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Long-Term Exercise Training for an Individual With Mixed Corticobasal Degeneration and Progressive Supranuclear Palsy Features: 10-Year Case Report Follow-up

Teresa M. Steffen, Bradley F. Boeve, Cheryl M. Petersen, Leah Dvorak, Kejal Kantarci

Background and Purpose. This case report describes the effects of long-term (10-year) participation in a community exercise program for a client with mixed features of corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP). The effects of exercise participation on both functional status and brain volume are described.

Case Description. A 60-year-old male dentist initially reported changes in gait and limb coordination. He received a diagnosis of atypical CBD at age 66 years; PSP was added at age 72 years. At age 70 years, the client began a therapist-led community group exercise program for people with Parkinson disease (PD). The program included trunk and lower extremity stretching and strengthening, upright balance and strengthening, and both forward and backward treadmill walking. The client participated twice weekly for 1 hour for 10 years and was reassessed in years 9 to 10.

Outcomes. Falls (self-reported weekly over the 10-year period of the study by the client and his wife) decreased from 1.9 falls per month in year 1 to 0.3 falls per month in year 10. Balance, walking endurance, and general mobility declined slightly. Gait speed (both comfortable and fast) declined; the client was unable to vary gait speed. Quantitative brain measurements indicated a slow rate of whole brain volume loss and ventricular expansion compared with clients with autopsy-proven CBD or PSP.

Discussion. This client has participated consistently in a regular group exercise program for 10 years. He has reduced fall frequency, maintained balance and endurance, and retained community ambulation using a walker. Combined with the slow rate of brain volume loss, this evidence supports the efficacy of a regular exercise program to prolong longevity and maintain function in people with CBD or PSP.

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Corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) are progressive neurological disorders that are manifested by parkinsonism as well as dementia.¹⁻³ Both are considered tauopathies.⁴ Tauopathies display insoluble intraneuronal aggregates of the tau protein seen in other neurodegenerative diseases, including Alzheimer disease, and in approximately half of those with frontotemporal dementia. Although similar with respect to signs of parkinsonism (rigidity, bradykinesia, postural instability), CBD and PSP differ in several ways. Corticobasal degeneration is characterized by an asymmetric rigid syndrome along with cortical dysfunction that includes impairments in executive function, language, social behavior, and sensory loss.⁵ Apraxia and the alien limb phenomenon also are common.⁶ Brain regions affected include the basal ganglia, prefrontal cortex, parietal lobe, and corpus callosum. Most people with CBD are diagnosed in their sixties, and the life span after diagnosis is usually about 7 to 10 years, with death caused by complications of immobility and dysphagia.⁷

Progressive supranuclear palsy is characterized by a rapid decline in executive function that is typically more pronounced than that seen in CBD.⁸ In addition, personality changes, apathy, impulsivity, and perseveration are often present, as is supranuclear vertical gaze palsy.⁹ Sensory symptoms are not usually evident. Clients with PSP display atrophy in the medial prefrontal cortex, basal ganglia, cerebellum, and midbrain. Progressive supranuclear palsy is typically diagnosed in the early sixties, and the average life expectancy after diagnosis is about 5 to 10 years, although survival as long as 16 years has been documented.^{10,11}

A number of studies have demonstrated the efficacy of exercise, including treadmill training in clients with Parkinson disease (PD).¹²⁻¹⁴ However, little is known about the effects of exercise on tauopathies or other parkinsonian disorders. A case report described the effects of repetitive facilitation exercise (RFE) combined with occupational therapy in a single client with CBD.¹⁵ Following 4 weeks of these exercises, both activities of daily living and finger motor function improved. The authors suggested that RFE may have prevented a decrease of neuronal or neural circuit loss.¹⁵ No other evidence describing the effects of exercise in clients with CBD was found in the literature.

More literature was found regarding motor dysfunction and rehabilitation for PSP. Progressive supranuclear palsy affects oculomotor control, gait, and balance. Recurrent falls are a common challenge. Vertical gaze palsy is one of the major oculomotor signs in PSP. As a result, common difficulties include seeing obstacles and curbs during ambulation, going up and down stairs, judging distances, and difficulty scanning the environment.¹⁶ Clients with PSP had decreased step length and step velocity and a significantly slower ability to break a fall from the center of gravity than controls.¹⁷ Lindemann et al,¹⁸ using dual-tasking paradigms to assess differences between clients with PSP who fell frequently and those who fell less often, found that clients who fell frequently had more ocular movement difficulties, decreased postural stability, and decreased cognition compared with clients who fell less often. The frequent fallers demonstrated a significant increase in cadence and a decrease in step length compared with the infrequent fallers, but the groups did not differ significantly under dual tasking for maximal gait speed. These find-

ings may reflect a first adaptation with dual tasking to produce safer walking by decreasing step length. A decrease in cadence was found to be the next adaptation, when needed. These findings also suggest that falls may result from cognitive and ocular dysfunction in addition to the parkinsonian features.

