CHARLES UNIVERSITY IN PRAGUE

THIRD FACULTY OF MEDICINE

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"The extent of calcification in cerebral arteries in correlation to age"

Diploma thesis

Prague, August 2010

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Master's programme of study

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Date and year of defence: August 2010

Written Declaration

I declare that I completed the submitted work individually and only used the mentioned sources and literature. Concurrently, I give my permission for this diploma/bachelor thesis to be used for study purposes.

Prague, August 2010

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BACKGROUND AND PURPOSE

It is a common experience of radiologists that the density of organs is changing during our life. This phenomenon is especially conspicuous as a decreasing density of bones, defined either as diffuse osteoporosis, or in more focal appearance as osteomalacia.

On the other hand we can observe an increasing density of the vascular wall with aging. One of the most influential elements is Calcium (Ca2+). We were attracted by these moves of Calcium, being washed out from the bones and being washed in into the vessel wall.

I have carried out an analysis of the intensity of vascular Calcium deposits in two different regions of the body. The abdominal aorta was investigated in 25 patients of which 13 were women and 12 were man, and cerebral arteries were investigated in 23 ischemic stroke patients of which 13 were women and 10 were male.

Previous studies on cerebral arteries have suggested that predilection for sites for atherosclerosis include the bifurcations of the common carotid artery, the sinus portion and the curved terminal part of the ICA and the proximal part of the VA. Most of the time, routine brain CT miss these sites, unless they are intensive. For these reasons only large and highly calcified plaques are detectable on brain CT. (7).

Other studies have also been carried out in order to analyse the progression of Aortic calcification during menopause. It has been found that progression of atherosclerotic calcification is associated with increase bone loss in women during menopause (1).

The best available method of measuring Calcium content in vivo is using the attenuation effects of hard minerals on the transmission of X-rays through the tissue.

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1.0 Introduction

The work, which has led up to this project

1.1 Calcium

Calcium (Ca 2+) is an important cation with its normal concentration of 2.4 mmol/l. It plays a key role in many physiologic processes, including signal transduction pathways where it acts as a second messenger. Its presence is also necessary for muscle contraction (skeletal, cardiac and smooth muscles), for blood clotting as well as for transmission of nerve impulses where neurons are very sensitive to changes in calcium concentration. This I will mention later.

Therefore the precise control of calcium is very essential. An important feature of extracellular calcium regulation is that only 0.1 per cent of the total body calcium is in the extracellular fluid, about 1 per cent is in the cells of the body and about 99 per cent comprised in the body is deposited in the bones and teeth.

Bone being a major storage of calcium ions, is basically dependent from Calcium resorption and secretion which is extensively regulated by hormones (mentioned later). Calcium exists in three forms; 41 per cent is protein-bound (1.0 mmol/l), 9 per cent calcium dwells in complex

with anions (0.2 mmol/l) and 50 per cent presents the ionized calcium (1.2 mmol/l). The latter being the most important in the heart, nervous system and bone formation.

Hormones such as parathyroid hormone, vitamin D, and calcitonin regulate calcium absorption and excretion, **fig 1.1**.

Parathyroid hormone is a hormone secreted by the parathyroid glands located behind the thyroid gland. It regulates the resorption of calcium from the bone; its reabsorption in the kidney back into the circulation is stimulated by the activation of **vitamin D3** to calcitriol and the latter hormone is responsible for the absorption of calcium from the intestines and the mobilization of calcium ions from the bone matrix.

In increased calcium concentrations another hormone must oppose the effects of parathyroid hormone; this hormone is known as **calcitonin,** and is secreted by the parafollicular cells of the thyroid gland.

In certain disorders that affect the balance between calcium and other minerals or chemicals in the body, calcium can be deposited in other parts of the body such as arteries (arteriosclerosis), kidneys, lungs, and brain (**Fahr's disease**).
Calcium deposits in these parts of the body can cause problems, influencing how these blood vessels and organs work.

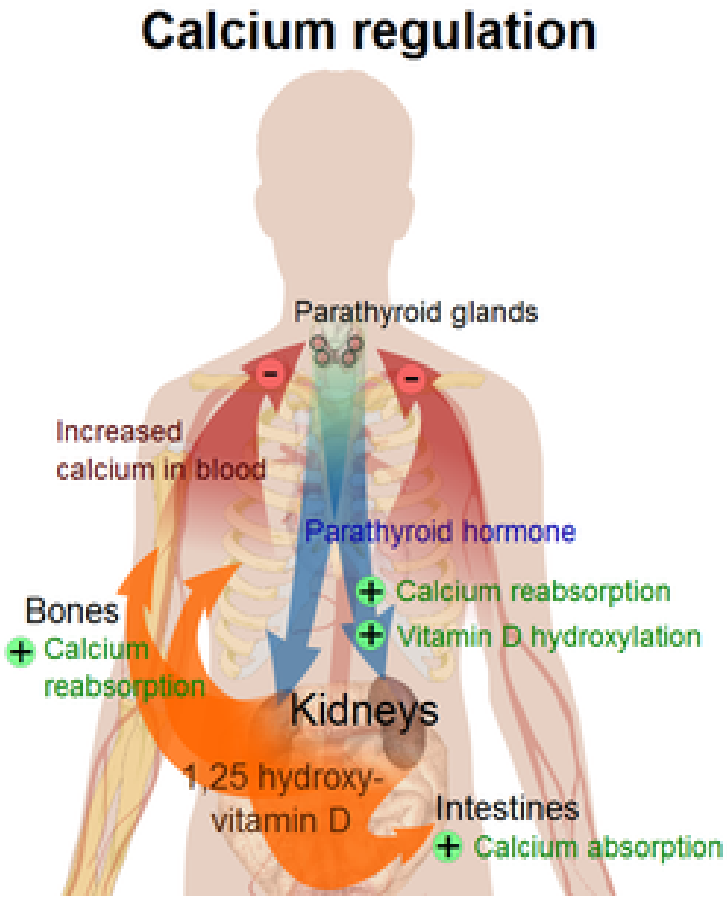

Fig 1.1 ***calcium regulation***

1.2 Calcification

..... It is a precipitation of calcium salts in tissues. It is normal in bone. Under abnormal conditions it can build up within the arteries, where it causes rigidity of the vessel.

