Binswanger's disease: case presentation and differential diagnosis

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Abstract

Binswanger's disease is a type of vascular leukoencephalopathy that can lead to cognitive impairment and neurological deficits and is sometimes difficult to diagnose. We present a case of Binswanger's disease with an interesting differential diagnosis based on clinical aspects, laboratory findings and imaging studies.

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Key Clinical Message

Establishing a diagnosis of Binswanger's disease requires a multimodal approach. As new pathophysiological mechanisms are revealed, tests that should yield greater specificity will become available in the years to come.

Introduction

The term "leukoencephalopathy" refers to a heterogeneous group of disorders characterized by the degeneration of the white matter of several etiologies: vascular, toxic, infectious and genetic. The last group includes the so called leukodystrophies [1].

The term Binswanger's disease was given by Elois Alzheimer in 1902 in honour of his professor, Otto Binswanger, who first described the clinical and pathological aspects of the disease in 1884[2]. Binswanger's disease, or "subcortical arteriosclerotic encephalopathy", as Olszewski called it 60 years after its first discovery [3], refers to a type of leukoencephalopathy linked to circulatory and vascular factors with significant clinical consequences frequently associated with arterial hypertension, arteriosclerosis and strokes [4].

Binswanger's disease represents one of the causes which lead to vascular cognitive impairment alongside cerebral lacunes, amyloid angiopathy and some forms of Alzheimer diseases, and it may coexist with any of these disorders [5]. Louis Caplan established in 1995 the first criteria for that are required for diagnosis and they are sub-divided into three categories which we will enunciate briefly in the following paragraphs [2]. These criteria still hold to the present day and have been adapted through the course of time along with a better understanding of the physiopathological and morphopathological characteristics.

I. The presence of known or hypothesized risk factors

The most important and frequently described risk factor associated with Binswanger disease is chronic, uncontrolled, arterial hypertension, therefore its absence in a patient with cognitive impairment and neurological signs should lead to questioning the diagnosis[5]. The explanation most often proposed is that chronic arterial hypertension is responsible for the narrowing of the small blood vessels due to lipohyalinosis and fibrosis with subsequent blood flow reduction and hypoxia. These phenomena lead to a local neuroinflammatory response which in turn result in myelin sheath degeneration [6]. Other risk factors such as diabetes mellitus, smoking, dyslipidemia, sleep apnoea, atrial fibrillation, although frequently present in these patients, have a smaller role in establishing the diagnosis of the disease [5]. Exclusion of other diseases which lead to white mater degeneration, such as multiple sclerosis, AIDS or radiation toxicity is crucial[2].

II. Clinical features

An essential element lies in the way the clinical aspects of the disease evolve, with stepwise or gradual progression of the cognitive impairment and other neurological signs and symptoms [2,5,7]. First symptoms usually appear between the fifth and the seventh age decade[7]. The clinical course of the illness is variable and evolves over a 5- to 10-year period. There doesn't seem to be any gender bias. Cognitive and behavioural changes are characterized by dementia and a dysexecutive syndrome (changes in attentional control, working memory, and short-term memory, impulse control and abulia in the final stages) [2,5]. Computations and mathematical functions are usually deficient [2]. Abnormalities of long-term memory, language and visual-spatial functions are not as prominent as in patients with Alzheimer's or Pick's disease and therefore the MMSE (Mini Mental State Examination) can often be within normal range, while the MOCA score (Montreal Cognitive Assessment) may evidence cognitive impairment [5]. History often reveals past strokes which can be sometimes typical to one of the multiple lacunar syndromes, pure motor hemiparesis being the most frequent of them [7]. In other patients, the focal neurologic deficits can have a subacute onset with progressions during days or weeks and are sometimes associated with strokes. Cognitive and behavioural impairment, motor and gait disturbances, falls, incontinence evolve with periods of stabilization, plateaus and periods of improvement. A mixture of pyramidal tract signs, extrapyramidal signs and pseudobulbar signs can often be seen [2,5,7].

