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From the nutcracker-phenomenon of the left renal vein to the midline congestion syndrome as a cause of migraine, headache, back and abdominal pain and functional disorders of pelvic organs

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Summary This paper presents the hypothesis, that pain and functional disturbances of organs which lie on the midline of the body might be caused by a venous congestion of these organs. Cause of their congestion is the participation of these organs (vertebral column, skull, brain, spinal medullary, uterus, prostate, left ovary/testis, urinary bladder rectum, vagina, urethra) in the collateral circulation of the left renal vein. In many patients with complaints of the above mentioned organs the left renal vein is compressed inside the fork formed by the superior mesenteric artery and the aorta. This so called nutcracker phenomenon is incompletely understood today. It can lead to a marked reduction of left renal perfusion and forces the left renal blood to bypass the venous compression site via abundant collaterals. These collaterals are often not sufficient. Their walls become stretched and distorted – varices with inflamed walls are formed. These dilated veins are painful, interfere with the normal organ's function and demand more space than usual. This way pain in the midline organs and functional derangement of the midline organs can occur. The term "midline congestion syndrome" seems appropriate to reflect the comprehensive nature of this frequent disorder. The rationale for this hypothesis is based on the novel PixelFlux-technique (www.chameleon-software.de) of renal tissue perfusion measurement. With this method a relevant decline of left renal cortical perfusion was measured in 16 affected patients before therapy (left/right ratio: 0.79). After a treatment with acetylsalicylic acid in doses from 15 to 200 mg/d within 14–200 days a complete relief of so far long lasting therapy-resistant midline organ symptoms was achieved. Simultaneously the left/right renal perfusion ratio increased significantly to 1.24 ($p = 0.021$). This improvement of left renal perfusion can be explained by a better drainage of collateral veins, diminution of their wall distension, thereby decline of their intramural inflammation, reduction of their mass effects (especially by the replaced spinal fluid inside the spinal canal and the skull), and altogether a reduction of pain and functional derangement in the affected midline organs. The proposed theory might influence the

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current understanding of such frequent and difficult to treat diseases as chronic back pain, headaches, frequent cystitis, enuresis, abdominal pain, flank pain and might spur new theories of arterial hypertension, placental insufficiency, prostate diseases and myelopathies.

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Introduction

The nutcracker phenomenon of the left renal vein (LRV) is an anatomical situation, in which the left renal vein shows a marked calibre reduction at the crossing with the aorta [1]. Observations of this situation and nephrologic sequelae date back to the early decades of the 20th century (as far as known) when first reports on the "syndrome de la pince mésentérique" were issued and forgotten later on [2]. In the seventies of the 20th century the situation was taken up again as a cause of otherwise unexplained hematuria and was diagnosed by evaluation of the late venous phase of renal arteriograms. De Schepper [3] was the first to link the calibre reduction – which he perceived as compression of the left renal vein between the aorta and the superior mesenteric artery – as a cause of hematuria of left renal origin whereas the link to the orthostatic albuminuria was seen already as early as 1923 [2]. He argued that this elevated backpressure leads to a mechanical induced bleeding of the upper urinary tract.

Numerous reports later on confirmed the causal relationship between left renal vein entrapment and hematuria [4]. Some reports of this constellation referred to other complaints as well [5,6]: abdominal pain and proteinuria. Consequently operations aimed successfully to correct this situation in severe cases of renal bleeding and pain (actual survey at [7]). Due to the first description of the nutcracker syndrome as a syndromatic combination of calibre reduction of the LRV and hematuria sometimes accompanied by flank pain most of the following observations were focussed on cases with exactly this symptomatology. As hematuria is a rather infrequent symptom in a general population nutcracker syndrome as defined by De Schepper and followers was regarded to be a rare situation.

Own routine sonographic observation of the aorto-mesenteric angle and the left renal vein in abdominal sonograms showed that aorto-mesenteric compression (what better should be termed nutcracker-phenomenon instead of nutcracker syndrome which includes an obligatory hematuria) is a rather frequent variant of the left renal vein at least in children and adolescents.

Materials and method

Patients

16 Patients (4–18 years; mean 12.8 years) with a nutcracker phenomenon of the left renal vein and long lasting complaints were included. They suffered from a variety of symptoms including migraine, flank pain, dysuria, pollakisuria, micturition disturbances, dyspareunia, back pain and abdominal pain.