Calcifications may be classified on whether there is mineral balance or not, and according to the location of the calcification. Two forms are seen:

- Dystrophic calcifications and Metastatic calcifications. Calcifications are present in the skeleton and pathologically in extraskeletal tissues and the brain.

Sometimes calcium can be deposited in the cerebral parenchyma itself and this rare condition is known as **Fahr disease**; this is a genetically dominant condition in which calcifications are seen in the basal ganglia.

Calcifications can be seen on X-rays as well as on computer tomography (CT).

Previous studies have shown that arterial calcification accompanies atherosclerosis. Two different layers in the vessel wall are prominently involved: the intima and the media. Intimal calcifications occur exclusively within the atherosclerotic plaques, while medial calcifications may develop independently *(7).*

So far calcifications of cerebral arteries has been understudied, in our study we evaluated the density of calcium within the cerebral arteries on brain CT of ischemic stroke patients as well as calcifications in abdominal aorta of different age groups.

1.3 Atherosclerosis

As its name indicates it is a disease of arteries, characterized by the presence of degenerative and proliferative alterations that lead both to the thickening and rigidity of the vessel wall on one side and to the formation of atheromas on the other. Usually it involves the intermediate sized arteries in which fatty lesions known as atheromatous plaques develop on the inside surface of the arterial walls, (**fig 1.3)**. Usually these plaques begin with the deposition of crystals of cholesterol in the intima and sub lying smooth muscles, and as the disease progresses more cholesterol crystals are deposited within the vessel wall accompanied by the proliferation of the surrounding fibrous and smooth muscle tissues. Thus larger plaques can be formed leading eventually to a total vessel occlusion and sclerosis.

In addition as the disease progresses “calcium salts often precipitate with cholesterol and other lipids of the plaques leading to bony-hard calcifications that make arteries at times rigid tubes” (*2*)

Affected arteries usually suffer ruptures due to the loss of their distensibility and elasticity. In the degenerative areas, where the plaques protrude into the blood, blood clots are more likely to develop a resultant thrombosis. In case of thrombus deliberation the embolus moves with the blood stream into the periphery and finally occludes the lumen of an artery. This mechanism is one of the most important causes of cerebral stroke.

We can clearly see how calcifications accompany the process of atherosclerosis.

So far the most important factor contributing to atherosclerosis is a high blood concentration of cholesterol in the form of low density lipoproteins. Other factors include diabetes mellitus, hypothyroidism and smoking.

Preventive measures should be considered to avoid this development and progression of the disease.

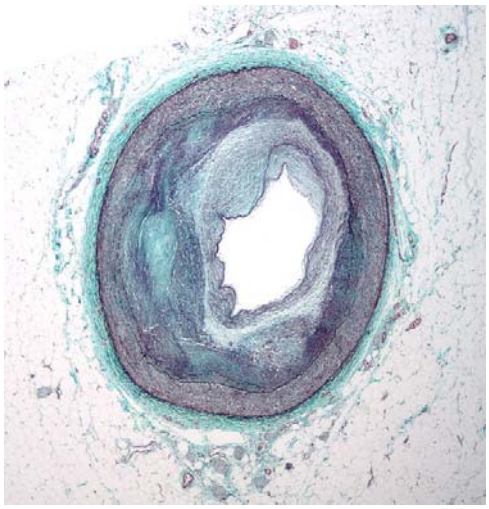

Fig 1.3 ***An atherosclerotic artery***

1.4 Arterial calcification

An arterial calcification consists mainly of calcium apatite. It takes place in two layers in the vessel wall; the intima and the media **fig 1.4**.

In case of a bone calcification, osteoblasts supposedly also secrete a substance into the osteoid to neutralize an inhibitor known as pyrophosphate that normaly prevents the crystallization of salts. However in abnormal conditions where calcium is being deposited in vessels, this inhibitor factor disappears from the tissue allowing the precipitation to occur. (*2*).

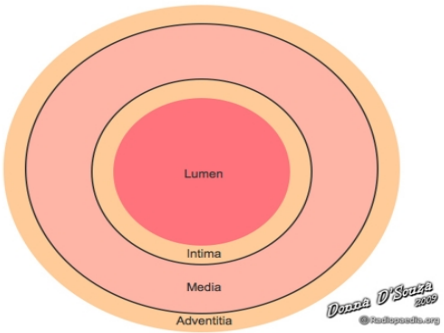

Fig 1.4 ***arterial layers***

Intimal calcifications occur exclusively within advanced atherosclerotic plaques, associated with lipid, macrophages and vascular smooth muscle cells.

Calcification of the tunica media, also known as Monckeberg's sclerosis may be present independently of atherosclerosis and is associated with elastin and vascular smooth muscle cells *(7)*.

Cerebral arterial calcifications have been understudied although frequently seen on brain CT. Therefore we investigated the density of calcium within the cerebral arteries and descending aorta in correlation to age.

2.0 Introduction and Aims of the Study

The aim of this project was to analyse the extent of calcification within the cerebral arteries and to evaluate its correlation with age, and on the other side we also evaluated calcifications within abdominal aorta and the density of sacrum in order to orient ourselves.
Calcifications can be best studied by Computer Tomography (CT).

