Journal of Psychological and
Educational Research
JPER - 2021, 29 (1), May, 140-153

THE EFFECTIVENESS OF COGNITIVE-BEHAVIOURAL PSYCHOTHERAPY IN WILSON'S DISEASE: SINGLE SUBJECT EXPERIMENT

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Abstract
Wilson's disease is a rare pathology, characterised by the uncontrolled accumulation of copper in the body predominantly affecting organs such as liver, brain, eyes. Multi-organ damage leads to a rapid deterioration of body functions, with major psychological and neurological impact. Therapeutic approaches are hampered by the low prevalence of the disease and by the impossibility of organising studies based on samples of subjects. For this reason, we set out to perform an experiment with a single patient diagnosed with Wilson's disease, in which we aim to highlight the effectiveness of psychotherapeutic interventions in mitigating the impact of the disease at the systemic level. Specifically, we want to analyse how the cognitive-behavioural therapy associated with relaxation techniques leads to the improvement of affective and motor symptoms, compared to thought suppressing techniques and techniques that involve the voluntary blocking of undesirable behaviour. The results indicate a significant improvement in behaviour and mood in the patient diagnosed with Wilson's disease following the use of cognitive restructuring techniques associated with muscle relaxation procedures.

Keywords: Wilson's disease; cognitive-behavioural therapy; muscle relaxation

Introduction

NORD (National Organization for Rare Disorders) defines Wilson's disease as a rare, autosomal recessive genetic disease (Gao, Brackley, & Mann,

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2019), characterised by excessive accumulation of copper in various tissues of the body, such as: liver, brain, cornea (Brewer & Askari, 2005). The disease occurs when each of the two parents transmits an abnormal gene responsible for the same trait. When a single gene is involved, the patient is only a carrier, without showing symptoms of the disease. Responsible for this disease is the ATP7B gene, on chromosome 13. The mutation identified in this gene prevents the ATPaza2 to function properly, therefore distorting the process of excreting copper from the liver into the bile to be eliminated from the body through the intestinal tract (Collins et al., 2021). It is a progressive disease, with highly lethal potential by major impairment of organ function in which copper is accumulated in excess (Schilsky, 2017).

Liver damage begins around the age of six and is progressive, so the first symptoms appear in middle or actual adolescence, around the age of 20. Liver damage is signalled by the skin, mucous membranes and scleral jaundice, oedema in the lower limbs and the abdomen (ascites) due to reduced blood osmolarity caused by the absence of compounds that the liver synthesizes, so that the blood fluid transfer is facilitated by growth on the one hand, and by vascular permeability, on the other hand (Taly et al., 2007). The appearance of hepatic encephalopathy, splenomegaly, anaemia, haemorrhage and, at the same time, thrombocytopenia, the development of portal hypertension upstream of the liver through hepatic stasis mechanism, with the development of oesophageal varices, denotes an evolution towards liver cirrhosis. Liver failure develops progressively, and patients with the disease discovered in adolescence have an advanced degree of liver failure (advanced cirrhosis, decompensated) requiring liver transplantation (Patil, 2013). Neurological impairment is another manifestation of Wilson's disease, either concomitantly with liver damage or as the first form of disease manifestation (Huster et al., 2014). The accumulation of copper in the brain tissue gives symptoms such as: tremor, involuntary movements, dysarthria, dysphagia, speech disorders (vocal tone, word articulation or dysgraphia), balance, coordination, sleep and memory disorders, spasticity, muscle dystonia. Due to neurological impairment, psychiatric manifestations of the disease may occur, which have a higher degree of specificity and interindividual variability: behavioural and personality disorders, depression, psychotic manifestations (Zimbrean & Schilsky, 2014). The onset of psychiatric manifestations denotes the presence of neurological substrate damage, which, within a maximum of 3 years, will bring out the

neurological disorders associated with the psychiatric ones (Sahoo et al., 2010). Rarely, hypoparathyroidism and cardiomyopathy, and heart rhythm disorders, associated with the clinical picture of the underlying disease, may also be present.

