Vascular incontinence: incontinence in the elderly due to ischemic white matter changes

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Abstract

This review article introduces the new concept of *vascular incontinence*, a disorder of bladder control resulting from cerebral white matter disease (WMD). The concept is based on the original observation in 1999 of a correlation between the severity of leukoareosis or WMD, urinary symptoms, gait disorder and cognitive impairment. Over the last 20 years, the realization that WMD is not a benign incidental finding in the elderly has become generally accepted and several studies have pointed to an association between geriatric syndromes and this type of pathology. The main brunt of WMD is in the frontal regions, a region recognized to be crucial for bladder control. Other disorders should be excluded, both neurological and urological, such as normal-pressure hydrocephalus, progressive supranuclear palsy, etc., and prostatic hyperplasia, physical stress incontinence, nocturnal polyuria, etc. Treatment involves management of small vessel disease risk factors and anticholinergic drugs that do not easily penetrate the blood brain barrier to improve bladder control.

Incidence of incontinence in the elderly

The incidence of urinary frequency/urgency (also called overactive bladder) with or without incontinence in the general population over 40 years in age is estimated to be 16.6% in Europe,[1] 16.4% in the USA,[2] and 12.4% in Asia (Japan).[3] However, the prevalence increases significantly with age so that out of a population over 65 years old, 35-50% are affected [3]. It is now widely acknowledged that urinary, frequency and poor bladder control has a significant impact on quality of life and that bladder dysfunction in elderly people adds to career burden and is an important factor leading to institutionalization.[4]

Urinary incontinence in the elderly is a multifactorial disorder and, as with many such conditions in the elderly, it is principally due to a failure of compensation.[5,6]

The cause of incontinence in the elderly: evolving concepts

There is an important body of work which has used electron microscopy to examine ultrastructural details of the detrusor muscle and its innervation in the elderly in an attempt to identify specific morphological features which correlate with detrusor overactivity, detrusor hyocontractility and the disorder DIHC (detrusor instability and hypocontractility).[7-12]

Such findings provide a strong indication that a significant contribution to the problem of incontinence in the frail elderly is age-related changes in the bladder itself. The recent view that has emerged that there may also be an important cerebral vascular component is, therefore, quite novel but certainly warrants close attention. This new line of thinking started with a publication of Sakakibara *et al.,* in 1999.[13]

Sakakibara *et al.*[13] investigated 63 subjects, 28 male and 35 female, mean age 73 years, (range 62-86 years) demonstrated to have varying degrees of cerebral white matter disease or leuko-araiosis (Figure 1).[13,14] Various clinical complaints were involved and included gait difficulty in 7, dysarthria in 5 and amnesia in 5: none was bed-ridden. Eleven had history of single lacunar infarct, including mild hemiparesis or hemisensory disturbance. Magnetic resonance imaging-defined white matter changes were graded on a scale of 0 to 4, according to that of Brand-Zawadzki *et al.*[15] Urinary function was assessed by questionnaire and dysfunction graded as *mild, with nocturnal urinary frequency of 2 or more* and *severe with urge urinary incontinence*. Cognitive disorder was graded as mild with score below 24 and severe below 19 of mini-mental state examination (MMSE). Gait disorder was graded as mild with 1 feature and severe with 3 features of slowness of gait, short-step/festination and loss of postural reflex.

The prevalence of nighttime urinary frequency in cases of grade 1 white matter changes was 60%, 58% in grade 2, 93% in grade 3, and 91% in grade 4, respectively, giving an overall prevalence of nighttime urinary frequency of around 75%. Similarly, urge urinary incontinence in grade 1 white matter change was 33%, 25% in grade 2, 57% in grade 3, and 45% in grade 4, respectively, with an overall prevalence of urge urinary incontinence in white matter changes estimated at around 40%. Nocturnal urinary frequency was a more common and earlier feature than urinary incontinence (Figure 1).[13] Of particular importance was the fact that urinary frequency, urgency with or without incontinence, was not always accompanied by gait disorder or dementia (Grade 1, Figure 1), so that it appeared that urinary frequency/urgency might be the first clinical manifestation of the observed white matter changes.[13]

