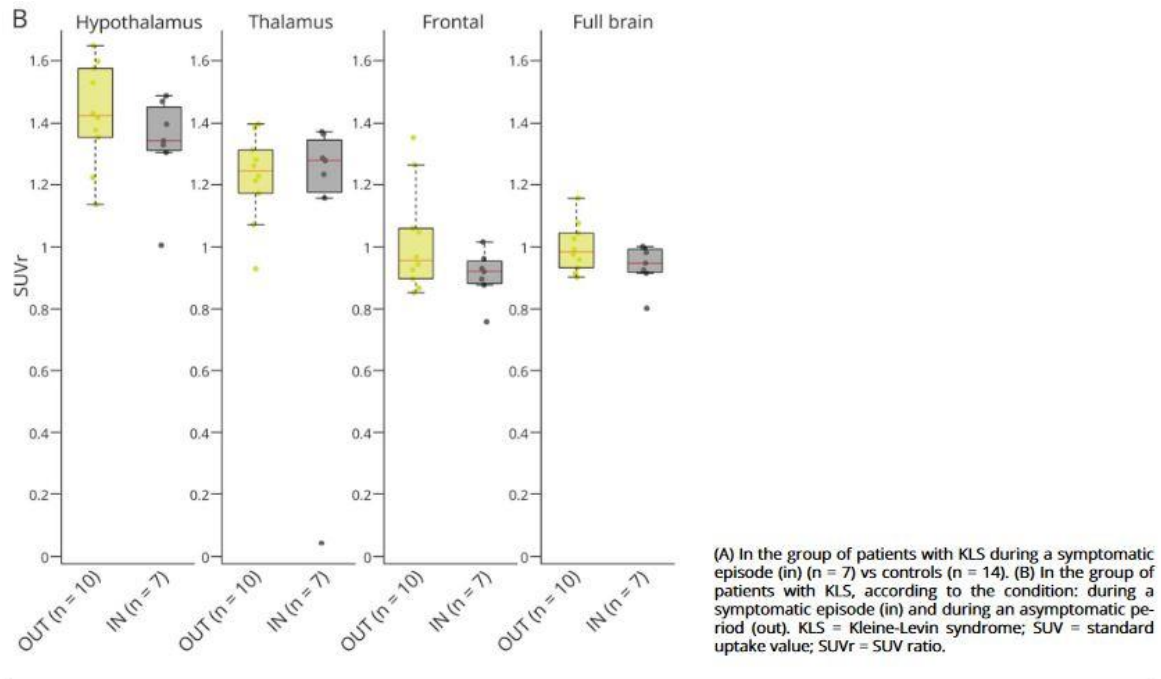
**Table 2** [<sup>18</sup>F]DPA-714 Standard Uptake Value (SUV) and SUV Ratio (SUVR) Data in Patients With KLS and Controls According to Anatomical Regions

	Whole population			High TSPO binders (HAB)			Mixed TSPO binders (MAB)		
	KLS N = 17	Controls N = 14	p Value <sup>a</sup>	KLS N = 10	Controls N = 6	p Value <sup>a</sup>	KLS N = 7	Controls N = 8	p Value <sup>a</sup>
<b>SUV</b>									
Hypothalamus	1.120 (±0.248)	1.163 (±0.315)	0.89	1.172 (±0.298)	1.391 (±0.356)	0.45	1.046 (±0.141)	0.991 (±0.124)	0.83
Thalamus	1.018 (±0.264)	1.00 (±0.313)	0.80	1.099 (±0.318)	1.212 (±0.376)	0.72	0.902 (±0.089)	0.841 (±0.119)	0.83
Frontal	0.780 (±0.157)	0.793 (±0.255)	0.89	0.818 (±0.175)	0.92 (±0.341)	0.72	0.726 (±0.118)	0.698 (±0.116)	0.97
Cerebellum	0.809 (±0.162)	0.736 (±0.24)	0.18	0.869 (±0.19)	0.84 (±0.345)	0.78	0.723 (±0.041)	0.657 (±0.073)	0.54
Whole brain	0.783 (±0.149)	0.786 (±0.234)	0.80	0.831 (±0.175)	0.917 (±0.305)	0.87	0.715 (±0.065)	0.689 (±0.098)	0.92
<b>SUVR</b>									
Hypothalamus	1.389 (±0.165)	1.670 (±0.603)	0.15	1.344 (±0.103)	1.880 (±0.905)	0.27	1.454 (±0.22)	1.513 (±0.155)	0.99
Thalamus	1.175 (±0.315)	1.338 (±0.641)	0.80	1.253 (±0.133)	1.619 (±0.769)	0.67	1.065 (±0.462)	1.127 (±0.471)	0.97
Frontal	0.972 (±0.147)	1.126 (±0.372)	0.15	0.946 (±0.116)	1.214 (±0.569)	0.45	1.065 (±0.462)	1.127 (±0.471)	0.83
Whole brain	0.973 (±0.079)	1.113 (±0.322)	0.15	0.959 (±0.052)	1.201 (±0.494)	0.45	0.992 (±0.109)	1.047 (±0.083)	0.83

