



# Significance of Cortical Micro-Infarcts in the Human Brain

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## Abstract

Cortical micro-infarcts are due to cerebral small vessel disease. In contrast to the arteriosclerotic type of cerebral small vessel disease, cortical micro-infarcts are mainly related and due to cerebral amyloid angiopathy. Alzheimer's disease is the most frequent neurodegenerative dementia disease associated to cerebral amyloid angiopathy and cortical micro-infarcts. Vascular dementia cannot only be due to lacunar infarcts and ischemic white matter changes, but can also be caused by cortical micro-infarcts. The latter are a frequent cause of vascular dementia and decrease globally the cerebral blood flow.

**Keywords:** Cortical micro-infarcts, Cerebral amyloid angiopathy, Cerebral small vessel disease, Alzheimer's disease, Frontotemporal lobar degeneration, Lewy body disease, Progressive supranuclear palsy, Vascular dementia.

**Abbreviations:** CSVD, Cerebral Small Vessel Disease; CoMIs, Cortical Micro-Infarcts; VAD, Vascular Dementia; MRI, Magnetic Resonance Imaging; CAA: Cerebral Amyloid Angiopathy; AD: Alzheimer Disease; LBD: Lewy Body Disease; FTL: Frontotemporal Lobar Degeneration; PSP: Progressive Supranuclear Palsy

## Introduction

CoMIs should best be defined as ischemic necrosis in the territory of a single cortical penetrating vessel.<sup>1</sup> The arterial angioarchitecture of the cerebral cortex is composed of perforating branches of different sizes: short-sized cortical branches ending in the superficial layers, middle-sized branches ending in the third and fourth layers and cortico-medullary branches ending in the deep cortical layers and in the sub cortical white matter.<sup>2</sup> The size and the location of the CoMIs will depend on which type of branches that was occluded. The lesion size varies from 0.5mm to less than 2.0mm, according to different neuropathological studies.<sup>3</sup> CoMIs could be considered as a CSVD comparable to arteriosclerotic type with lacunar infarcts, cerebral micro-bleeds and white matter changes.<sup>4</sup> However atherosclerosis can also be a cause of CMIs with a recurrence rate of 6.7%.<sup>5</sup> CSVD is the best predictor of vascular cognitive impairment leading to vascular VaD.<sup>6</sup>

However, CoMIs are considered as invisible lesions and undetectable in clinical-radiological correlation studies that rely on conventional structural MRI.<sup>7</sup> They are also nearly visible on naked eye inspection of post-mortem brains and best detected by light-microscopic examination.<sup>8</sup> Only post-mortem macroscopic and microscopic examination together with 7.0-tesla MRI detected cortical high-intensity lesions are the most reliable methods to evaluate their incidence and distribution.<sup>9</sup> However, in vivo detection of CMIs can now be obtained with 7.0-tesla MRI, which is more sensitive<sup>10</sup> than the generally used 1.5 and 3.0-tesla ones.<sup>11</sup> The present review will mainly cover data concerning post-mortem histological confirmed CMIs and their detection with 7.0-tesla MRI of cerebral and cerebellar sections.<sup>12</sup>

## Cortical Micro-Infarcts

In normal brains of middle-aged and elderly persons CoMIs are rarely observed, compared to the increasing number of cortical

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micro-bleeds and the severity of the white matter changes during the aging process.<sup>13</sup> CoMIs are significantly prevalent in brains with neurodegenerative and cerebrovascular diseases mainly associated to CAA. Most CoMIs involve to a different degree the cortical layers according to the length of the occluded penetrating branch. In AD and in VAD all cortical layers are concerned. In LBD, on the other hand, the CoMIs are restricted to the deep cortical layers.<sup>14</sup> CoMIs are mostly present in the pre-frontal and post-central cerebral sections in VAD, while no differences in topography are observed in AD and LBD brains.<sup>15</sup> CAA is frequently associated to AD but only the severe forms display more CoMIs. LBD is the second most common disease associated to CAA and CoMIs.<sup>16</sup>

CoMIs appear to be a very common vascular co-morbidity in brains with spontaneous intracerebral haemorrhage.<sup>17</sup> Also in pure CAA brains without AD, CoMIs are more frequent and mainly involve the central and the occipital sections compared to brains with AD.<sup>18</sup> FTLN shows only a limited number of CoMIs, with a similar incidence as in normal control brains.<sup>19</sup> The number of CoMIs is also low in brains with LBD without CAA.<sup>20</sup> The incidence of CoMIs in PSP brains with CAA is as low as in those without CAA.<sup>21</sup> VAD can be due to arteriosclerotic CSVD but also caused by CAA. While lacunar infarcts and ischemic white matter changes are the main post-mortem observed lesions in the former, CoMIs can also be responsible for VAD due to CAA. In our post-mortem study we observed that the frequency of brains with VAD, due to CoMIs, was similar to the incidence caused by arteriosclerotic CSVD.<sup>22</sup>

Mixed dementias have a higher incidence of CoMIs than single neurodegenerative diseases. They are mostly due to an association of AD and LBD features with cerebrovascular lesions, mainly due to CAA.<sup>23</sup> However, the incidence of CoMIs in AD brains with associated to LBD pathology but without CAA is lower than in the pure AD brains.<sup>24</sup> CoMIs predominate in the occipital lobes in mixed dementias compared to their prevalent location in the frontal lobes and cerebellum of CAA-related VAD brains.<sup>25</sup> Cerebellar CoMIs are in contrast to cerebral ones not related to CAA, but mainly due to arteriosclerotic cerebrovascular disease in VAD as well as in the different neurodegenerative diseases.<sup>26</sup>

## Conclusion

CoMIs are mainly related and due to CAA and to a lesser degree to arteriosclerosis. AD is the most frequent neurodegenerative disease with associated CAA-related CoMIs.<sup>27</sup> Some neurodegenerative diseases, mainly part of the Pick's complex diseases, such as the Tau type of FTLN, PSP and corticobasal degeneration, have a favourable vascular profile with a very low or even absent incidence of CoMIs.<sup>28</sup> VAD is not exclusively due to lacunar infarcts and ischemic white matter changes, but can also to a large extent be due to CAA and CoMIs.<sup>22</sup>

CoMIs have to be distinguished from atypically shaped perivascular spaces on 7.0-tesla MRI. Their features are similar to gliotic CoMIs with and without cavitation, but these "CoMI mimics" are always located sub cortically in the U-fibres.<sup>29</sup> CoMIs at baseline are associated with accelerated decline in memory and language domains.<sup>30</sup>

In memory clinic patients they are primarily responsible for a global reduction in cerebral perfusion.<sup>31</sup> In summary, CoMIs are important lesions, contributing to vascular cognitive decline, leading to dementia.

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## Conflicts of interest

Author declares that there is no conflict of interest.

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