Until around the time of Sakakibara's observations, white matter disease (WMD), variously described as white matter hyperintensities , white matter change, white matter ischemia, multiple cerebral infarction of the white matter type, had been thought to be of little clinical relevance, and regarded as an incidental phenomenon in aging. The first pathological description of white matter changes in the aged brain dates back to Durand-Fardel in 1854, who named the condition *atrophie interstitielle du cerveau* (*interstitial atrophy of the brain*), and believed it to be asymptomatic.[16] Binswanger in 1894 described it pathologically as *arteriosklerotische hirnerkrankung/ hirnatrophie* (*arteriosclerotic brain atrophy*), since *it is very likely that the subcortical loss of fibers is caused by the deficiency of the blood supply resulting from arteriosclerosis*.[17] In 1987, Hachinski coined the name leukoaraiosis, which he derived from the Greek word leukos meaning white and araios meaning rarefied, in order to describe the radiological images of

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loss of density of the periventricular white matter observed by computed tomography (CT) scan.[18] Advances in neuroimaging, particularly magnetic resonance imaging (MRI) at that time, enabled early recognition of white matter changes pathological to white matter rarefaction.[19,20]

Geriatric syndromes and white matter disease

Recent population-based MRI studies suggest that the incidence of moderate white matter lesions (periventricular white matter lesions grade >4/9 and subcortical white matter volume >1.5 mL) to be around 10% (7.6-24%) in the general population over 55 years of age,[21-23] comparable to that of type 2 diabetes. It is now recognized that WMD can develop into three different geriatric syndromes, *e.g.* i) vascular dementia: usually mild in the Mini-Mental State Examination and other general cognitive function, while the Frontal Assessment Battery might be low;[24] hallucination and delusion are rare; sometimes stepwise deterioration;[25] in most advanced stages, emotional incontinence may occur; ii) vascular parkinsonism: gait disorder or easy falls, slow, short-stepped gait, often with wide-based gait, usually lacking apparent tremor and rigidity in the hands.[26] It is otherwise called lower body parkinsonism and the gait disturbance may manifest as frontal gait apraxia, sometimes with frontal release signs (palmomental, snout, or grasping); in advanced stages, dysphagia and aspiration pneumonia may occur; and 3) following the paper of Sakakibara *et al*.[13] and since confirmed by others,[27,28] *vascular incontinence*, *i.e.* urinary frequency/urgency with or without incontinence. These three features can present in any combination; howev-