Color Doppler sonography

All investigations were carried out with a Sequoia 512 Ultrasound equipment with a curved array transducer to depict the kidneys in B-mode and color Doppler mode (frequencies 4–8 MHz). To measure the flow inside the left renal vein stenosis (compression site) a vector transducer with frequencies from 1.75 to harmonic 4 MHz was applied.

Color Doppler sonography encompassed an overview of abdominal vessels' anatomy with special attention to the occurrences of abnormal flow phenomena as displayed by the variance mode of the ultrasound equipment. This mode displays turbulences as green–yellow signals thus making them visible at a first glance. All examinations were carried out with a fixed preset of the ultrasound parameters as color gain, color frequency, type of transducer, spatial and time resolution to mention the most important ones. All images and video clips were recorded digitally (DICOM format).

Diagnosis of nutcracker phenomenon

A nutcracker phenomenon was diagnosed when a calibre reduction of the left renal vein with more than 50% while crossing the abdominal aorta was found. For measurement a longitudinal section of the vein was recorded and the maximal and minimal diameter of the vein as well as the trans-sectional diameter of the aorta were measured. Inside the compressed venous segment the flow velocity was measured. Fig. 1 demonstrates a

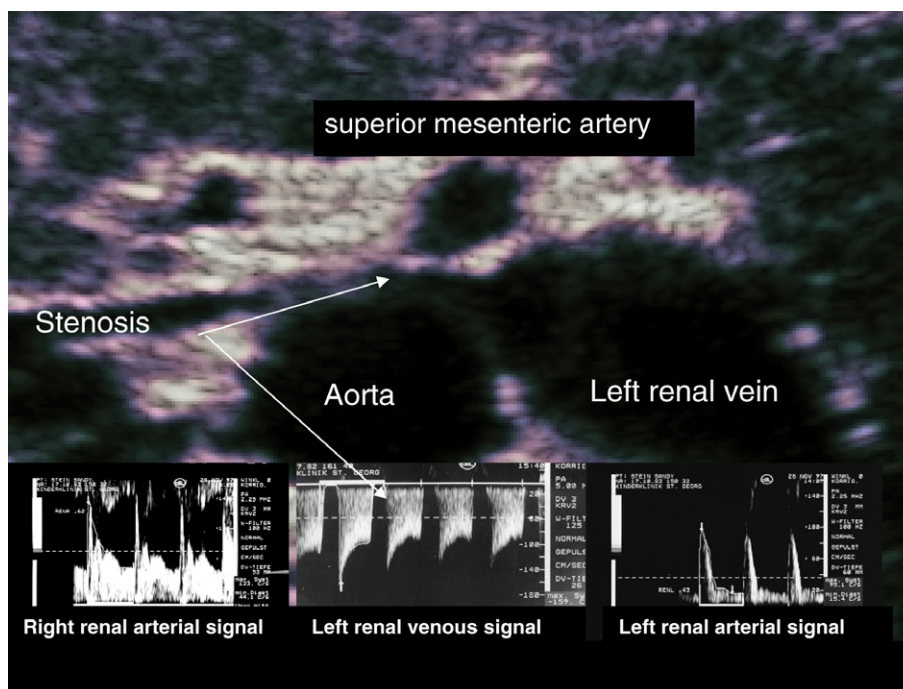


Figure 1 Typical B-mode sonogram of the left renal vein entrapment between abdominal aorta and superior mesenteric artery in a transverse section of the so-called arterial nutcracker (consisting of both arteries). Hemodynamic effects are illustrated by the flow velocity recordings below: centre: marked flow acceleration inside the venous stenosis with profound change of flow pattern. Here venous flow is completely interrupted in the late systole of the compressing arteries. In diastole and early systole a flow resembling an arterial jet is recorded as far as velocity and also change of flow velocity concerns. Striking elevation of pulsatility left renal artery's perfusion in a child with nutcracker phenomenon. Left lower corner: right renal arterial perfusion.

typical example of sonographic findings in a patient with nutcracker phenomenon. The abrupt calibre reduction is easily depicted by conventional B-mode ultrasound.