Two studies have demonstrated evidence of exercise efficacy in clients with PSP.^{19,20} A combination of falls prevention exercises, corrective postural reaction training, and eye movement/visual awareness training can improve clients' ability to shift their gaze downward, resulting in a moderate effect on general mobility as measured by the Timed "Up & Go" Test (TUG) and increased gait speed compared with balance training alone in patients with PSP.¹⁹ An 8-week rehabilitation program for a single client with PSP that used body-weight-supported treadmill training 3 times per week showed improvements in timed standing on a foam surface, functional reach, and gait speed and a decrease in falls.²⁰

Studies have demonstrated that brain volume declines somewhat after age 70 years in people without neurological disease.²¹⁻²³ More significant brain volume decreases have been demonstrated in people with CBD²⁴ and PSP.^{24,25} A growing body of evidence supports the efficacy of exercise to maintain both function and brain volume in aging adults who are healthy.²⁶⁻²⁸ Exercise also has been demonstrated to have positive effects on neuroplasticity in animal models of PD.²⁹⁻³¹ However, there are no studies demonstrating the effects of exercise on brain volume in people with CBD, PSP, or a mixed diagnosis of CBD and PSP.

Previous work by 2 of the present authors showed that physical therapy utilizing treadmill training combined with other balance and exer-

cise activities delivered through community programming (2 times per week for 1 hour) appeared to slow the decline in physical performance over a 2.5-year period in a client diagnosed with mixed CBD and PSP.³² The purpose of the present article is two-fold: (1) to describe the effects of this community programming (including treadmill training) for the same client over a longer period of time (10 years) and (2) to examine the possibility that the intervention has minimized brain volume changes in this client. To our knowledge, this is the only case in the literature of a client with a mixed diagnosis of CBD and PSP who has participated in an exercise program for 10 years.

Patient History and Review of Systems

The client's history was described in detail in a previous case report.³² Briefly, the client was a dentist with no family history of any neurological disorders. He first noticed changes in limb coordination and gait at around age 60 years. He reported changes in speech (dysarthria) at age 65 years and experienced his first fall at age 66 years. At an initial neurological interview and examination at age 66 years, conducted by a movement disorder specialist physician, the client achieved a score of 32/38 on the Kokmen Short Test of Mental Status,³³ with mild impairment of complex reasoning, attention, and working memory. He also displayed apraxia and rigidity in the upper extremities that were more pronounced on the left side and were accompanied by left-sided cortical sensory loss. Lower extremity tone was increased bilaterally, and alternating motion rates of the limbs were decreased, especially on the left side. He displayed a wide-based stance, a short stride with decreased arm swing, and a positive Romberg sign. No alien limb phenomenon, tremor, or dystonia were present.

Magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (PET) showed parietofrontal cortex abnormalities that were more evident on the right side of his brain.

The initial diagnosis of atypical CBD was made when the client was 66 years old.³² He was titrated upward on carbidopa/levodopa dosing to a maximum of 300 mg of levodopa taken 3 times daily on an empty stomach, with no improvement noted, and this agent was tapered off. Aggressive treatment with pramipexole failed to improve any of his symptoms or signs. He was subsequently evaluated annually by specialists in movement disorders and behavioral neurology with expertise in CBD and PSP, and he displayed a mild progression in asymmetric rigidity and apraxia, dysarthria, speech apraxia, and gait impairment. Falls continued to be frequent. He underwent standard physical therapy and occupational therapy measures over 2 months when 66 years old, but because no apparent benefit was appreciated, no further intervention was commenced until age 70 years (see below).

By age 68 years, the client had fallen many times and reported numerous bruises and lacerations as a result. He also reported occasionally choking on liquids. The client noted severe asymmetric limb dyspraxia by age 70 years and mild emotional lability and apathy at age 71 years. However, he reported no changes in cognition, which was corroborated by his family members. He also lacked any tremor, incontinence, and executive, language, memory, or visuospatial dysfunction (he continued to work part-time in nonprocedural duties in the dental practice despite his motor impairment). At age 72 years, eye-blink frequency had decreased significantly, and he displayed mild saccadic pursuits and

mild restriction on vertical extraocular movement testing. These changes resulted in a modified diagnosis of mixed CBD and PSP; the diagnosis will be confirmed at autopsy.