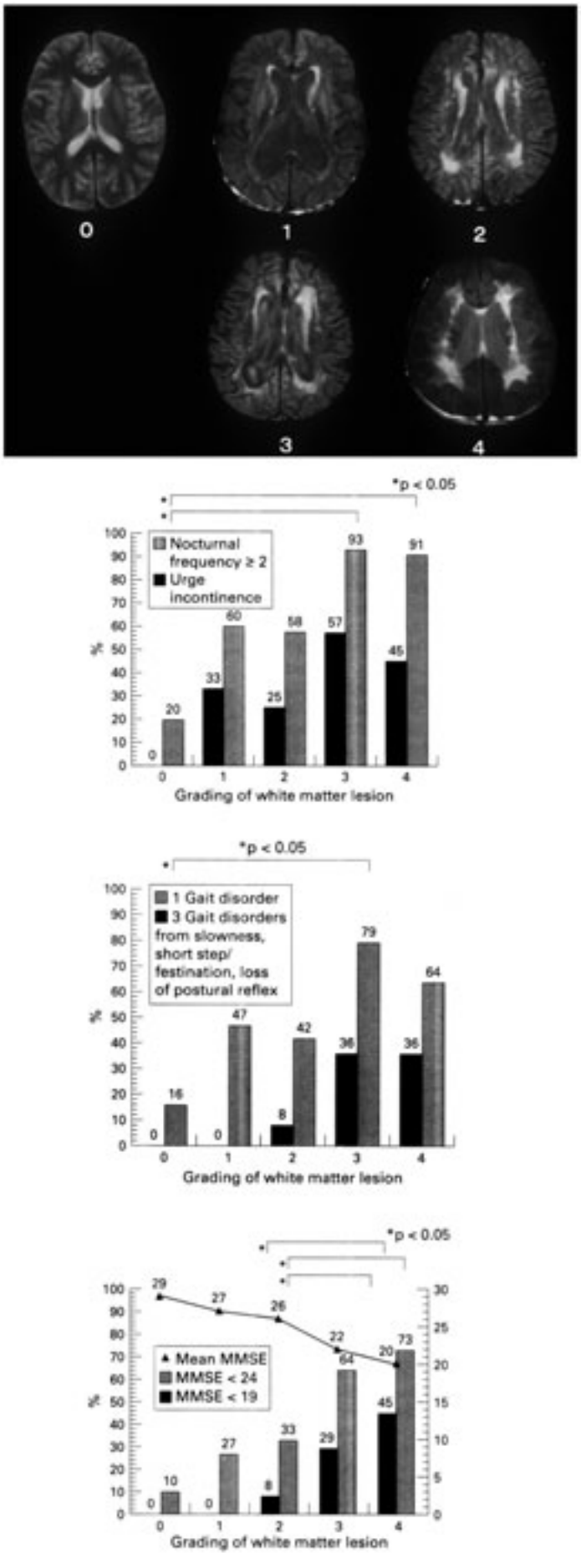

Figure 1. Cerebral white-matter changes and urinary dysfunction. Schematic presentation of the grading of white-matter lesions on MRI: Grade 0, none. Grade 1, punctate foci with high signal intensity in the white matter immediately at the top of the frontal horns of the lateral ventricles. Grade 2, white-matter lesions were seen elsewhere but remained confined to the immediate subependymal region of the ventricles. Grade 3, periventricular as well as separate, discrete, deep white-matter foci of signal abnormality. Grade 4, discrete white-matter foci had become large and coalescent. Graphs: urinary dysfunction and white-matter lesions on MRI; cognitive disorder and white-matter lesion on MRI. MMSE: mini-mental state examination. Gait disorder and white-matter lesion on MRI. Reproduced with permission.[13]

er, clinically, urinary and gait disorders are more prominent than dementia, and usually precede it.

Pathology of white matter disease

Diffuse abnormalities are seen in the small deep perforating vessels of the hemispheric white matter, basal ganglia and brain stem. These changes have been described as *segmental arteriolar disorganisation* by Miller Fisher and pathological changes range from lipohyalinosis to fibrinoid necrosis and disintegration of small vessels. Occlusion of these vessels results in hypoperfusion and ischemia. Atherosclerosis, the predominant pathological finding in large vessel disease, is an uncommon finding.[29] Disruption of the blood brain barrier is likely to precipitate or worsen progression of WMD.[30] Cerebral microbleeds (small, perviascular haemorrhages) are commonly seen. Small vessel disease may lead to loss of autoregulation of cerebral blood supply, which results in a higher susceptibility of white matter to undergo drops in blood flow during episodes of systemic hypotension.[19,20] Recent positron emission tomography imaging with 18F-fluoromisonidazole showed higher susceptibility to ischemia of white matter than gray matter in stroke cases.[31,32]

Although there is some debate, it is known that the incidence of white matter change significantly increases with atherosclerotic risk factors, *e.g.* hyperlipidemia, diabetes, obesity, metabolic syndrome, hypertension,[21-23] cigarette smoking, carotid plaque,[33] high cardio-ankle vascular stiffness index (CAVI), and gene polymorphism of aldosterone synthase,[34] angiotensinogen, angiotensin II type 1 receptor,[35] nitric oxide synthase,[35] and angiotensin-converting enzyme,[36] (hypertension), methylenetetrahydrofolate reductase gene (homocysteine metabolism),[37] matrix metalloproteinase-3 and -9 genes (vascular remodeling),[38] fibrinogen gene (fibrin clot formation),[39] genes of apolipoprotein E and Paraoxonase 1 (lipid metabolism),[40,41] and C-reactive protein gene (inflammation).[42] Rare but well-established genetically transmitted white matter changes also exist: one is cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)[43] with NOTCH3 gene mutation (endoplasmic reticulum dysfunction), and the other is cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL)[44] with high-temperature requirement A serine peptidase 1 (HTRA1) gene mutation (transforming growth factor -beta dysfunction). Experimental studies have suggested that other factors contributing to white matter changes include transient brain edema and blood-brain barrier damage.[45-47]