The density of organs in Computed Tomography is dependent from the content of chemical elements with high atomic number in the tissue. Density is defined in Hounsfield units (Godfrey Hounsfield – discoverer of the CT). The CT convention attributes a zero density to water, - 1000 Hounsfield units (HU) and + 1000 HU to the compact bone. Values over + 1000 in the routine measurements are not reliable. Neurological CT takes advantage of tiny differences in density of normal and abnormal tissues: The cerebrospinal fluid (CSF), similar to water, has usually 0 – 3 HU, cerebral white matter around 28-32 HU, and the gray matter 32 – 36 HU. Pure fat is below zero, having – 150 HU, fatty tissue with a component of fibrous structures has about – 100 HU. Blood with its haemoglobin content of erythrocytes within the surrounding plasma has a density higher than the brain, namely around 50-55 HU, but the clotted blood in haematomas, with its haematocrit of 100 achieves values of 80 – 85 HU. These values are given here in order to allow comparison of our vascular wall densities.

In the diagnostics of stroke in its hyperacute stage usually no CT signs in the tissue can be distinguished. This is caused by the fact, that any therapeutical measures in stroke can be effective only if administered with an utmost urgency. According to the doctrine “Time is brain”, the modern service hurries up to bring the patient to hospital as quickly as possible. The most effective treatment, the thrombolysis is presently limited to the time interval of 4,5 hours, but its effectivity decreases substantially with any interval from the onset of the stroke.

Therefore the majority of patients are admitted in a phase still void of any apparent lesion on CT. The maturation of the lesion to visualized stages takes hours and days. Consequently any tiny changes serving to recognize the infarcted area are welcome and eagerly looked for. Among them an important role plays the so called “High density sign (HDS)” or “hyperdense middle cerebral artery” sign. It is believed, that a thrombus in the artery, causing its occlusion, increases the density of the initial horizontal segment of the middle cerebral artery (MCA). However, the power of the clotted blood in the thrombus has no more effect on the density, as some 60 – 70 HU. Providing, that the vessel wall would be calcified, much more intensive density increments would arise: hundreds of HU. Therefore even the low contents of Ca in this segment could mimick the thrombosis of MCA and lead to false conclusions.

Fig 2.1 Calcification of the horizontal segment of Middle cerebral artery (MCA) on the right. Potential source of mimicking the High density sign, produced by a thrombus.

Calcifications in the brain can appear also in extravascular places. Physiologic calcifications occur in the pineal gland. The so called “acervulus cerebri” means growing deposits of calcium in the pineal during life. Physiologic calcification is also a growing calcium content in choroid plexuses. Relatively rare is precipitation of calcium in the parenchyma itself. Most known is its collection in basal ganglia, known as “Morbus Fahr” or Fahr disease **(Fig 4.2).** Otherwise calcifications are found in pathological tissues, like meningiomas, arteriovenous malformations, neurofibromas or hamartomas.

3.0 Methods and Materials

In order to orient ourselves, two different cohorts of individuals were analysed; first we looked at how calcifications looked like in abdominal aortas and then we continued with the analysis of cerebral arteries in patients with cerebral stroke.

3.1 Measurement of aortic calcification

We have recruited the patients for the aorta analysis randomly from a CT database of our radiological departments, between the years of 2009 and 2010.

1/ CT axial scans of 25 random patients (12 men and 13 women) examined for various diseases in the abdominal region were picked up. The individuals were divided into groups of different age, mean age: 34 (range 30-38) for the younger group, 55 (range 52-57) for the middle age group and 70 (range 61-84) for the elderly group. All the scans crossing the abdomen were evaluated in regard to the density of the aorta. Hyperdense segments of the aorta were measured by the density probe in individual voxels of the calcification **(Fig 3.1)**. The highest numbers were registered in order to realize the highest possible content of

Calcium (**Table 1)**. The values were compared with the same measurements in the pedicles of the vertebras, or with the density of the sacrum. The selected locations in the skeleton were chosen with the intention to have a compact bone for comparison.

3.2 Measurement cerebral arteries calcification.

The total number of patients planned for analysis was 30. However I could collect only 23 patients as data of patients were missing.

2/ CT axial scans of 23 stroke patients (10 men and 13 women) were collected from the Department of Neurology of our Hospital. All these patients had their examination on their admission for stroke between 2009 and 2010. Calcifications on the vertebral arteries (VA), on the basilar artery (BA) and on the internal carotids (ICA), as well as middle cerebral arteries (MCA) were evaluated. The individuals were also divided into groups of different age. Mean age: 63 (range 50-66) for the middle age group and 83 (range 75-93) for the elderly group. **(Table 2)**

On admission, brain CT was performed; arterial calcification was defined as a discrete, well circumscribed region in the cerebral arteries of those investigated; vertebral artery (VA), basilar artery (BA), middle cerebral arteries (MCA), and internal carotid arteries (ICA). Calcifications appeared hyper dense (whiter) than the surrounding parenchyma. (**Fig 3.2)**