The PRNP gene identified at brain level provides instructions for the proper functioning of a prion protein. In patients with the ATP7B gene, methionine replaces valine in this prion protein at locus 129, which is associated with an increase in neurological symptoms, tremor being especially mediated by this translocation (Chang & Hahn, 2017).

A large percentage of patients with Wilson's disease have the Kayser-Fleischer ring on the iris, which can be identified by the ophthalmologist or is seen as a circular brown stain on the large circumference of the iris.

A wide variety of symptoms of the disease are mentioned, which can differ depending on sex when it comes to genital dysfunction (menstrual disorders, amenorrhea), kidney stones, nephron damage, arthritis, osteoporosis, osteophytosis (Beinhardt et al., 2014).

The differential diagnosis is required with diseases such as: viral cirrhosis, Sindenham or Hungtington chorea, Gilles de Tourette, neuroacanthocytosis, biliary cholangitis, heavy metal poisoning, cerebral palsy, which can be sources of confusion/errors in the diagnosis of the disease. Fluid tests (blood and urine) demonstrate low levels of ceruloplasmin (plasma protein that transports copper to the blood) and high levels of urinary copper, increased transaminases, clotting disorders, hypoglycemia (Kalita, Kumar, Chandra, Kumar, & Misra, 2014). Molecular genetic analysis identifies the haplotype of genes involved in the disease, identifying whether it is one (single gene) or two carrier parents, carrier or manifesting patient (pair of genes) and first-degree relatives; this analysis can be supplemented with liver biopsy and eye examination to identify the Kayser-Fleischer ring (Aggarwal & Bhatt, 2018).

Through this research we aim to bring additional information about Wilson's disease and its treatment, in the context of a deficit of experimental research, given the low prevalence of the disease, on the one hand, and on the other hand, low number of studies and unilaterality of data regarding the current case presentations in the specialized literature. Despite a major psychological impact of the disease on patients and their relatives (Zimbrean & Schilski, 2014), very little data refer to the complete treatment of the disease, including psychotherapeutic and psychophysiological relaxation, added to

etiopathogenetic treatments. This study aims to detect relevant aspects of the Wilson's disease treatment by combining medicine administration with methods that include rehabilitation therapy, in which an important role is given to psychotherapy and psychophysiological relaxation therapies.

Objectives

Through this research we aim to perform an experiment on a 28-year-old male patient diagnosed with Wilson's disease, to whom we applied cognitive-behavioural psychotherapy techniques (Roman, 2011; Marian & Filimon, 2010) associated with muscle relaxation therapy, compared to the suppression of thoughts and the intentional blocking of undesirable behaviours (muscle contractions) in order to improve the psychopathology associated with the underlying disease. The present research aims to bring new information related to the complete and complex therapeutic approach to Wilson's disease, starting from the existing data in the literature.

Method

Case description

The problem

The current disease began in the second half of August 2020 with dysphonia, dysarthria and dysgraphia, upper limb tremor at the beginning, predominantly the right upper limb. The patient admitted to a rehabilitation ward was evaluated by a doctor specializing in medical rehabilitation and was sent to a psychologist for diagnosis and specialised treatment for adaptation disorder with depressive reaction manifested by: fatigue, sleep disorders (mixed insomnia), modified mood - melancholy, easily crying / affective lability. These events began in September 2020, one week after the introduction of Cupripen treatment. Since September, the patient has had several hospitalizations in order to diagnose him and to establish a therapeutic conduct. At the beginning, the affective manifestations included notable affective lability, decompensated with a depressive episode caused by the reduced capacity of adaptation to the disease.

Personal history: physiological - insignificant, notable fatigue; pathological - diagnosis of Wilson's disease with neurological and hepatic impairment (macronodular liver cirrhosis), in 2010, together with family screening. Secondary Parkinson's disease, progressive cognitive impairment, dysarthria, adjustment disorder with emotional lability and depressive reaction, unspecified hypoparathyroidism, liver cirrhosis, moderate thrombocytopenia, hypocholesterolaemia, mild mitral and tricuspid insufficiency, proteinuria, microscopic haematuria, chronic bilateral maxillary sinusitis, bilateral gynecomastia, dysphagia to liquids.