The incidence of white matter change significantly increases with age.[21-23] White matter change slowly progresses after being identified;[48,49] and mildly increases the rate of new-onset stroke (constituting a prodrome of future stroke).[50] White matter changes are rarely noted in subjects with transient ischemic attack (TIA), whereas they are common in small vessel ischemic stroke.[51,52] T2*-weighted gradient-echo MRIs in subjects with white matter change sometimes show comorbid cerebral microbleeds. At present, the etiology of cerebral microbleeds includes atherosclerosis (seen in both the basal ganglia and subcortical area)[14,53] and age-related amyloid angiopathy (in the subcortical area). Whether cerebral microbleeds alone present with clinical symptoms remains a matter of debate.[54]

Cause of bladder dysfunction in white matter disease

Detrusor overactivity is the major underlying pathophysiology of vascular incontinence. The incidence of detrusor overactivity in cases of white matter change is reported to be 70-91% of patients,[13,55] and is more common than following hemispheric stroke.[56] Detrusor overactivity is a urodynamic observation characterized by involuntary contractions during the filling phase which may be spontaneous or provoked.[57] In the study of Sakakibara *et al.*[13] urodynamic studies were performed in 33 of the subjects, divided into 2 groups according to the above criteria (grade 0, 11 elderly subjects as described above, 2 with nocturnal urinary frequency ≥2 but no urge urinary incontinence, grade 1-4, 22 subjects, 14 male 8 female, mean age 72 years, 19 with nocturnal urinary frequency ≥2 and 12 with urge urinary incontinence). They found that subjects with grade 1-4 white-matter lesion had detrusor overactivity more commonly (82%) than those with grade 0 white-matter lesion (9%) (I<0.05). Post-micturition residuals, low compliance, detrusor-sphincter dyssynergia and uninhibited sphincter relaxation were also more common in grade 1-4 white-matter lesion than in grade 0 white-matter lesion, though there was no statistical significance.

Cerebral control of the bladder and how it is affected by white matter disease

The frontal cortex is now recognized as an important the higher center for micturition: damage to the prefrontal cortex, medial superior/middle frontal gyri, anterior cingulate cortex, supplemental motor area and insula have been shown to result in marked lower urinary tract dysfunction in humans.[56,58] These clinical observations have been corroborated by functional neuroimaging in humans.[59-61] The connection between the prefrontal cortex and the micturition circuit is still uncertain, but it is known that the prefrontal cortex projects fibers directly to the hypothalamus-periaqueductal gray. The prefrontal-striatal pathway may also have a role.[62] Detrusor overactivity is considered to be an exaggerated spinobulbospinal micturition reflex that normally promotes micturition in brain lesions.[63] Functional neuroimaging studies showed that the prefrontal cortex was deactivated in elderly subjects with urinary frequency/urgency as compared with controls.[64]

Cortical white matter change in MRI looks diffuse. However, within the brain, detailed pathology studies confirmed that the frontal lobe is most severely affected.[65] This is in line with the fact that MRI volumetry showed frontal lobe atrophy,[66] where glucose and N-acetyl-aspartate metabolism was most severely reduced.[67,68] Corresponding to this, brain perfusion was most severely reduced in the frontal lobe of subjects with white matter change,[69] a finding that must still be fully explained. However, in these patients, hypoxic-ischemic damage to oligodendrocytes was marked in the frontal lobe thus impairing not only the frontal micturition pathway, but also the frontal gait and cognitive pathways, relevant also to cerebrovascular parkinsonism and dementia.[70-73]