Renal cortical tissue perfusion measurement with the PixelFlux-technique

Renal cortical tissue perfusion was calculated with the PixelFlux-technique [8]. Digital color Doppler sonographic videos, which had been recorded under strictly standardized conditions, were analyzed numerically with respect to perfusion intensity. A standardized region of interest (ROI) consisting of the whole central renal segment fed by one interlobar artery, was investigated. This segment was sliced horizontally and in the proximal 20% of the ROI perfused area and mean perfusion velocity as encoded by the pixels' color were calculated automatically by the PixelFlux-software for each frame of a video sequence. This calculation was repeated from the beginning to the end of a full heart cycle and mean values of the aforementioned raw parameters were calculated. Perfusion intensity is the

product of mean perfused area and mean perfusion velocity of the entire sub-ROI (here the proximal 20% of the ROI). Perfusion measurements were done for both kidneys and a perfusion ratio was calculated to compare the amount of suppression of the renal perfusion of one side.

Statistical analysis

Perfusion ratios immediately before initiation of therapy and at the onset of relief of symptoms were calculated and compared by the Mann-Whitney-U-test. The significance threshold was set at $p < 0.05$.

Results

In a series of 16 patients with a nutcracker phenomenon and long lasting symptoms a variety of symptoms was noted:

Any pain	100%
Any headache	88%
Abdominal pain	88%
Headache	75%
Migraine	56%
Backpain	38%
Flank pain	31%
Dysuria	13%
Pollakisuria	13%
Bloody stools	13%
Nasal obstruction	13%
Epistaxis	13%
Breathing difficulties	13%
Scoliosis	6%
Pain at defecation	6%
Dyspareunia	6%
Enuresis	6%
Diarrhea	6%
Hematuria	0%

The renal cortical tissue perfusion measurements were carried out at the day of beginning and at the first consultation after complete relief of symptoms. With the relief of the individual symptoms of any patient a significant ($p = 0.021$ – Mann-Whitney U-Test) amelioration of the left renal perfusion could be found. The ratio of left to right renal proximal cortical tissue perfusion was compared (Fig. 2 as an individual patient's example). Initially left renal perfusion was less than at the right side – the mean ratio was calculated as 0.79. A significant increase of perfusion to a ratio of 1.24 was reached with ASA therapy simultaneously with the complete relief of the individual symptoms. ASA dose ranged from 15 to 200 mg/d and therapeutic effect was described between 14 and 209 days of therapy. ASA was orally administered as a single morning dose.

Discussion

The nutcracker phenomenon of the left renal vein is regarded a rather rare constellation [9,10]. There are numerous case reports and few larger series published focussing on the classical symptoms hematuria and flank pain. In routine ultrasound investigations the left renal vein entrapment is but rather frequently observed. In the own laboratory the prevalence of a substantial compression with flow acceleration above 100 cm/s is found in as much as 16% of children and adolescents (unpublished data, example see Figs. 1 and 2). The question is whether the simple compression of the left renal vein per se might be the cause of

the diverse symptoms in these patients or if this situation is only a minor anatomical variant without any consequences.

To answer this question the hemodynamic consequences of the venous congestion were monitored. With quantitative Doppler sonographic techniques (PixelFlux-method [8]) it is easy to demonstrate profound hemodynamic changes of the left renal perfusion in many patients with nutcracker phenomenon – even if proteinuria and hematuria are absent (Fig. 2). It is not rare that left renal arterial perfusion is compromised. This becomes already evident by simple comparisons of the RIs (resistance index) of both kidneys. The RI as a marker of the of perfusion pulsatility is often much higher on the left than on the right side (Fig. 1 lower part, left vs. right corner). This points to the relevant obstruction of the left renal venous outflow. The resistance against the arterial influx is elevated because of the increased venous back-pressure. The first reaction of arterial flow dynamics is then the drop of the diastolic flow velocity because diastolic pressure is much lower than systolic one. In this unphysiologic situation counter-mechanisms aim to compensate the decreased renal perfusion of the left side, hence it is not only the perfusion velocity but also the perfusion volume that is diminished in such cases.