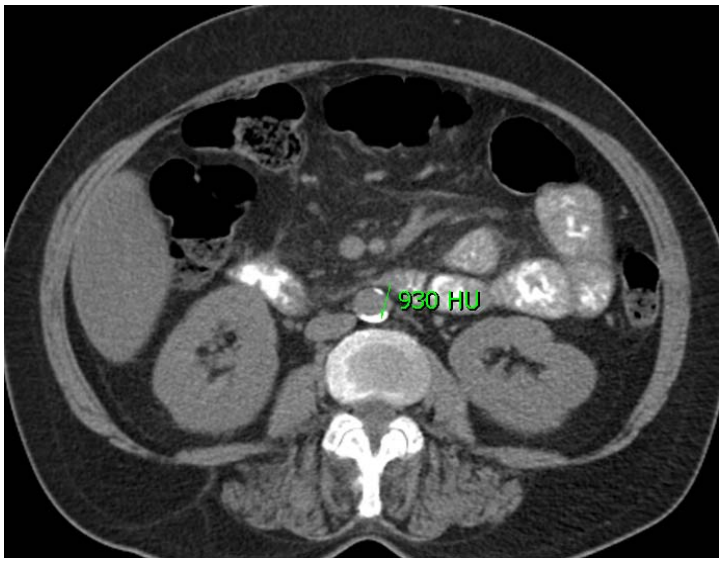

Fig 3.1 ***Abdominal aorta CT showed calcification of 930 Hounsfield Units(HU)***

Calcified ICA ad VA

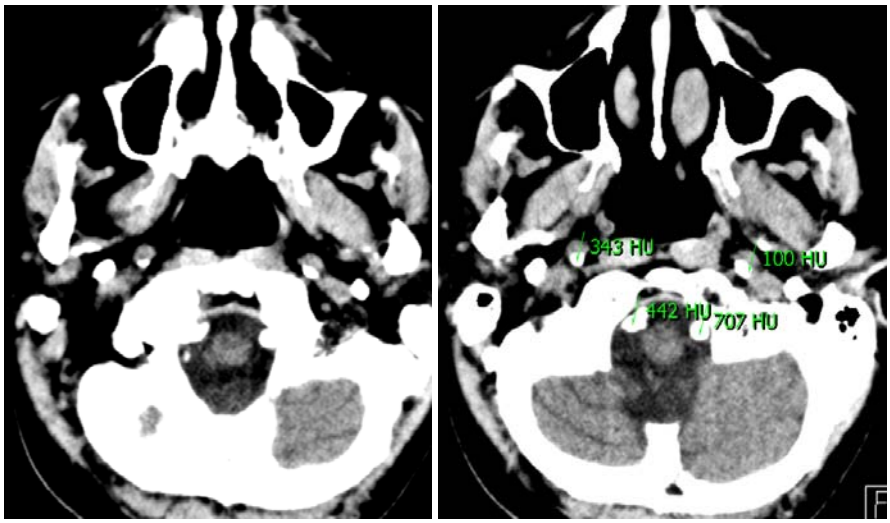

Fig 3.2 ***Brain CT on admission showing bilateral internal carotid artery (ICA) and vertebral artery (VA) calcification. The highest density on VA presents 707 Hounsfield Unit (HU).***

4.0 Results

The increasing content of Calcium in vascular walls does not develop in a diffuse manner. It is not an ubiquitus phenomenon. It occurs in a way of small focal lesions. Segments of 0,2 – 1 cm gather Calcium in the vessel wall, with a relatively abrupt transit into a normal vascular wall in its neighborhood.

While the normal vessel wall has its CT density around 35 – 45 Hounsfield units (HU), the calcified segments vary in its intensity between 50 and 1000 HU.

Abdominal aorta calcifications on CT were investigated in 25 patients in a total of 25 arteries. Nineteen patients showed calcifications (76%) and again the patients with calcifications tended to be older than those without abdominal calcifications. The characteristics of the study population are shown in table 1 and 2 (the higher the calcification the higher the density)**.**

The extent of calcification is usually shorter than 1cm and affects only a part of the circumference. In 2 cases the calcification was shaped around the whole circumference, thus forming a cuff. **Table 1**

What regards brain arteries: Cerebral artery calcifications on brain CT was found in 23 patients, in a total of 92 arteries.

Twenty two patients showed calcifications in more than 3 arteries (72%). Calcifications were observed to be most intensive in vertebral arteries (VA): 23 arteries. Next were the internal carotid arteries (ICA) - 23 arteries, the basilar artery (BA) - 23 arteries and the middle cerebral arteries (MCA) 23. The density vlaues ranged between **33 to 804 Hounsfield Units (HU).** The patients with most calcifications tended to be older than those with less calcifications. (**Fig 4.1)**

In addition two extra brain CT were examined which showed a patient with Morbus Fahr disease **(Fig 4.2)**. The high density sign (HDS) was found in 2 others indicating a thrombus on MCA (**Fig 4.4)**.