Based on a recognition of the importance of WMD in elderly and the new understanding of the cerebral control of micturition, Kuchel *et al.*[27] analyzed the location of white matter change and urinary dysfunction in 97 community-dwelling individuals (age 75-89 years). Baseline incontinence status and related symptoms were evaluated using validated instruments (3IQ, Urinary Incontinence Severity Index, Urogenital Distress Inventory, and Incontinence Impact Questionnaire). Regional white matter change was measured and analyzed using reference brain atlases [white matter parcelation atlas [WMPA] and the International Consortium on Brain Mapping (ICBM)]. They chose seven brain regions representing relevant white matter tracts: anterior corona radiata, inferior fronto-occipital fasciculus, cingulate gyrus, cingulate hippocampal portion, superior frontooccipital fasciculus, uncinate fasciculus, and genu of the corpus callosum. These anterior regions are known to have a potential role in bladder control. The anterior corona radiata contains both descending prefrontal corticopontine projections and ascending thalamocortical (frontal/prefrontal) projections. Sixty-two (64%) of the participants were incontinent,

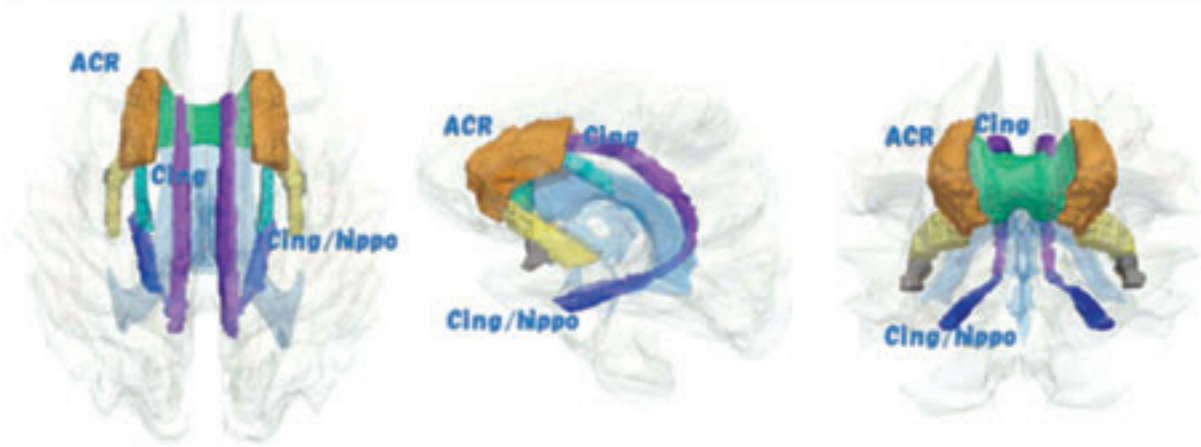

Figure 2. Cerebral white-matter changes and urinary dysfunction. The presence of white matter change in right inferior frontal regions and relevant tracts (anterior corona radiata and superior fronto-occipital fasciculus) is related with incontinence, incontinence severity, and degree of bother. ACR, Anterior corona radiata; Cing, Cingulate gyrus; Cing/hippo, Cingulate hippocampal portion. Reproduced with permission.[27]

mostly with urgency (n=37, 60%) and moderate-severe symptoms (n=36, 58%). As a result, the presence of white matter change in the right frontal and right inferior frontal regions predicts incontinence severity, while no significant relationship was seen with incontinence, incontinence type, bother, or functional impact (Figure 2).[27] As regards white matter-relevant tracts, white matter change that overlapped the anterior corona radiata predicted severity and a degree of disturbance, cingulate gyrus predicted incontinence and severity, whereas cingulate (hippocampal portion) and superior fronto-occipital fasciculus predicted severity. The same group reported that the volume of white matter change predicts executive function, mobility, and urinary incontinence.[74]

Most recently the Pittsburgh group studied 25 older women (age 71.5±7.5 years) with urgency incontinence.[28] Mean MMSE score was 29.2; none had cognitive problems. In these patients, volume and location of white matter change, specific white matter tracts, and regional brain activity by fMRI during bladder filling and reported *urgency* were analyzed. As a result, brain responses to bladder filling during self-reported *urgency* were most prominent in the frontal regions, including medial/superior frontal gyrus adjacent to dorsal anterior cingulate gyrus (ACG) and other areas. Regional activations (*e.g.* medial/superior frontal gyrus adjacent to dorsal ACG) and deactivations (*e.g.* perigenual ACG adjacent to ventromedial prefrontal cortex) became more prominent with increased global white matter change (Figure 3). Looking at the fiber tracts within the white matter, *e.g.* anterior thalamic radiation (ATR), uncinate fasciculus (UNC), inferior fronto-occipital fasciculus (IFO), inferior longitudinal fasciculus (ILF) and superior longitudinal fasciculus (SLF), the main effect