It is interesting therefore to rethink the constellation of nutcracker phenomenon with respect to possible complaints related to the disturbed perfusion of the left kidney. Such a disturbance has at least two aspects: the reduction of perfusion volume and the collateralization of the venous flow. Until recently it was almost impossible to quantify renal tissue perfusion by simple, reliable and affordable means. With the introduction of the sonographic PixelFlux-technique to quantify tissue perfusion from conventional color Doppler videos a workable method is available. We used this to compare renal cortical perfusion of both kidneys in patients with nutcracker phenomenon. As to be expected from the distortion of the flow pattern inside the left renal artery in cases with pronounced nutcracker phenomenon a reduction of left renal perfusion could be established. Without therapy the perfusion intensity of the left renal cortex was only 74% compared to the contralateral kidney. This can be regarded as a measure of the functional compromise of the left kidney due to venous congestion. This congestion is the driving force for the formation of collateral pathways to drain the rather high perfusion volumes of the kidney. Renal perfusion is second only to the brain in the greater circulation. Blood flow of one kidney at rest is about 11% whereas cerebral blood flow at rest

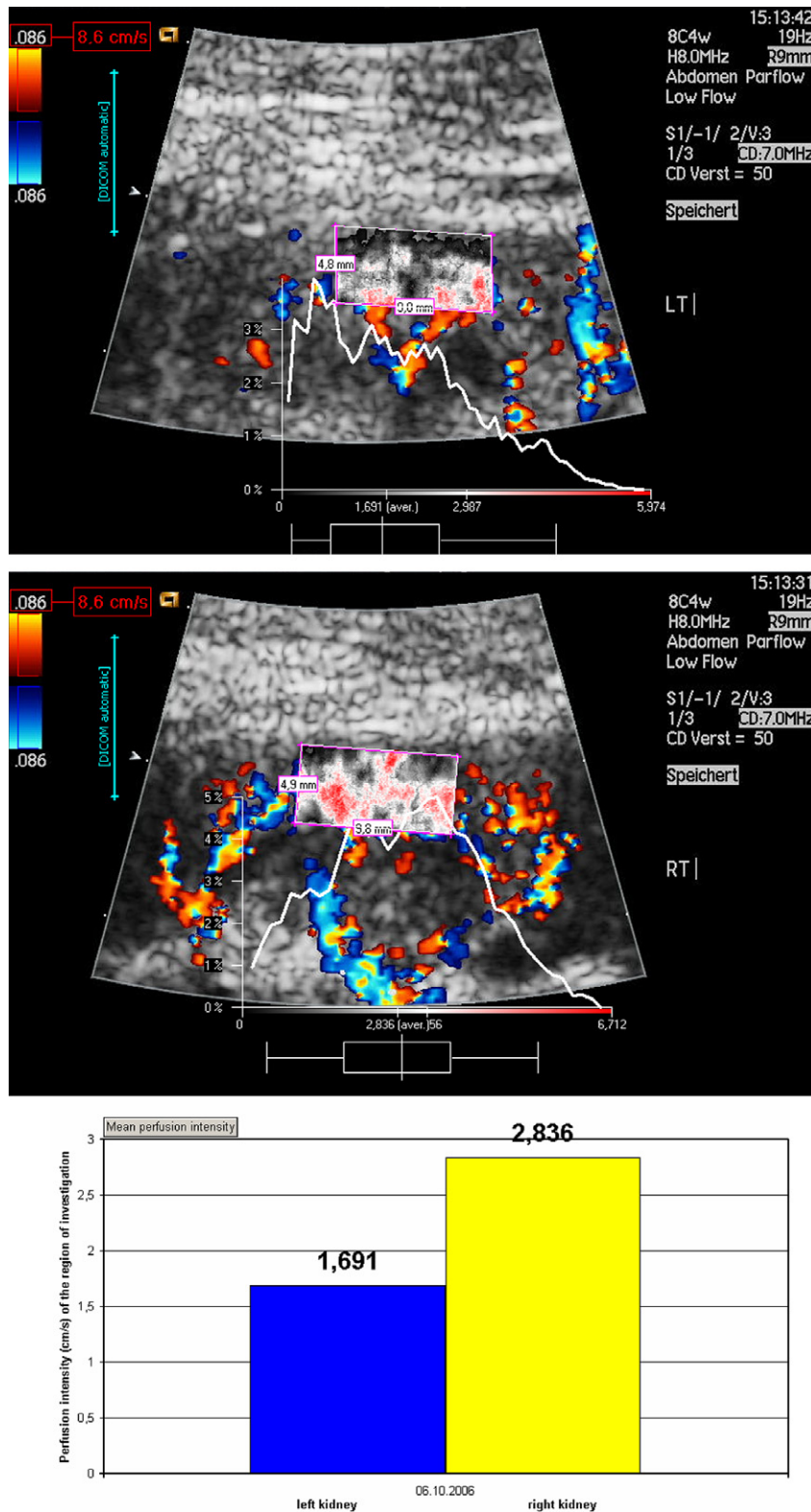


Figure 2 Example of a patient’s renal perfusion at the time of typical complaints of midline congestion: severe headaches recurrent during more than three weeks, abdominal pain. Above left kidney, below right kidney: striking differences of the cortical perfusion are highly visibly due to PixelFlux perfusion measurement: lower overall perfusion (see also Fig. 4) of the left kidney (homogeneous cortical perfusion intensity 2.79 vs. 1.81 cm/s; ratio left/right: 0.60!) is accompanied by an obvious shift of perfusion intensity distribution towards higher perfused areas inside the right kidney (diagrams inside the sonograms).

ranges at 14% of cardiac output [11]. Thus even minor obstruction leads to relevant volumes which have to be bypassed. Such bypasses are embryologically preformed and consist mainly of the left ovarian (spermatic) vein, the so called *tronc reno-rachidien* (a large tributary connecting the left renal vein with the hemiazygos vein) and the epidural plexus, and lumbar veins draining the renal blood down to the pelvic organs as urinary bladder, urethra, vagina, uterus, prostate and rectum.