Favouring factors of the current disease: after diagnosis, the patient did not take any secondary prevention measures of the disease, psychotrauma related to the death of his older sister in 2010.

Drug treatment: Cupripen 2 x 1/day, Isicom tablets 250/25 mg½-1/2-1/2 tablets for 6 months, Cerebrolysin ampoules im 5 ml 1/week/chronic, Neuromultivit tablets 1-0-0, 10 days/month for 6 months, Neurovert forte tablets 1-0-0, 10 days/month for 6 months, Thiolin complex tablets, 1-0-0, 10 days/month, 6 months, Zinc gluconate: 15 mg 3-3-3 capsules/day, Lagosa 150 mg 1-0-1 capsules/day for a month, Vitamin B6, Melatonin, Mirzaten, Rivotril.

Inheritance-collateral history

Mother and father carrying the gene responsible for Wilson's disease; older sister diagnosed with Wilson's disease, deceased; younger sister diagnosed with Wilson's disease; maternal grandfather who died of tongue cancer.

Family history. He is the second child of a family with three children, diagnosed with Wilson's disease, from a rural area.

Personal history. Graduate of higher education, employed in 3 work places, in areas related to his professional qualification.

Significant emotional relationships: family, girlfriend with whom he has had a relationship for 1 year, broke up with him when the first symptoms of the disease began.

Alcohol and drug use: the patient denies.

Suicidal thoughts or plans: the patient mentions suicidal ideation at the beginning of the disease; at the time of evaluation, he mentions the lack of such thoughts.

Disease history

In 2010, the older sister died of this disease, diagnosed subsequent to a family screening. Following the family screening, all three children of the family are diagnosed with Wilson's disease, the older sister being symptomatic, having a disease with a sudden evolution, which led to death. The patient had no symptoms until August, 2020. The younger sister has no symptoms of the disease, being prescribed a strict diet, which excludes all foods containing copper.

Additional investigations were performed from 2013 to September 2020, establishing the primary and associated diagnoses, thus initiating the Cupripen treatment. After initiating this treatment, in the first 3 weeks the patient develops notable affective lability and an adjustment disorder with a depressive episode.

Examination of current mental status

The patient was hospitalized in February in a medical rehabilitation department. He underwent rehabilitation treatment with the following procedures: individual physiotherapy, massage, psychotherapy, speech therapy, magnetotherapy with a slowly favourable evolution.

Conscious patient, temporal and spatial orientation, visual contact maintained, adequate posture and attitude, postural and resting tremor of the upper limbs, predominantly right and cephalic extremity, global bradykinesia, extrapyramidal hypertension, predominantly right, without asymmetry and changes in sensitivity. IQ (Progressive Matrices Raven, 99 - medium /low intellect), MMSE (Mini Mental State Evaluation) - 26 points mild cognitive impairment, predominantly mnemonic and attentional, mood swings: affective lability with episodes of laughter incongruous to mood.

Psychological evaluation during hospitalization reveals the following: temporal and spatial orientation, mild cognitive impairment (MMSE; Mini Mental State Evaluation - 26 points) memory deficits, impaired working memory, abstract mental operability deficits, IQ - 99 (Progressive Matrices Raven Standard) - medium level intellect, hypoprosexia, verbal-logical reasoning, coherent, bradylalia, dysarthria, diminished verbal tone, jerky language, affective status: BDI II depression scale 16 points - moderate depressive symptoms at the time of evaluation, Rosenberg Self-Esteem Scale, 25 points - very low self-esteem level, anxiety (Hamilton Rating Scale for

Anxiety, 22 points average degree of anxiety), notable emotional lability, self-efficacy scale (SES) ≤ 25 very low level, Dysfunctional Attitude Scale (DAS, 145 points) - high level of dysfunctional attitudes, automatic thoughts 30 points - high level, Scale of irrationality ABS II short form: high irrationality (9p-class IV), low rationality (1p-class II). Reduced self-care capacity, ideas of helplessness and uselessness, mixed insomnia (drug-adjusted).