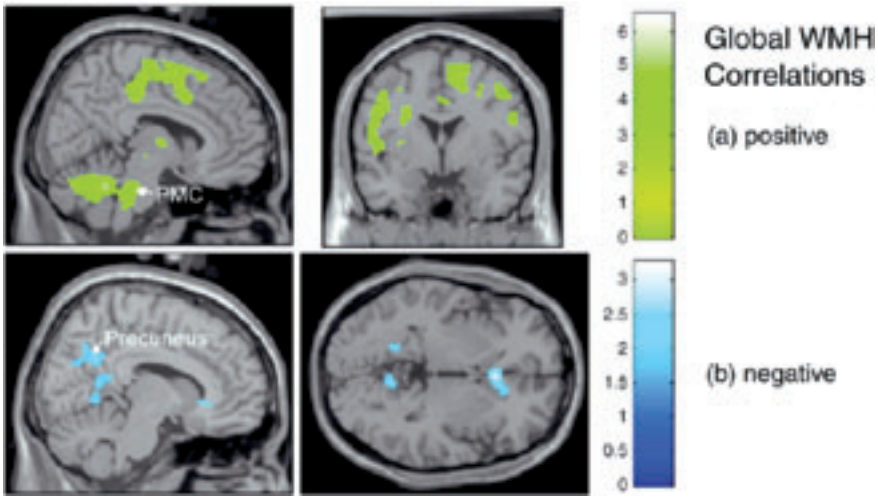

Figure 3. Cerebral white-matter changes and urinary dysfunction. Regional activations (*e.g.* medial/superior frontal gyrus adjacent to dorsal anterior cingulate gyrus, cerebellum and pontine micturition center [PMC]) have positive correlations with global white matter change (upper panel), while some regional activations (*e.g.* precuneus, etc.) have negative correlations. Reproduced with permission.[28]

activations and deactivations were superimposed with ATR (anterior, semi-horizontally projecting fibers to the medial prefrontal cortex and perigenual ACG, and also to several areas that were deactivated; 55% consisting of global white matter change) and SLF (middle, semi-vertically projecting fibers to dorsal ACG, insula, and inferior frontal gyrus; consisting of only 8% of global white matter change), respectively (Figure 3).[28] The results indicated that the white matter changes, particularly the anterior portion that includes ATR, are clearly related with overactive bladder in cognitively-intact, elderly women.

Differential diagnosis

Urological problems are an important cause for incontinence in the elderly. Detrusor overactivity may occur in men with benign prostatic enlargement. However, in 25-93%, detrusor overactivity is reported to remain unchanged after prostatectomy, the figures increasing with age.[75,76] Concomitant white matter changes are reported in this group by Sakakibara *et al.*[77] and are likely to contribute to detrusor overactivity. Elderly women may present with stress incontinence, which can be differentiated by history.

Diabetes, when uncontrolled, may manifest with overactive bladder symptoms due to polyuria. However detrusor overactivity is also seen and recent surveys suggest that diabetic neuropathy is often accompanied by white matter change, because of atherosclerosis in the cerebral arteries.[78] In Kaplan's study of cases with diabetes,[79] there was a negative correlation between detrusor overactivity and features suggestive of sacral neuropathy (decrease in perineal sensation, sphincter tone, and bulbocavernosus reflex). In Rapidi's study of cases with diabetes,[80] detrusor overactivity tended to parallel a prolonged central conduction time by somatosensory evoked potential, suggesting a central etiology. Nocturia may result from nocturnal polyuria (more than 33% of urine production during night-time) which can be detected by a bladder diary and may result from several medical conditions, such as chronic heart failure, chronic kidney dysfunction, postural hypotension partial pituitary diabetes insipidus and obstructive sleep apnea syndrome.