Physiology of nutcracker phenomenon

The obstruction of left renal venous outflow elevates the blood pressure inside the proximal venous segment thus leading to the diagnostically important dilation of the vein (Fig. 1) and hematuria. Own series (unpublished data) nevertheless show, that nutcracker phenomenon without hematuria is much more frequent and accounts for about 16% of all sonograms in a tertiary ultrasound center. In 8% of an unselected series of renal venograms ureteral varices were found – always on the left side [12]. Both prevalences are much higher than that of hematuria and stresses that enlarged collaterals occur more frequently than hematuria which has been so far regarded the guiding symptom of nutcracker phenomenon. All collaterals have to fulfil the purpose of directing blood from the left hemisphere of the body to its right side. Organs

of the midline therefore play a major role in the redirecting left renal blood to the tributaries of the caval veins. Midline organs such as vertebral column, spinal cord, urinary bladder, uterus (prostate), rectum, vagina, urethra and the pelvic venous plexus fed via lumbar veins and the left spermatic (ovarian) vein have naturally venous connections to both hemispheres. They can bridge renal blood to inferior or superior caval veins via their proprietary venous network. But these veins are not laid out to receive large volumes of blood from the left kidney. Many of these organs have a usually low perfusion due to a high flow resistance as they are muscular organs (urinary bladder, uterus) or they are metabolically weakly active (vertebral column, spinal cord, prostate) or of small size (urethra, ovary). These potential collateral pathways are connected in parallel and are exposed to the same pressure as they all have direct venous circuit with the left renal vein. Individual disposition then decides which pathway will become the main route of pressure alleviation. This disposition is predefined by embryological structures (remnants of the abundant venous predecessors in the region of the left retroperitoneum). Some individuals have a relatively large lumbar venous system draining the blood towards the pelvis. Others have a markedly developed pathway directed to the hemiazygos vein and giving rise to a remarkable influx into the spinal canal (see