III. Imaging

The first imaging descriptions of the lesions were given using Computer Tomography (CT). The ubiquitous characteristic of the illness is represented by the changes to the subcortical white matter which has a bilateral presentation, described as low dense lesions without contrast enhancement. These lesions are most often present in the periventricular regions, especially adjacent to the frontal horns. These changes were named leukoaraiosis by Hachinski and they denote the rarefaction of the subcortical white matter. Juxtacortical white matter ("U"-association fibers) is often spared. It is important to mention that these changes can be

present without any neurological signs and can be also associated with aging [7]. White matter disorders are better characterized on MRI which has a greater sensitivity than CT. The areas of demyelination are described on MRI as large, confluent, white mater hyperintensities (on T2WI and FLAIR sequences), with ill-defined borders. The lesions are discretely hypointense on T1WI sequences. Lesions are usually bilateral, symmetric and grouped around the frontal horns, but can have variable degrees of extension, and both the periventricular and deep white matter can be affected, but the juxtacortical white matter is always spared, as mentioned before. Subcortical lacunes and "mini-strokes" are often found and the Virchow-Robin perivascular spaces are frequently enlarged[4,5, 8]. Lesions can also be present in the white matter of the brainstem, especially the central pons (the medulla oblongata and the midbrain are also more often than not spared)[9]. Mild to moderate white matter atrophy is also a common finding [5]. Diffusion weighted imaging (DWI) can detect acute ischemic lesions. Subcortical microbleeds can be seen in Binswanger's disease and can be detected on SWI sequences, but their presence in large numbers or if they are located in the cortical regions should raise the suspicion of amyloid angiopathy [5].

Case presentation

A 50-year-old Caucasian male, residing in an urban area, with right laterality and no history of any chronic illnesses, was admitted to our Neurology department with the complaint of weakness in the right limbs. The patient's symptoms had an acute onset 2 days prior to presentation. Family history revealed that the patient's mother suffered from an ischemic stroke at the age of 87. The patient was an artist and a painter, admitted to being a cigarette smoker (1 pack of cigarettes per day for over 30 years) and to consuming alcohol daily (about 50 cmc of spirits per day). There was no history of head trauma or any known allergies.

The general examination revealed that the patient was conscious and aware, had normal body temperature, no signs of recent trauma, a BMI (Body Mass Index) of 21 $kg/m^{2.}$ The blood pressure was 234/146 mmHg, and the heart rate 104 beats per minute. The neurological examination showed the following:

1. Pyramidal tract signs characterized by hemiparesis regarding the right limbs with a score of 4/5 (on the MRC – Modified Research Council scale). Extensor plantar reflex was objectified in the right leg. The patient also had central face palsy on the same side.
2. Extrapyramidal signs characterized by slowness, left upper limb rigidity, hypomimia and a low-volume, monotonous speech.
3. Mild cognitive impairment on MMSE testing (a score of 27/30) and on MOCA testing (25/30). The abilities affected in our patient were: visuospatial/executive functions, short term memory and mathematical functions.

*Paraclinical investigations:*On admission a head CT without contrast dye was performed (Figure 1. A-E). The CT revealed a small hypodense lesion (Figure 1. B), with ill-defined borders, located in the posterior limb of the left inner capsule that was interpreted as an acute lacunar stroke.

Diffuse white matter hypodensity was observed, with symmetrical pattern, regarding the periventricular region, the centrum semiovale and the inner capsule. The juxtacortical arcuate fibers were spared. The hypodense white matter lesions extended in the brainstem, cerebellar peduncles and the cerebellum.

For a more precise evaluation of the white matter changes a native MRI was performed (Figure 2. A-N).

MRI revealed an acute ischemic lesion (10/19 mm), hyperintense on the DWI, FLAIR and T2WI sequences (Figure 2. B, 2. L), located in the posterior limb of the inner capsule that extended to the lenticular nucleus on the left. Diffuse hyperintense areas on T2WI and FLAIR sequences were also observed in the white matter, with the same distribution (supratentorial and infratentorial) as the hypodense areas described on head CT (Figure 2. A-K), without abnormal restricted diffusion (Figure 2. L). On the SWI sequences, conglomerate hypointense lesions adjacent to the midline of the pons ware observed (Figure 2. N) that were

interpreted as old hemosiderin deposits. Similar lesions were observed in the centrum semiovale (Figure 2. M).

Complete bloodwork was done. No notable laboratory changes regarding the hematological profile, liver and kidney functions, coagulation parameters were observed. No biological inflammatory syndrome was present on admission and during hospitalization. Other notable bloodwork parameters will be mentioned below in the differential diagnosis subchapter. ECG was within normal range. A carotid Doppler ultrasonography was performed which showed bilateral non-stenotic atheromatous plaques, with heterogenous echogenicity; irregular surface and a thickness ranging from 2.7 mm in the left common carotid artery to 4.2 mm in the right common carotid artery were observed.*Differential diagnosis:* Using the imaging aspects of the disease on MRI we decided taking into account for the differential diagnosis disorders which are compatible with the pattern of the white matter lesions as presented in the article written by Schiffmann et al.[10] These disorders where afterwards excluded using clinical and biological findings.