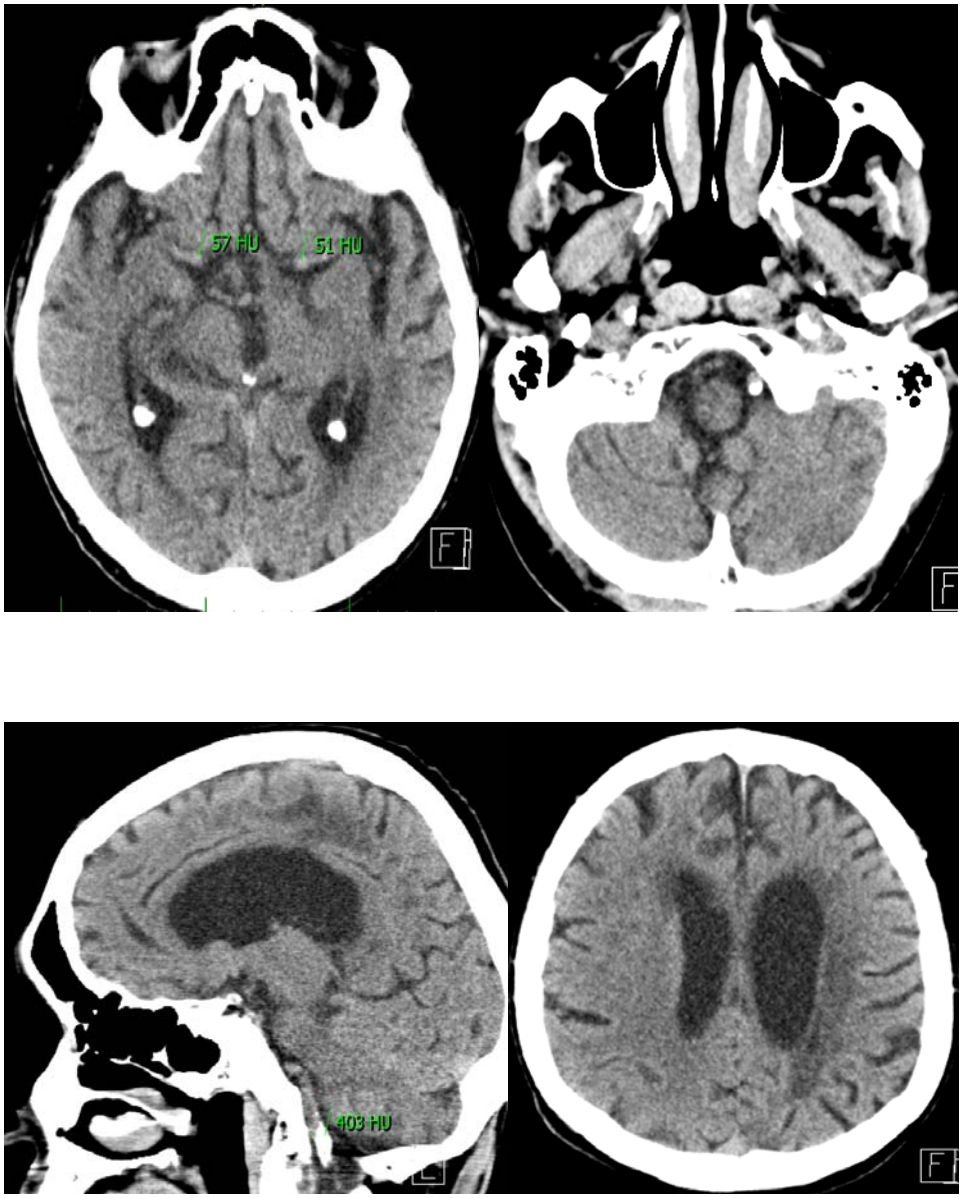

Fig 4.1 ***An 85 year old male with an intensively calcified vertebral artery in lateral view on the left and a diffuse periventricular leukoaraiosis on the right***