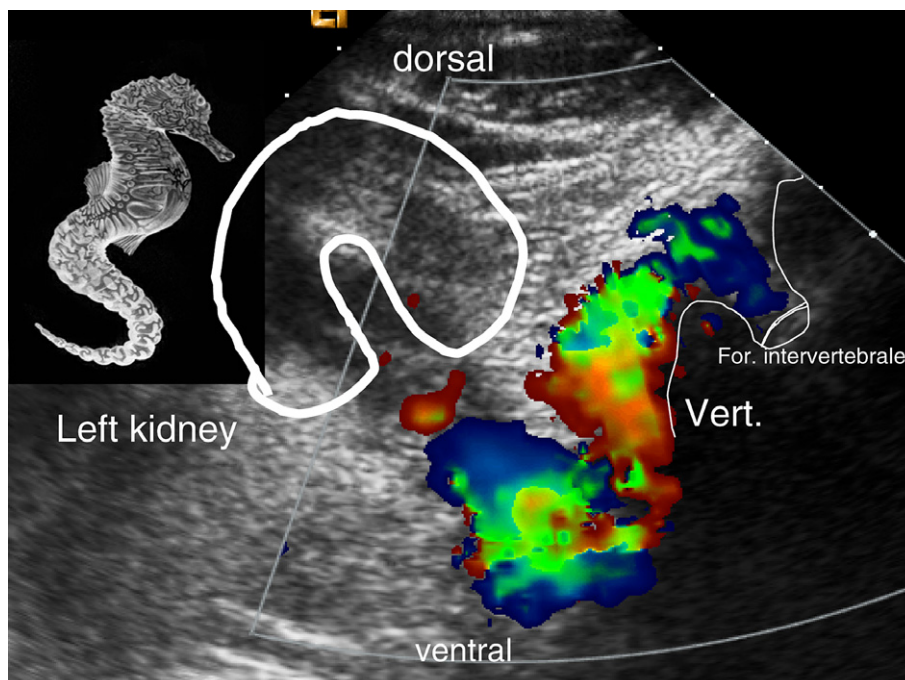


Figure 3 “Sea-horse-sign”— large collateral vein (so called “*tronc reno-rachidien*”), connecting the dilated left renal vein (tail of the sea-horse) with the venous network of the spine – the “snout” of the Sea-horse is directed to an intervertebral foramen draining the blood into the epidural plexus.

Fig. 3). Some exhibit a spacious dilation and even umbilical cord-like tortuosity of the left spermatic (ovarian) vein, leading to a pronounced ovarian varicosity or varicocele of the left scrotum. Many women with such a condition develop large varicose uterus veins [13] or an enlarged retropubic venous network often also encompassing the distal rectum and the urethra [14]. The rectum is swollen and the hemorrhoidal plexus is filled with blood. Even the urinary bladder may show atypically large veins often with knot-like focal distensions.

From nutcracker phenomenon towards a more comprehensive understanding – the “midline congestion syndrome”

Such a volume overload has consequences for the affected ones. Forced venous dilation in the above mentioned organs may affect their function and may cause pain emanating from the distended and convoluted veins which develop an inflammatory response to the damaging effect of shear stress [15].

The common goal of all compensatory mechanisms is to transport blood from the left kidney to the inferior or superior caval vein. All organs of the central axis may serve as a bridge to the right side, where the caval veins are situated. Many symptoms seem to arise from their involvement in an unphysiological transport of venous renal blood. The midline organs may become congested too. Thus many of the fancy symptoms of the patients with nutcracker phenomenon can be traced to the fact of venous congestion of midline organs. From my point of view it is suitable therefore to expand our view from the nutcracker phenomenon of the left renal vein to a more comprehensive appreciation of the complex situation. The term “midline congestion syndrome” seems more appropriate as pain and functional compromise may occur in all midline organs.

Examples for this are as follows:

The congested pelvic veins become painful – a situation which is well known as pelvic congestion syndrome [4]. Pain is one consequence of the inflammatory cascade triggered by congestion and venous wall distension [15–17]. This is predominantly reported in multiparous women, some of them also demonstrating external (vulvar [4,18,19] and thigh [20] varices) in addition to their internal pelvic varicosity [20–22]. Only recently the ties between left renal vein obstruction and this syndrome have been clarified [4,23].

The blood assembly inside the rectal wall supports the genesis of haemorrhoids [14]. Congestion of the vagina may contribute to painful sexual intercourse [13,21,23] (a condition reported even

in an adolescent of our small series), congestion of the urethra and urinary bladder may lead to hematuria and urgent voiding, despite only small urinary volumes, and burning pain at the end of micturition [13].