1. CADASIL (Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy) usually has an earlier onset, during the third decade. The lack of findings in the family history of our patient, the absence of lesions on imaging anterior to the temporal horns of the lateral ventricles and of the migraines makes this diagnosis improbable. Also, the presence of vascular risk factors (arterial hypertension and smoking) plead for an acquired microangiopathy. [8,10].
2. Multifocal Progressive Leukoencephalopathy may present itself with similar imaging features to Binswanger's Disease, but cerebral lacunes should be absent [8]. Characteristic lesions on MRI are more often localized at the grey-white matter junction with damage to the juxtacortical association fibres [11]. On clinical examination, motor coordination and gait disturbances are frequently found alongside visual field deficits and language abnormalities [11]. A normal haematological and immunological profile and the absence of opportunistic infections and other infectious events in the past that would suggest an acquired or intrinsic immunodeficiency are also favourable for excluding this diagnosis [12].
3. HIV-associated dementia is associated with a symmetrical, periventricular pattern of changes to the white matter with sparing of the juxtacortical and infra-tentorial white matter, atrophy of the grey matter of the cerebral cortex, atrophy of the deep white matter and volumetric changes of the basal ganglia [18], changes that were not present in our patient. Also, the lack of criteria that would suggest and acquired immunodeficiency as mentioned in the previous paragraph makes this diagnostic much less probable
4. Cerebral vasculitis as part of a systemic disorder may have various features on MRI imaging, and the clinical and biological features of the disease include: signs of a systemic disease, headaches, elevated acute-phase reactants, inflammatory microcytic anemia, the presence of auto-antibodies [13]. None of these changes were found in our patient. Antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, circulating immune complexes where all in normal range.
5. Primary angiitis of the central nervous system (PACNS) is rare disorder and should be suspected in younger patients with strokes, without any known vascular risk factors. The major symptoms of this disease include headaches (60% of cases), cognitive impairment (50% of cases), neurological focal signs. Systemic and biological changes that were described in the cases of systemic vasculitis are often absent. On MRI, the lesions are typically multifocal, bilateral, hyperintense on T2WI and FLAIR sequences, and can be found in the superficial and deep white matter, and in the cortical grey matter and basal ganglia [14]. Of cardinal importance are the bilateral stenosis and dilation of various sized blood vessels[14] which were absent in our patient. The gold standard for diagnosing or excluding PACNS is represented by cerebral biopsy [14], which we preferred not to perform due to lack of sufficient arguments that would justify the risk of the investigation.
6. Toxic leukoencephalopathy develops in the context of chronic exposure to leukotoxic substances such as some illicit drugs (opioids, cocaine, amphetamines). Leukoencephalopathy caused by use of heroin, also known as "chasing the dragon" syndrome, is one of the most studied of these rare occurrences, and it usually presents on MRI with white matter hyperintensities that are symmetrical, especially with changes in the corticospinal tracts of the pons, perirolandic white matter, cerebellar white matter

with sparing of the juxtacortical white matter and the grey matter [15, 16]. These lesions are similar to those seen in our case. The patient denied any use of illicit substances, did not have any signs of chronic toxicity of the substances mentioned above and did not develop any withdrawal events during the 2-week hospitalization period. Toxic leukoencephalopathy may also develop after chronic exposure to toluene. Our patient was a painter and toluene can be found in many paints and solvents. and the main neurological feature of chronic toluene toxicity is the cognitive impairment [17]. The patient refused to give any information about the ingredients of the paints used by him. Nevertheless, the presence of other lesions associated on MRI, other than the white matter hyperintensities, are not typical in chronic toluene toxicity. There were also no other systemic disturbances that would suggest chronic toluene toxicity (altered kidney function, respiratory, dermatological, gastrointestinal or musculoskeletal abnormalities).