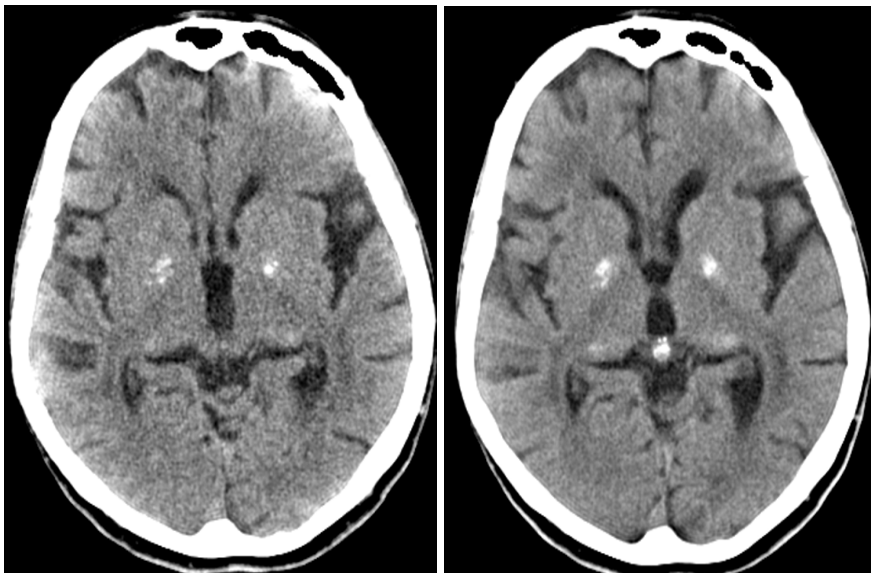

Fig 4.2 ***Morbus Fahr. Calcifications in basal ganglia.***

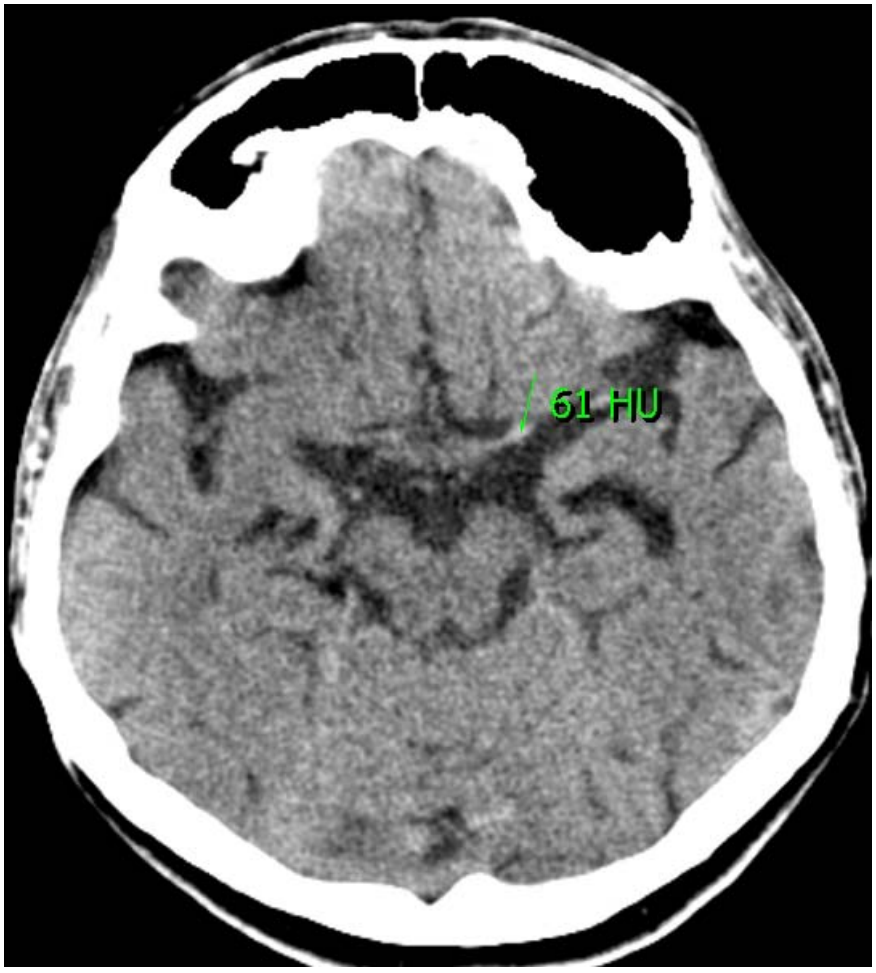

Fig 4.3 ***calcification in MCA (midle cerebral artery) due to a thrombus in a patient with Morbus Farh.***

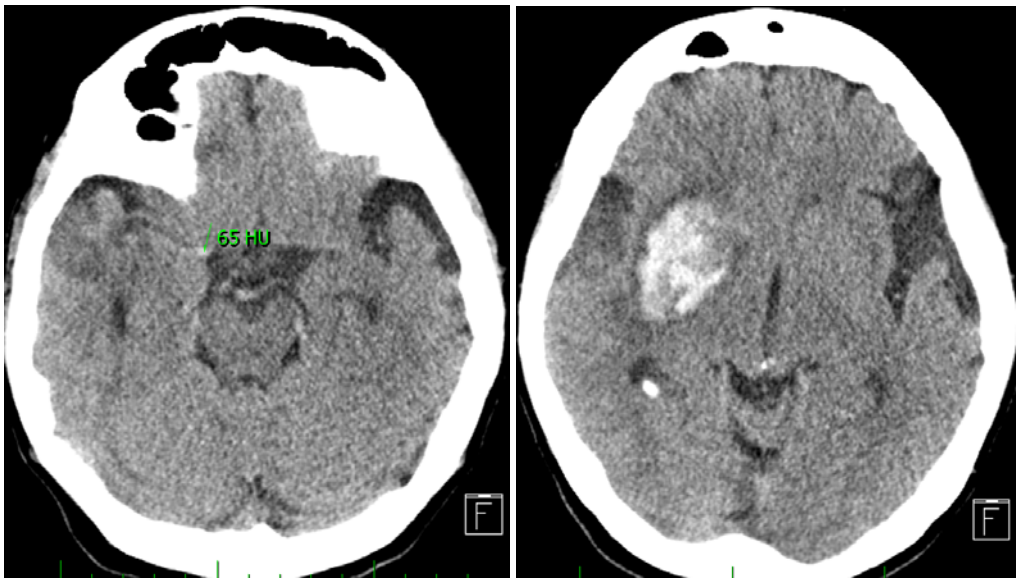

Fig 4.4 ***High density sign on the middle cerebral artery (HDS), causing an infarction. This infarction underwent haemorrhagic transformation, visualized the next day as a hyperdens district (right picture).***