Venous congestion of the spine may have sequelae so far not associated with renal blood flow obstruction. The vertebral column has large capacitive vascular pools. These are the lumbar veins, hemiazygos and azygos vein, and the epidural venous plexus. They are fed by an inconstant but frequent major tributary connecting the pressured left renal vein to these pools – the so called *tronc réno-rachidien* [6] (reno-spinal trunk) or “canal rénoazygo-lombaire” [6,24]. Increase of pressure inside the spinal canal will produce sensations not only at the lumbar spine, the entrance of the additional volume to the fixed space of the spinal canal, but also at distant places due to an upward shift of cerebrospinal fluid. The dominant reaction are headaches, often reported as tension-like headaches but also very often described as typical migraine or most often as a mixture of a variety of painful discomfort. Some patients describe their headaches as commencing in the nape of the neck and many complain of worsening with physical activity. This hypothesis is supported by the observation that a 30 s lasting obstruction of the cervical venous outflow by means of the Queckenstedt manoeuvre (compression of both internal jugular veins thus raising intracranial and cerebrospinal pressure) leads to aggravation of migraine-type headaches pointing to a causal relationship [25,26]. It is interesting that with a shorter duration of venous obstruction by the Queckenstedt manoeuvre (10 s) such an effect on headache could not be provoked [27] and that the effect was more pronounced in a supine than in a sitting position [25,26] which stresses the causative or at least aggravating role of venous congestion for migraine. It is known that a tight relationship between intracranial venous pressure and cerebrospinal fluid pressure exists. In patients with tension-type headaches a withdrawal of cerebrospinal fluid led to an improvement of their complaints whereas a head-down tilt amplified headache [28]. Lumbar injections of only small epidural volumes can produce relevant rises of cerebro-spinal fluid (CSF) pressure [29].

With the aforementioned relations of headache, venous drainage of the skull and their interrelationships with CSF pressure changes it is easily comprehensible that an injection of greater volumes of left renal blood towards the lumbar epidural space can produce headache via compression of the lumbar dural sac upward shift of CSF and a congestion of the intracranial structures due to the following

rise of intracranial CSF-pressure and may be responded by headaches of several subtypes [25,30,31].

Overfilling of the epidural plexus can also provoke radicular symptoms [32] and may even mimic disk protrusion [33]. Some reports link sciatica to such a venous congestion of the spine in cases of inferior caval vein obstruction [32] and even myelopathies are reported in chronic venous congestion of the spine no matter if the congestion was caused by caval [34] or renal vein obstruction [35,36].

Individual collateralization patterns lead to a broad spectrum of symptoms which may baffle the clinical investigator about their true nature. Their origin in left renal vein obstruction is therefore easily overlooked. The extraordinary diversity of complaints, their distant locations and the often picturesque descriptions may mock the physician.

Therapeutic strategies

In the case of nutcracker phenomenon the symptoms can be traced back to the obstruction of the left renal vein. As a logical consequence all measures are promising which improve the drainage of the left kidney. To restore the anatomical situation interventions are necessary and effective. Complete symptomatic relief after dissection and caudal reinsertion of the left renal vein into the inferior caval vein has been repeatedly reported [37–39] but internal and external stenting of the stenotic segment as well as gonadocaval bypass proved to be successful too [13,37,40]. Transposition of the superior mesenteric artery was less successfully performed [40]. Nonsurgical therapies have not been proposed so far.

Acetylsalicylic acid (ASA) as an alternative non-invasive therapy

Given the high prevalence rate of nutcracker phenomenon in the general population and the overall high rates of complaints from a variety of organs the need of a remedy on the one hand as well as the demand of a non-invasive therapy on the other hand is obvious. With respect to the etiology of the complaints as a primarily obstructive vascular disease with low-flow states in enlarged venous segments, elevated shear stress, increased wall tension (which can promote thrombogenic pathways [41]) and varix formation and known inflammatory venous wall infiltration in varices [15–17] therapy with acetylsalicylic acid suggests itself

(see Fig. 4). Moreover acetylsalicylic acid is effective [42–44] for migraine therapy and prophylaxis in children and adults [45–47]. Many patients with nutcracker phenomenon just suffer from diverse forms of headaches including migraine.

In cases of nutcracker phenomenon with long lasting and otherwise therapy resistant complaints in 16 cases a prophylactic treatment with ASA was started after informed consent was given. The symptoms consisted predominantly of headaches and pain sensations of the lower trunk. All patients received a low dose acetylsalicylic acid treatment within the range of 15–200 (mean 54) mg/day as a single oral dose in the morning. Therapeutic effects were documented in questionnaires. Additionally a global statement of the patients and their parents was requested as whether a significant relief of symptoms had occurred. All patients showed a complete resolution of their symptoms within 14–209 days. Moreover, simultaneously a significant increase of left renal perfusion was measured which is a strong argument for a causal link of both phenomena.