Abbreviations: BMI = body mass index; KLS = Kleine Levin syndrome; SUV = standard uptake value; SUVR = SUV ratio; TSPO = 18 kDa translocator protein.  
<sup>a</sup>Crude association (nonparametric test), with FDR correction for SUV and SUVR data.

**Figure** Box Plot Representation of Global and Regional [<sup>18</sup>F]DPA-714 Standard Uptake Value Ratio (SUVR) Data





## Discussion

We explored the neuroinflammation *in vivo* in patients with KLS and found no increased microglia density using the [<sup>18</sup>F]DPA-714 PET, during symptomatic episodes compared with asymptomatic periods and with controls.

In recent years, molecular imaging advancements have shed new light on neuroinflammatory processes in neurologic disorders.<sup>4,6,9</sup> A recent PET study using the same [<sup>18</sup>F]DPA-714 TSPO ligand revealed increased binding in patients with MS, correlating with disease severity.<sup>4</sup> By contrast, our findings did not support the presence of neuroinflammation in KLS, with similar findings reported recently in narcolepsy type 1, another rare hypersomnolence disorder.<sup>8</sup>

The mechanisms of KLS are unknown, but inflammatory hypotheses have been suggested. Episodes are often triggered by infections, and postmortem signs of encephalitis were reported,<sup>2</sup> decreased activity in hypothalamic/thalamic areas in SPECT,<sup>2</sup> and mild decreased CSF orexin-A levels during episodes,<sup>10,11</sup> and key changes in CSF proteins during KLS symptomatic episodes belong to the microglial-monocyte-macrophage axis.<sup>12</sup> Another recent study suggested links between KLS, circadian regulation, and bipolar disorder, and indicated that the *TRANK1* polymorphisms may predispose to KLS.<sup>13</sup>

Despite the common belief that increased TSPO expression indicates proinflammatory microglial activation (in rodents), it does not consistently increase in activated human microglia *in vitro*.<sup>14</sup> Although the TSPO signal is linked to microglia in active lesions, its expression could reflect cell density rather than cell activation. TSPO seems not exclusive to proinflammatory microglia but is also present in reparative microglia, suggesting a diversity



of microglial responses.<sup>15</sup> However, nowadays, no PET tracer is sensitive enough to differentiate between microglial proinflammatory and neuroprotective activation.

A limitation of our study is the low number of patients. As KLS is an extremely rare disease, the inclusion of patients was a real challenge, especially during symptomatic episodes being unpredictable. Extensive procedures during hospitalization are difficult to perform during KLS crisis. Due to this small sample size, we could not adjust the results for age nor categorize symptomatic patients according to TSPO-binding affinity. Images were processed twice, by 2 investigators blinded to the condition, confirming the findings concordance. The hypothalamus is a particularly small structure, delineated manually, but we also analyzed larger areas, the thalamus encompassing the hypothalamus.

To conclude, we explored for the first time microglial density in vivo in the brain of patients with KLS, in and out of episode, compared with controls, and found no increase in microglial density. These unexpected findings do not support the presence of neuroinflammation in KLS pathophysiology. Further research is needed to identify reliable biomarkers in KLS.

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<b>Isabelle Jausset, PhD</b>	Institute of Neurosciences of Montpellier, University of Montpellier, INSERM, France	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data

## Appendix *(continued)*

<b>Name</b>	<b>Location</b>	<b>Contribution</b>
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<b>Pierre Payoux, MD, PhD</b>	ToNIC, Toulouse Neuroimaging Center, UMR 1214, INSERM, Université Paul-Sabatier; Nuclear Medicine Department, CHU Toulouse, France	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
<b>Yves Dauvilliers, MD, PhD</b>	Sleep-Wake Disorders Unit, Department of Neurology, Gui-de-Chauliac Hospital, CHU Montpellier; National Reference Centre for Orphan Diseases, Narcolepsy, Idiopathic Hypersomnia, and Kleine-Levin Syndrome, Montpellier; Institute of Neurosciences of Montpellier, University of Montpellier, INSERM, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data