7. Other illnesses that have a genetic etiology are usually detected during childhood or adolescence and are frequently associated with systemic abnormalities. Out of these pathologies, Fabry disease is still worth mentioning. There are some rare cases described in literature, in men, that had a late-onset at adult age and in which only one or two organ systems were affected. The kidneys (chronic kidney disease), and the cardiovascular system (hypertrophic cardiomyopathy, valvular anomalies, conduction disorders) were most frequently affected [19,20]. Our patient had no clinical or paraclinical evidence of a kidney or heart abnormalities. When present, central nervous system affliction leads to frequent ischemic strokes and cognitive impairment. On MRI, white matter lesions are present in 80% of cases and can be heterogenous, ranging from small, scattered and punctuate T2-weighted hyperintense foci to bilateral diffuse, patchy and partly confluent white matter hyperintensities. An important characteristic is that the lesions in Fabry disease only present themselves in the supratentorial white matter, which was not the case in our patient [19].

Outcome and follow-up The therapeutic management targeted lowering of blood pressure in accordance to the actual guidelines and secondary stroke prevention using antiplatelet monotherapy and statins. Neurotrophic medication and vitamins were administered. Blood pressure was especially difficult to control requiring multiple associations of anti-hypertensive drugs. The patient was also evaluated in the first 72 hours after admission by a kinetotherapist, and daily sessions of active and passive mobilization were performed. Regarding the clinical and neurological evolution, the motor deficit, fine motor control and prehension improved during admission and during the first month after discharge from hospital.

Discussion

A diagnosis of Binswanger's disease was proposed for our patient based on the clinical features regarding the risk factors, general and neurological examination, the white matter changes observed on CT and MRI and also a thorough differential diagnosis. More than 20 years have passed since Benett and Caplan proposed a diagnostic criterion for Binswanger's disease [2]. The pathophysiology of the disease has been better understood since then and besides the usual clinical features and imaging, ancillary tests can be used in difficult cases [5]. Changes in CSF biochemistry may reflect the neuro-inflammation present in small vessel disease. Neuro-inflammation leads to blood-brain barrier dysfunction with increased permeability on the one hand and important changes in the protein and cytokine expression patterns in glial cells on the other hand. These changes may be reflected by an increased albumin index in the CSF (due to increased permeability) and in increased levels of inducible matrix metalloproteinases, such as MMP-3 and MMP-9 (due modified protein expression) [5,6,22]. A recent biomarker identified as having larger levels is patients with Binswanger's disease is lipocalin 2 (LCN2). LCN2, also known as oncogene 24p3, a glycoprotein involved in NVU damage in patients with vascular disease. It had promising results and was found having larger levels in patients with vascular dementia as opposed to Alzheimer's disease or other types of dementia [24].

Various imaging studies such as MRI diffusion tensor imaging (to evaluate white matter tracts integrity) or dynamic contrast enhancement MRI (to reveal disruption of the blood-brain barrier) can aid the clinician

in establishing the diagnosis. These imaging techniques and many others have unknown reproducibility and lack validation for Binswanger's disease in larger populations. It is important to mention that the diagnosis cannot be given solely on CT or MRI imaging and requires a careful clinical examination. [5,22, 23]

Establishing the diagnosis for Binswanger's disease requires a multimodal approach. None of the biomarkers alone are adequate to diagnose the disease, but using clinical data alongside imaging and ancillary tests can prove helpful in patients with cognitive impairment and neurological signs with uncertain or unknown etiology[5,6,22,23].

Conclusions

Binswanger's disease is a complex neuro-psychiatric disease and its pathophysiology is only partially understood. As new pathophysiological mechanisms are revealed, other tests will become available in the years to come and also novel therapies will specifically target these mechanisms (inflammation, arterial stiffness and clearance of cerebral waste) in order to better treat these patients. The particularity of our case resides in the fact that the white matter lesions were diffuse, extending from infratentorial to the brainstem, cerebellar peduncles and the cerebellum, which is not common in Binswanger's disease and is rarely described in literature.

Author contribution

1. Vitalie Văcăraș: head of department, consultant neurologist in charge of the patient. Given approval of the final version.
2. Adrian Mihai Cordoș: resident doctor, conception and design of the case report.
3. Imelda Rahovan: resident doctor, revising the case report and drafting the discussion section
4. Sorina Frunze: resident doctor, revising the case report and comparing it to the current literature
5. Dafin Fior Mureșanu: coordinator of the team.

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Figure 1. A) Axial cross-section at the level of the body of lateral ventricles. B) Axial cross-section of the basal ganglia. C) Axial cross-section of the midbrain. D) Axial cross-section of the pons E) Axial cross section of the cerebellum and the medulla oblongata

Figure 2. A-F) Axial cross-sections MRI images of the brain at different levels, T2 weighted. G-K) Coronal cross-sections MRI images on FLAIR. L) DWI sequence at the level of the internal capsule. M-N) SWI sequences.