A decrease of blood viscosity may contribute to the higher perfusion volumes across the stenotic venous segment. Besides this the perfusion through smaller collateral veins may be eased. Both will decrease the prestenotic left renal venous pressure and reduce wall shear stress which is a known promoter of vessel wall inflammation, oedema and thrombosis. Afterwards perfusion across the collaterals will augment because of increasing distensibility of the venous walls. The capacity of the collateral pathways will thus increase further. Both factors promote each other and initiate a steadily flow augmentation away from the hypertensive venous segment. Suppression of the venous wall inflammation will reduce direct inflammatory pain sensations. Along with the drop of venous pressure in and around the spine the compression of the dural sac and the raised intracranial and intraspinal pressure will drop. This might explain the alleviation and full reversal of headaches and back pain in these patients.

Larger series are necessary to follow the traces explained above. If the concept of midline congestion syndrome holds true many nowadays imperfectly understood diseases and phenomena might find a new explanation. Tissue perfusion measurement is a valuable tool to describe venous congestion in the midline organs – as far as they are accessible for ultrasound. Its principles are useful for other radiological techniques too as the software [8] can work with MR, DSA and CT images as well. With a more refined appreciation of living tissues and their perfusion we could overcome

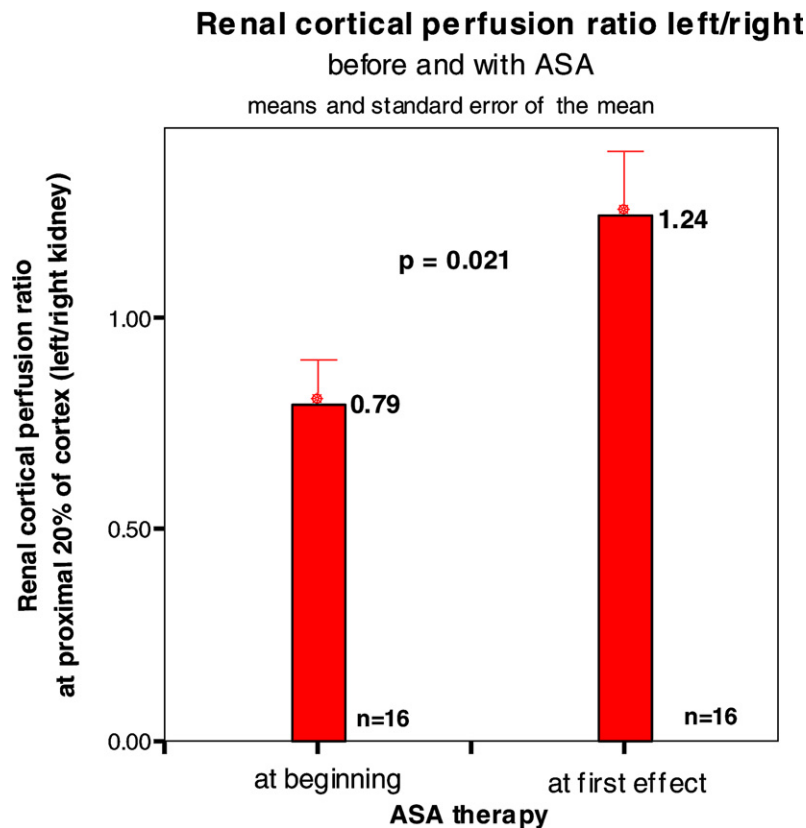


Figure 4 Significant rise of left renal perfusion ($p = 0.021$) simultaneously with symptom relief during ASA therapy.

diagnostic restrictions. A functional differentiation of so far morphology based diagnoses from so called normal variants becomes feasible. The dynamic aspect of perfusion and its changes can contribute significantly to the understanding of a living organism since some diagnoses are based upon anatomical knowledge perceived from corpses and static radiological techniques. Interesting further fields of research are uterus diseases, deviations from normal pregnancies and placental insufficiency, prostate, and functional bowel and urinary bladder disorders. The concept of midline congestion syndrome might spur new theories of arterial hypertension (elevated blood pressure as physiologic response to diminished perfusion of the left kidney?), placental insufficiency, prostate diseases and myelopathies.

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