Neurological examination reveals: The patient has postural and resting tremor of the upper limbs, predominantly on the left, mild global bradykinesia, extrapyramidal hypertonia, predominantly on the left side, with postural instability, no motor deficit, globally good response in deep tendon reflexes, right plantar clonus, plantar skin reflex in bilateral flexion, inconstant saccades, without other changes in the cranial nerves, without dysmetria or objective changes in sensitivity.

The objectives of the intervention

1. At the affective level: improving the emotional mood by reducing the intensity of depressive symptoms and anxiety,
2. At the cognitive level: improving the level of adaptation to the disease by: improving the cognitive processing related to the disease with the aim of increasing rationality and reducing irrationality, improving self-esteem,
3. At the behavioural and psychophysiological level: improving the tremor in order to increase the feeling of self-efficacy and reduce the level of dysfunctional attitudes, improving the quality of life by improving the capacity for self-care, improving sleep.

The proposed intervention includes cognitive-behavioural psychotherapy (cognitive restructuring according to the REBT model) focused on the above objectives (Roman, 2011), muscle relaxation techniques (Schultz method) in addition to the rehabilitation medical procedures prescribed by the attending physician, mentioned above.

Instruments

The Rosenberg Self-Esteem Scale (RSES; Rosenberg, 1979) is a one-dimensional and global self-esteem assessment tool. It is a Guttman scale, whose Alpha Cronbach coefficient varies between .77 and .88.

The Dysfunctional Attitudes Scale (DAS; Weissman & Beck, 1978) allows the evaluation of attitudes that may constitute a predisposition for the

onset of depression, dysfunctional attitudes reflecting the content of stable cognitive patterns. The alpha Cronbach's coefficient of the scale is .86.

The Attitudes and Beliefs Scale (ABS; David, 2007) includes 8 items that measure a person's rationality and irrationality. Alpha coefficient values range from .56 to .78.

The Beck Depression Inventory II (BDI; Beck, Rush, Shaw, & Emery, 1979) has an Alpha Cronbach's coefficient of .89 on the general population and of .90 on the clinical population. It is a tool for self-assessment of the severity of depression in patients diagnosed with this disorder.

The Self-Efficacy Scale (SES; Schwartzer & Jerusalem, 1989) has an internal Alfa Cronbach consistency of .84 and measures individuals' beliefs about their ability to cope with specific situations.

The Automatic Thought Scale (ATS; Hollon & Kendal, 1980) measures long-term mental structures, past experiences that influence the processing of current information. The internal consistency Alpha Cronbach coefficient is .92.

The Hamilton Rating Scale for Anxiety (HRSA; The Hamilton Rating Scale for Anxiety; Hamilton, 1967) has an inter-evaluator consistency of .84, measures mental and somatic anxiety, and people with more than 20 points are considered to have clinical intensity anxiety.

Procedure and design

In order to follow the effectiveness of the intervention and to monitor the patient's evolution, we aimed to perform a single-subject experiment.

The ABAB design of the experiment aims to: a. identify the basic level of the pathology by applying clinical scales: depression, anxiety, self-esteem, dysfunctional attitudes, perceived self-efficacy, automatic thoughts, rationality / irrationality, muscle contractions measured for one minute; b. introduction of the intervention: cognitive-behavioural psychotherapy and muscle relaxation by Schultz method, c. replacement of the intervention with alternative methods (suppression of thoughts and blocking of undesirable behaviour), which can validate or invalidate the null hypothesis d. continuation of the intervention by cognitive-behavioural psychotherapy and muscle relaxation and quantification and monitoring of results (*see* Figure 1). We are interested in highlighting how cognitive-behavioural therapy (CBT) associated with relaxation therapy by the Schultz method reduces depressive-anxiety symptoms, improves the frequency

