European Journal of Neurodegenerative Diseases
ISSN 2279-5855 / 2022 vol. 11, ISSUE N. S1, July-December

DISRUPTION OF THE EXTRAPYRAMIDAL SYSTEM - WILSON'S DISEASE

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ABSTRACT

The extrapyramidal system (EPS) includes both nerve centers and bundles of nerve fibers that are controlled by the niger locus and the subthalamic nuclei. The EPS is involved in the control of body position and movements, and the contraction of skeletal muscles, contibuting to voluntary movement as well as playing a key role in automatic movements. When the EPS is disrupted, central nervous system (CNS) disorders with akinesia, tremor, athetosis, chorea, and hyperkinesia can occur, as is highlighted in Parkinson's disease (PD). In chorea, which can involve the face, mouth, trunk and limbs, involuntary and repetitive, short, irregular and rapid movements can occur. In addition, neurological syndromes and disorders of uremic pathology due to chronic kidney disease may also occur. Disruption of the EPS at a certain level can also cause stiffness and suppression of reflexes. In the injured EPS, there may be hypotonic muscles before contraction (and more rarely, hypertonia), with the presence of grimaces on the face, speech disorders, and dysarthria. Involuntary, abrupt, and arrhythmic choreic movements may occur suddenly and are often accompanied by muscle hypotonia, and there may be torsional spasms consisting of slow muscle contractions. In the genetic disorder Wilson's disease (WD), which is characterized by copper metabolic dysfunction, neuronal degeneration affecting axons may be present.

KEYWORDS: *extrapyramidal system, CNS, copper, neurodegeneration, axon, Wilson's disease*

INTRODUCTION

The extrapyramidal system (EPS) is a complex circuit of nerves that includes both nerve centers and the bundles of nerve fibers that connect the centers to the rest of the central nervous system (CNS) (1). The EPS is under the control of the locus niger and the subthalamic nuclei (2). The main parts of this system include the central grey nuclei, caudate nucleus, globus pallidus, putamen, and thalamus, including the area of the cerebral cortex of the frontal lobe (3). The EPS includes the structures of the CNS that contribute to the control of the position and movements of the body and the contraction of the skeletal muscles, contributing to the maintenance of body posture (4). The EPS is involved in voluntary movement and also plays a key role in automatic movements such as walking. Dysregulation in the EPS can lead to CNS disorders, including Wilson's disease (WD) which involves copper metabolic dysfunction.

DISCUSSION

Damage to the EPS can cause CNS dysfunction characterized by akinesia, tremor, and hyperkinesia, clinical signs that occur especially in Parkinson's disease (PD) (5). Extrapyramidal hypertonia is very characteristic of PD and involves

Received: 12 December, 2022
Accepted: 29 December, 2022
2279-5855 (2022)

the upper limbs which are prevented from extending due to limb rigidity (6). Disruption of the EPS at the level of the striatum is characterized by muscular rigidity, consequent disturbances of postural tone and coordinated movements, and the appearance of involuntary movements such as tremors, athetosis, and chorea (7).

Chorea usually involves the face, mouth, trunk, and limbs and is characterized by repetitive, brief, irregular, and rapid and involuntary movements that begin in one part of the body and move abruptly, unpredictably, and often continuously, towards another side (8). Rigidity can manifest in various ways depending on the height of the interruption of the extrapyramidal pathways. If the interruption extends from the quadrigeminal tubercles to an area located at the level of the red nucleus, the rigidity is intense and accompanied by the suppression of reflexes. If the extrapyramidal pathway is interrupted below the striatum, there is rigidity of decerebration (9). However, if the damage occurs at the level of the skull, excluding the connections of the basal nuclei with the extra-pyramidal areas of the cortex, there is still rigidity, but the reflexes persist and this case is called decortication rigidity (10).

The alteration of the basal nuclei has consequences that depend on the severity of the damage. Athetotic movements can be unilateral or bilateral, are generally absent during sleep, and are accentuated immediately before voluntary movements (11). The muscles involved are generally hypotonic before contraction, but more rarely there is hypertonia. Affected subjects often have the appearance of grimaces on their faces. The muscles of the tongue can also be involved, as well as the palate, resulting in speech disorders and dysarthria (12). Choreic, involuntary, abrupt, and arrhythmic movements can appear suddenly and are often accompanied by muscular hypotonia (13). Patients may also present with torsion spasms consisting of slow muscle contractions that lead to severe twisting of the trunk and limbs (14). Other abnormal movements are called hemiballismus which are rapid and sudden, similar to choreic ones, while spasms consist of a long-lasting contraction of the muscle bundles with sometimes accompanied by pain (15). The main diseases associated with damage in the basal nuclei are: WD, PD, athetotic syndromes, choreic syndromes, and hemiballismus syndrome (16).