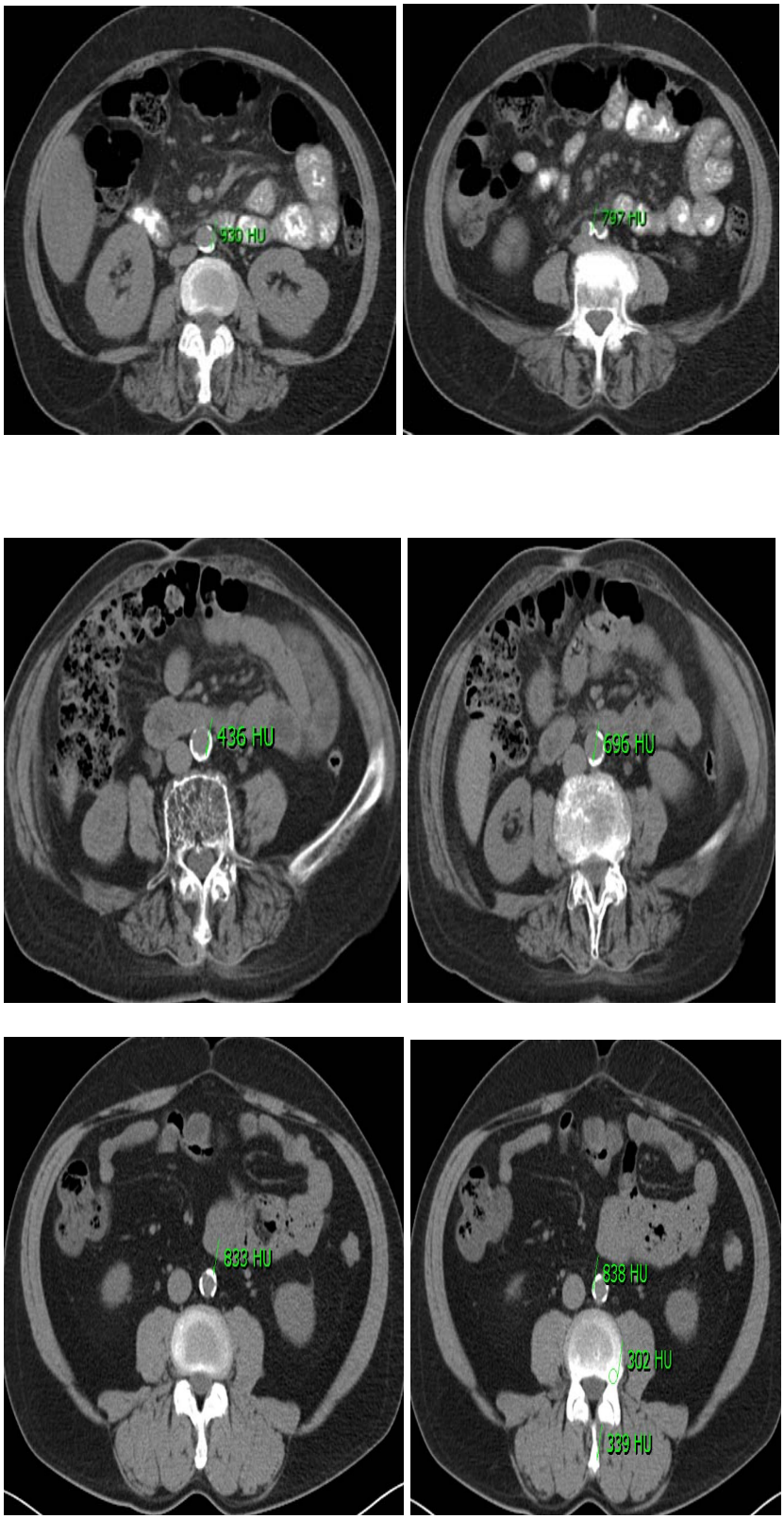

Fig 4.5 ***Calcifications within abdominal aorta with density values demonstrated***

TABLE 1- VASCULAR DENSITY WITHIN ABDOMINAL AORTA AND SACRUM

BIRTH	GENDER	DENSITY VASCULAR (AORTA)	DENSITY SACRUM	DATE OF EXAM
1925	F	1218/1cm, 360/1,292/1,604/1	566	1.02.2010
1927	M	459/1,732/5	493	24.04.2009
1928	F	1085/5,805/1,696/1,436/1,cuff	347	12.05.2009
1931	M	917/2,230/1,366/1,440/1	658	3.03.2010
1936	M	1119/2,732/2,588/1,594/1,965/3,407/5, 510/3 cuff	560	18.01.2009
1937	M	916/3,360/1	394	28.10.2009
1938	F	619/2,308/1,233/1,415/1	208	3.03.2010
1941	F	773/1,705/1,389/1,668/1	482	16.04.2009
1941	F	615/2,366/1,287/1	596	8.01.2009
1942	M	436/1,307/1,262/1	598	26.05.2009
1942	M	616/1,588/1	442	23.06.2009
1945	F	1152/2,902/2	614	1.10.2009
1945	F	603/1,533/1	354	30.03.2009
1945	F	930/1,797/1	466	12.01.2009
1946	F	551/1,533/1,392/1	346	12.01.2009
1948	F	678/1,389/1	325	11.12.2009
1948	M	635/1,438/1,234/1,408/1	440	10.02.2010
1952	M		553	6.12.2009
1953	M	838/3,438/1,833/2,438/1	339	27.04.2009
1955	M		497	4.05.2009
1955	F		550	8.09.2009
1957	F	773/1,499/1,253/1,751/1,680/2,483/1	363	11.02.2009
1971	F		546	12.11.2009
1975	M		500	1.07.2009
1979	M		360	22.09.2009

Density in the aorta is shown with a denominator defining the length of the calcification.

TABLE 2- VASCULAR DENSITIES OF CEREBREAL ARTERIES ***(colours in red are the same patient) R-right and L-left***

BIRTH	GENDER	VA	BA	MCA
1916	F	82/R ,68/L,432/R,61/L	47,52,49	51/R,56/L,48/L,
1924	F	72/R,55/L,47/R,82/L,122/L	58,54,55	47/R,44/L
1924	M	804/R,360/L,730/R,564/L,552/L	36,51,56	49/R,43/L,52/R,57/L,239/L
1925	F	70/R,49/R,67/L	57	54/R,62/L,43/R,44/L
1925	F	33/R,45/L	54,60	47/R,49/L
1925	F	54/R,52/L,68/L,75/L	54,65	51/R,53/L
1927	M	68/R,69/L,64/R,56/L,62/R,55/L	46,51,61	48/R,48/L,53/R
1928	F	61/R,64/L	40	46/R,53/L
1931	F	67/R,62/L,106/R,76/L	47,40,48	47/R,50/L
1934	F	57/R,53/S,80/R,89/S	50	49/R,58/L,36/R,45/L
1934	F	64/R,53/L,58/R,49/L,111/R,104/L,124/R,167/L	48	43/R,40/L
1934	F	65/R,55/L,109/R,111/L	56	44/R
1943	M	55/R,56/L,59/R,60/L	57	57/R,50/L
1943	M	71/R,69/L,71/R,118/L,74/R,54/L	54	50/R,59/L
1943	F	49/R,44/L,56/R,61/L,61/R,65/L	54	51/R,47/L
1944	M	61/R,47/L,65/R,46/L	38	?,46/L
1944	F	52/R,46/L	77	46/R,56/L
1945	M	57/R,170/L,59/R,62/L,64/R,64/L	51,54	50/R,49/L,46/R,54/L
1945	F	57/R,65/L,147/R,213/L,165/R,179/L	45,59,42	46/R,48/L,44/R,49/L
1945	F	48/R,61/L,50/R,60/L,64/R,62/L	53,52,60	48/R,43/L
1946	F	46/R,59/L,65/R,61/L	61,48,	47/R,44/L
1947	M	66/R,91/L	45	48/R,47/L
1952	M	60/R,63/L,80/R,46/L,62/R	45,49	44/R,47/L
1952	M	53/R,50/L,70/R,53/L,56/R	105,40	42/R,46/L
1957	M	53/R,60/L,47/R	40	51/R,22/L,40/R
1959	M	60/R,56/L	63	41/R,46/L

CONTINUED.....