Other neurological conditions may also manifest with incontinence. Normal-pressure hydrocephalus (NPH) presents with a similar clinical triad as WMD, namely gait disorder, urinary incontinence, and dementia.[81] However it is one-tenth as common as WMD.[82] Brain imaging is essential to differentiate the two conditions. Bladder disorder in NPH mimics that in white matter change (detrusor overactivity, 95%),[83] presumably reflecting frontal lobe hypoperfusion.[84] Importantly, bladder dysfunction and frontal lobe hypoperfusion in NPH can be reversed after shunt surgery. Other differential diagnoses include: for dementia, Alzheimer's disease (detrusor overactivity, 40%);[85] for gait disorder, Parkinson's disease (detrusor overactivity, 45-93%);[86] and for dementia and gait disorder, dementia with Lewy bodies (detrusor overactivity, 71%)[87] and progressive supranuclear palsy (detrusor overactivity, 67%).[88]

Treatment and prevention of vascular disease

Though the vascular changes may not be reversible, early identification of risk factors and initiation of secondary prevention might arrest the disease progress. The results from studies exploring control of vascular risk factors, such as hypertension,[89] dyslipidemia and diabetes,[90,91] do not provide conclusive evidence. Falls in blood pressure may, in fact, worsen gait by counteracting the high-set cerebral autoregulation.[89] The prevention of small vessel disease is controversial. Antiplatelet medication for white matter change has been suggested; however, at present there are no large prospective studies available. On the other hand, there is a risk of hemorrhagic complication of antiplatelet drug use when there are comorbid microbleeds.[92] Carotid endarterectomy improved cognitive function in one study in white matter changes accompanied by carotid stenosis.[93] Although edaravone, a free radical scavenger, has begun to be used in acute ischemic stroke, its use in slowly progressive white matter change awaits further study.[94] None of these studies have specifically studied improvement in bladder symptoms.

Treatment of urinary frequency/urgency

Medications used to treat vascular incontinence include anticholinergic agents, such as oxybutynin, propiverine, detrusitol, solifenacin,and imidafenacin.[95] Mori *et al.*[96] performed urodynamics in 46 dementia patients, and found detrusor overactivity in 91% of patients with white matter change and 58% of Alzheimer's patients. They conducted an open trial with 20 mg/day of propiverine hydrochloride for two weeks irrespective of the presence of detrusor overactivity, and found increased bladder capacity or lessened frequency of incontinence in 40% of patients. Both groups responded almost equally, and patients with detrusor overactivity showed a more satisfactory response. Treatment for urinary frequency/urgency may be of particular benefit in subjects without marked immobility or dementia.

The use of medications with anticholinergic side-effects in the elderly is of concern, particularly when there is a risk of exacerbating cognitive impairment. Crossing the blood-brain barrier, they can act at the M1-muscarinic receptors in the cerebral cortex and hippocampus, or M4-receptors in the basal ganglia. Factors predisposing to cognitive side effects include: i) central muscarinic receptor affinity, *e.g.* high M1-receptor selectivity; and ii) permeability across the blood-brain barrier: size, lipid solubility, less number of hydrogen bonds, neutral or low degree of ionization and number of rotatable bonds.[29,97,98] Darifenacin is an M3-selective antagonist and thus has less cognitive side effects, while trospium, a quaternary amine, has a high polarity and, therefore, poor permeability across the blood-brain barrier. Other common anticholinergic side-effects are dryness of the mouth (M3) and constipation (M2,3). Extended-release formulations may lessen these adverse effects.[99]

Conclusions

Small vessel disease of the brain affecting the deep white matter characteristically manifests with neurological syndromes, such as vascular dementia and vascular Parkinsonism. There is, however, compelling evidence to suggest that white matter disease can also cause incontinence, and in some patients this may be the initial manifestation. Functional imaging studies have shown that anterior lesions, especially of the deep white matter of the frontal lobe, more often result in incontinence.

The pathophysiology basis for vascular incontinence is detrusor overactivity and management options are centered on the use of anticholinergics. Management of vascular risk factors is likely to arrest progression of vascular disease, but studies are required to evaluate whether this may improve incontinence.

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