Wilson's disease (WD)

WD was described for the first time by Samuel Alexander Kinnier Wilson in 1912 (17). In an interesting article, he highlighted some fundamental characteristics of WD such as heredity, the concomitance of liver diseases (cirrhosis), and neurological deficits of the extrapyramidal type (18). The gene responsible for this rare disease is called ATP7B, which encodes a P-type ATPase that modifies the level of the $Cu2^{+}$ in the tissue and blood (19). In WD, copper metabolic dysfunction can cause isolated degeneration of neurons with axonal trafficking and peripheral sensory neuropathy (20) (Fig.1).

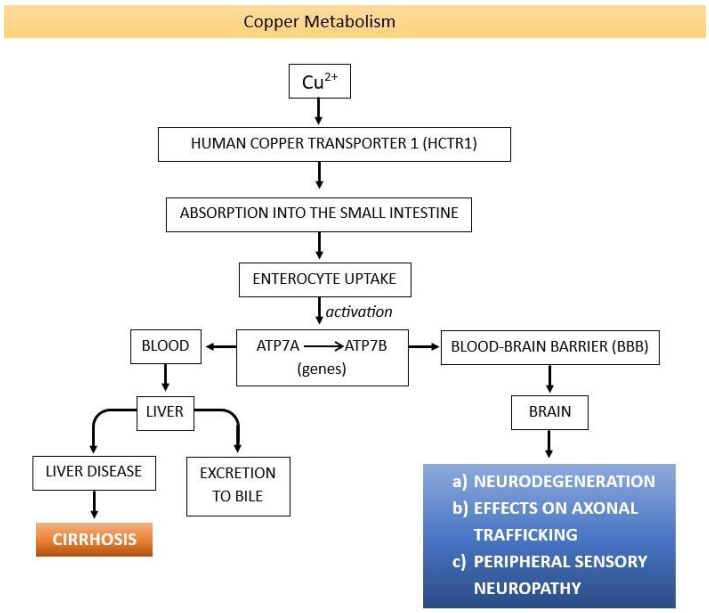

Fig. 1. *In Wilson's Disease (WD), copper metabolic dysfunction leads to liver disease such as cirrhosis and neurodegeneration, impaired axonal trafficking, and peripheral sensory neuropathy.*

The pathogenesis of WD is characterized by muscular rigidity, involuntary movements, emotional crises, and neurological symptoms, and non-neurological signs such as liver cirrhosis and greenish pigmentation of the cornea which

can occur in some cases (20). The diagnosis is performed on clinical laboratory samples where low levels (below 200-350 mg/l) of serum ceruloplasmin can be found, but sometimes levels of this protein can also be normal (21). In addition, WD patients may present increased urinary copper excretion and increased hepatic copper content (22).

The muscle stiffness progressively affects the muscles at a systemic level, predominantly affecting the flexor muscles. The contracted muscles present a resistance that has been called "lead pipe". Active movements are difficult, as is the production of sounds or noises using the vocal organs (23). Swallowing may also be impaired. Involuntary movements manifest as diffuse tremors or athetotic movements with a continuous flow of slow, steady, and writhing movements. Patients may experience mood changes with a predisposition to crying and laughing (24). Muscle hypertonicity often leads patients to remain with their mouths wide open, but with essentially normal reflexes.

Neurological damage mainly occurs at the level of the base of the telencephalon, the putamen, in the caudate which works with the putamen to receive input from the cerebral cortex, and in the pallidum, the two internal portions of the lenticular nucleus of the striatum (25). Patients affected by WD are often distinguished into 3 types: hepatic, hepato-neurological, and predominantly neurological. Patients with neurological dysfunction present with hypokinetic and hyperkinetic extrapyramidal symptoms and often contract PD. Accumulation of copper in the brain leads to dysfunction of the basal ganglia with movement disorders (26). Hyperkinesia often results in attention deficit disorder (27).

WD causes increased concentrations of copper in the brain and liver which can be chelated by penicillin (28). Increased copper causes clinical disorders that are different from those caused by other heavy metals such as Alzheimer's and PD (20).

CONCLUSIONS

The EPS is controlled by the niger locus and the subthalamic nuclei and mediates both voluntary and involuntary movements and the contraction of skeletal muscles. Damage to the EPS is associated with CNS disorders, as occurs in PD. This class of pathologies is characterized by the level of disruption to the EPS which can involve various parts of the body and different muscles. WD is characterized by copper metabolism dysfunction and causes neuronal degeneration and axonal dysfunction. There is currently no satisfactory therapy for WD, and future research is indispensable to improve treatment and the quality of life for patients.

Conflict of interest

The author declares that they have no conflict of interest.

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