BIRTH	GENDER	ICA	EXAM DATE
1916	F	51/R,55/L	13.10.2009
1924	F	106/R,95/L,124/R	19.12.2009
1924	M	50/R,239/L,113/L	1.12.2009
1925	F	40/R,48/L	
1925	F	68/L	8.10.2009
1925	F	94/R,31/L	12.10.2009
1927	M	61/L,49/R	19.06.2009
1928	F	45/R,50/L	22.09.2009
1931	F	53/R,79/L	13.11.2009
1934	F	?	6.12.2009
1934	F	41/R,52/L	10.12.2009
1934	F	44/R,55/L	16.12.2009
1943	M	56/R,57/L	16.11.2009
1943	M	59/R,52/L	3.12.2009
1943	F	?,83/L	21.10.2009
1944	M	41/R,48/L	22.10.2009
1944	F	60/R,56/L	29.09.2009
1945	M	47/R,43/L,40/R,48/L	13.12.2009
1945	F	59/R,62/L	6.12.2009
1945	F	56/R,50/L	29.12.2009
1946	F	46/R,40/L	4.12.2009
1947	M	50/R,54/L,46/R,49/L	15.10.2009
1952	M	50/R,60/L	15.10.2009
1952	M	62/R,57/L	26.02.2010
1957	M	44/R,55/L,46/L	22.12.2009
1959	M	41/R,55/L	18.12.2009

5.0 Discussion

We have analysed vascular calcifications in general population. The predominant location was the high density sign (HDS) in the middle cerebral artery (MCA).

Our results have shown, that arterial calcification is not a diffuse process neither in the aorta nor in smaller vessels of the brain. They are focal segmental deposits and they were found to be in about 76% of aortas in older patients. They appeared to be present in higher percentage with increasing age. Over 90% of calcification showed in persons above the age of 56 and less than 26% of the calcification were found below the age of 52; even younger patients with mean age 34 (30-38) showed no calcification at all.

Intensity of calcification can achieve values of a compact bone. In the brain they are present in some segments in more than 70% of people above the age of 60-65. If the calcification is situated in the middle cerebral artery they could it could mimic the high density sign (HDS). However values over 100 make no problem in distinguishing the thrombus, because the thrombus can never achieve such a density.

In summary we found that older people tend to have more calcifications when compared to young people and this finding was in concert with previous studies. Our observations suggest a significant role of calcifications within the cerebral arteries in correlation to age. Our study will be continued.

Acknowledgments

I thank professor Kalvach, for being a great supervisor and the staff at the department of Neurology.

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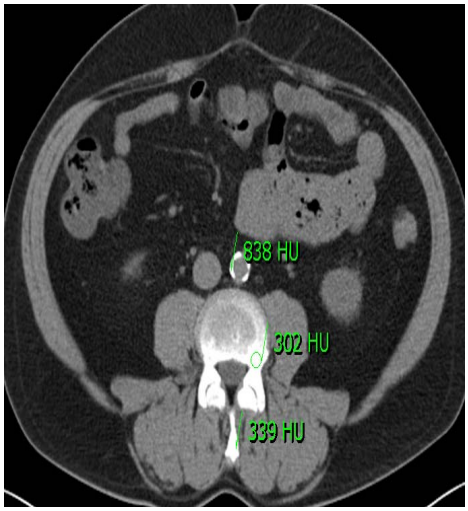
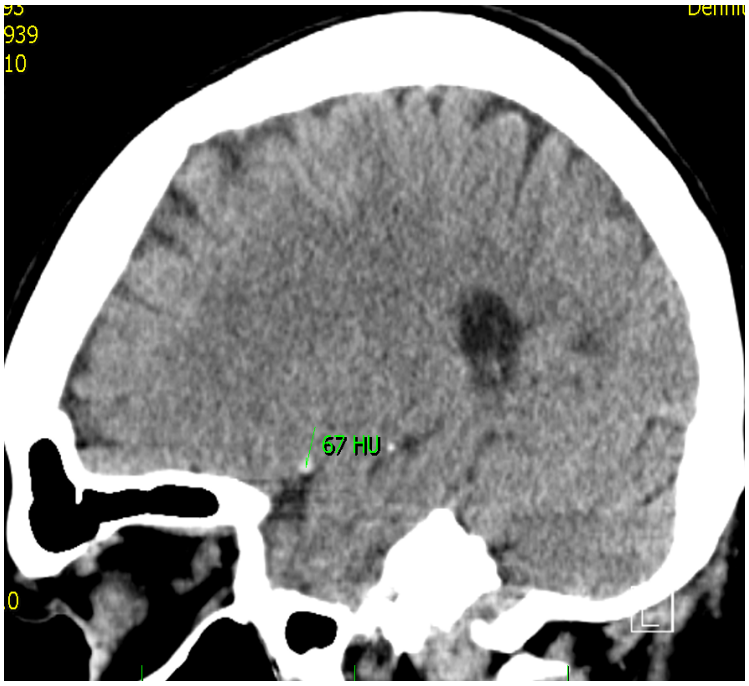
Appendices



Examples of calcifications within the abdominal aorta



Example of intracranial artery calcification. CT images of intracranial artery calcification