of muscle contractions, compared to conscious self-control techniques. Thus, we are interested in the frequency of muscle contractions over the course of one minute manifested during relaxation techniques compared to the situation when the patient uses the suppression of thoughts (Szentagotai & David, 2009) (activities that require the patient to participate in a simple task such as the analysis of a Toulouse-Pieron image, with multiple stimuli, which predominantly requires attention) and the blocking of undesirable behaviour through verbal cues prohibiting behaviour, such as "do not move your hand". Thus, we also take into account the way in which the patient's perception of the reinforcements determines certain behavioural consequences, in our case the reduction of the frequency or the acceleration of the frequency of the muscular contractions. In the first two cases there is the problem of considering reinforcements as a consequence of certain behaviours, in the last case, as a determinant of unwanted behaviour.

Regarding cognitive-behavioural psychotherapy (CBT), the patient was taught psychotherapeutic techniques according to the ABC model (A: trigger event, B: information processing, and C: consequences). The informational processes we disputed were the descriptions, inferences (Beck, 1976) and irrational cognitions mentioned in the context of REBT therapy (Ellis, 1994). Following this model, we proceeded to dispute irrational thoughts and learn their rational counterpart in order to practice a new lifestyle (Marian, 2011). These cognitive restructuring techniques were applied in daily 40-minute sessions.

Regarding the motor pathology, we identified an average number of 108.33 (SD=9.07) muscle contractions in the upper limbs for one minute in the first 3 days after hospitalization, when the psychodiagnosis was performed; this was a period without psychotherapeutic intervention. The measurements were performed at 3 different times of the day: morning, noon and evening, to identify possible correlations with physical fatigue. The Kendall test (*tau*=0.33, p>.60) indicates that there are no average trends in data variability at the baseline level. In order to improve the motor stereotype behaviour (muscular contractions) we had 3 experimental conditions: the Schultz method, the thought suppression method and the method of blocking the undesirable behaviour administered by the physiotherapist. Each time one of the 3 intervention methods was applied, the muscle contractions were counted for 1 minute.

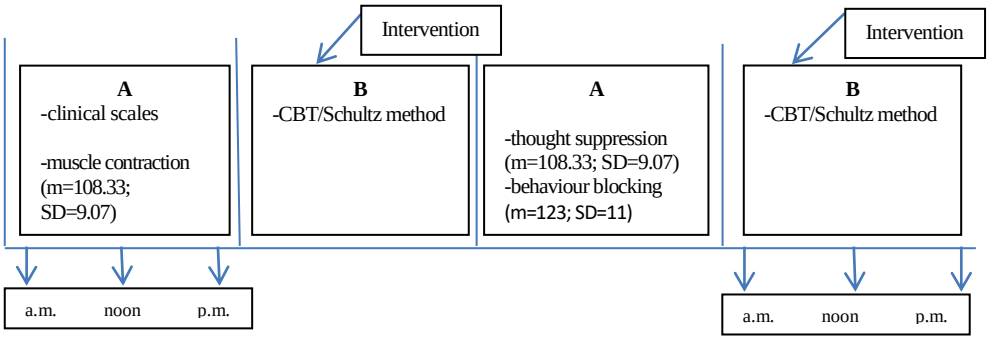

Figure 1. ABAB Design (A-no intervention; B-target intervention)

Results

The results indicate two categories of responses: cognitive-behavioural psychotherapy combined with the Schultz technique led to an improvement of movements until their suppression at the upper limbs (measured by natural observation and patient feedback) for 5-8 minutes at the end of the relaxation sessions, which lasted 40 minutes. The thought suppression technique had no impact on the muscle contractions, and the behaviour blocking technique led to a spontaneous acceleration of the muscle contractions, reaching an average of m=123 muscle shakes (SD=11) for one minute. The Schultz technique resulted in a progressive decrease in the frequency of the upper limbs movements to their suppression. Verbally, the patient and his companion (mother), mention that after the application of the relaxation technique an improvement of postural tremor in general can be noticed subjectively and based on natural observation, fact correlated with the improvement of sleep, both during the day and overnight.

Table 1. The results of pretest-posttest research according to clinical scales

	Kendall test							
	BDI	HRSA	DAS	RSES	ATS	ABS i	ABS r	RSES
pre-test	16	22	145	25	30	9	1	25
post-test	13	14	111	28	19	2	6	31

Note: BDI- Beck Depression Inventory; HRSA-The Hamilton Rating Scale for Anxiety; DAS-Dysfunctional Attitudes Scale; SES-Self Efficacy Scale, ATQ-Automatic Thoughts Scale, ABS-Attitudes and Beliefs Scale-Short Form: i-irationality, r- rationality, SES- Rosenberg Self-Esteem Scale

Table 1 shows the results obtained by the patient at admission (pre-test) and at discharge (post-test), before and after the psychotherapeutic intervention. Table 1 displays the quantitative data obtained by the patient at the applied clinical scales, following the reporting against the standards. The results obtained after the psychotherapeutic treatment (post-test) followed in the rehabilitation department are: at the BDI II depression scale 13 points - mild intensity depressive symptoms, Rosenberg Self-Esteem Scale 31 points - average level of self-esteem, anxiety (Hamilton scale 14 points - low degree of anxiety), self-efficacy scale (SES) - 28p - low level, dysfunctional attitudes scale (DAS, 111 points) - low level of dysfunctional attitudes, automatic thoughts 19 points - low level, Scale of irrationality ABS II short form: low irrationality (2 p-class II), high rationality (6p-class IV). We mention that there are important differences in terms of results, a decrease in the intensity or clinical frequency of psychological characteristics, close to those found in the general population. However, these results are indicators of long-term patient vulnerability.

Cognitive restructuring has led to improvements in emotional symptoms, anxiety, self-efficacy, dysfunctional attitudes and self-esteem. A certain state of emotional vulnerability remained, for which psychotherapeutic treatment is recommended at home for a longer period of time, maintaining qualitative social support, along with monitoring biological parameters and prioritizing interventional liver transplant treatment.

Conclusions

Wilson's disease is a complex pathology, whose treatment must involve a multidisciplinary team. Psychotherapeutic treatment addresses not only the psycho-affective and cognitive level of the personality, but also the behavioural and psychophysiological level. Progressive muscle relaxation impacts the body of the patient affected by Wilson's disease, causing an improvement in neuro-muscular symptoms.

Rehabilitation therapies have generated a state of improvement of the patient's physical and mental condition, the clinical and functional status imposing the need to continue them at home and through periodic hospitalization. Therapeutic success depends to a significant extent on the patient's adherence to the diet that requires the exclusion of foods or substances

containing copper, which is often associated with a certain level of distress, anxiety, compulsivity and low levels of frustration tolerance.

Cognitive-behavioural psychotherapy can be included in the therapeutic protocol of patients with Wilson's disease, requiring multilevel adjustments through psychotherapeutic intervention. Progressive muscle relaxation is an effective treatment method in controlling muscle symptoms, but further studies should provide additional information on this. Wilson's disease is a complex pathology, which involves the intervention of a multidisciplinary team, but also additional studies on samples of subjects, which is difficult to achieve. The single-subject experiment or case study remains a research alternative, insufficient to generalize the results. However, multiple individual approaches may in the future allow meta-analytical studies that may provide additional information regarding this pathology.

The important resources in terms of patient rehabilitation were: adequate family support and the remaining intellectual level optimal enough as a result of copper storage at the level of brain structures. Affective lability, of predominantly neurological cause, remains a desire for further stabilization of the patient.

The study also has some limitations: the patient followed a complex therapeutic program of a short duration of two weeks, which does not allow a generalization of the results. Long-term therapies, addressing etiopathogenetic and symptomatic mechanisms, must bring new information in terms of patient rehabilitation. The impact of other models and psychotherapeutic techniques deserves to be investigated in the treatment of Wilson's disease in further studies.

Conflicts of Interest

The authors declare no conflict of interest. The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

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Received February 15, 2021
Revision April 21, 2021
Accepted May 1, 2021