Exercise and Physical Therapy Intervention (1–3 Years)

At age 70 years, the client and his wife self-referred him to a university physical therapy clinic and to a community exercise group for people with PD.³⁴ The exercise protocol was designed and led by a physical therapist based on the best evidence then available for exercise and PD and has been described in detail elsewhere.³⁴ Briefly, the group members exercised twice a week for 1 hour at a community center that provided basic equipment such as floor mats and treadmills. The program consisted of 20 minutes of trunk and lower extremity stretching and strengthening, 10 minutes of upright balance and strengthening exercises, and at least 20 minutes of treadmill walking (10 minutes backward and 10 minutes forward). No modifications to the group program were made for this client, although he always received close supervision while on the treadmill by a physical therapist or occupational therapist due to his history of falls. The exercise program did not include specific functional training activities. Treadmill speed initially (and during years 1–3) and amount of handhold were determined collaboratively by the client and the physical therapist so that the client would be both safe and appropriately challenged. The detailed program is available at the Exercise With Parkinson Disease website.³⁵

The client's wife walked him in and out of the exercise area. He did most of the floor activities (stretching, strengthening) on his own and participated socially in the program (eg,

Table 1.
Average (SD) Number of Falls per Month, Average Monthly Attendance, and Average Annual Treadmill Speeds

Year	Falls (Average Number of Falls Over the Year)	Attendance (Average Monthly Attendance Over the Year)	Treadmill Speed (mph) Forward (Month 12)	Treadmill Speed (mph) Backward (Month 12)
1	1.9 (1.7)	6.0	1.3	0.8
2	1.4 (1.2)	8.0	1.4	1.0
3	1.3 (1.6)	8.0	1.7	1.0
4	0.9 (0.9)	7.0	1.9	1.0
5	1.0 (1.0)	7.0	1.5	0.9
6	0.9 (1.0)	6.0	1.4	1.1
7 ^a	1.0 (1.0)	6.0	1.4	1.0
8	0.6 (0.9)	6.0	1.4	1.1
9	1.0 (1.0)	5.0	1.4	1.1
10 (4 mo)	0.3 (.05)	7.0	1.4 (April)	1.1 (April)

^a Client started using 2 lower extremity weight machines in year 7.

remembering people’s names and sports scores, describing work experiences and places he visited). The client was concerned about coughing or choking; therefore, he never drank liquids while exercising. He had no other medical diagnoses and took no medications other than vitamins.

In addition to the community program, the client participated in one weekly physical therapy session at the university in years 2 and 3. This session lasted 1 hour and included body-weight-supported treadmill training. The body-weight-support system was used for safety as a falls prevention precaution and was not available at the community center.

Outcomes for years 1 through 3 were described in a previous case report.³⁴ The client’s fall frequency decreased over the 2.5-year course of the study, and functional balance tests showed improvements in both limits of stability and maintained balance. A small decline in walking performance was observed; the client was able to remain ambu-

latory within the community with a 4-wheeled walker.

Clinical Impression: Exercise and Physical Therapy Intervention (4–10 Years)

Since the initial case review on this client was published,³⁴ the client continued to participate in the community exercise program designed for people with PD. The physical therapist regularly interacted with and observed the client. As a result, one modification to the general program was made for this client beginning in the seventh year. Observation by the physical therapist revealed lateral hip instability that appeared to result from improper coordination of hip abductors. Typically, sideways walking on the treadmill would be one way to promote functional hip abduction, but the client did not want to try it due to concerns about falling. In response, the therapist devised a hip abductor exercise program using an exercise machine in the exercise facility that provided eccentric resistance training. Following the floor exercises, the client used the exercise mach-

ine to perform hip abduction (30 repetitions) and knee extension (30 repetitions). Knee extension was added because the physical therapist observed that the client began to display a flexed posture at the knees while standing. No ankle weights or other devices were used as part of this training; resistance was provided by the exercise machine. The client performed these exercises bilaterally in an effort to make both of his lower extremities work together in a smooth, coordinated manner. The resistance training was followed by treadmill walking in a backward direction for 10 minutes and in a forward direction for 10 minutes. Thus, this client exercised for 60 minutes per session. The order of the various exercises was usually floor activities, resistance training, and then treadmill training.

This client’s average attendance at the group community exercise program from year 4 until year 10 was 6.3 visits per month (SD=0.85). His range of attendance was 5 to 8 times per month (Tab. 1). In total, he has been exercising approximately 6 times per month for 1 hour for 10 years. His frequency of attendance was one of the best, inclusive of all of the group participants, and he is by far one of the longest-attending participants. The client’s goals for the exercise program were to prevent or minimize falls and to maintain function, including both basic activities of daily living and instrumental activities of daily living so that he could continue to live at home.

Brain Volume Measurement

The client participated in a longitudinal research program at a large medical center, at which annual assessments were performed by movement disorder and behavioral neurologist specialists. The assessments included a detailed clinical examination, neuropsychologi-

cal testing, and quantitative MRI measures. These assessments have been performed at the medical center on clients with features typical of CBD and on those with features typical of PSP. Although the medical center has examined many clients with mixed features of CBD and PSP, the client described here was the first with a mixed diagnosis of CBD and PSP to participate in this longitudinal research program at the medical center.

Quantitative boundary shift integral (BSI) methods were used to measure the annualized rate of change in whole brain volume (WBV) and ventricular volume (VV) over the 10-year course of the study. The MRI studies were performed on a single 1.5T system (GE Healthcare, Waukesha, Wisconsin). Three-dimensional spoiled gradient echo (SPGR) and magnetization prepared rapid gradient echo (MPRAGE) sequences were included in the BSI analysis. Changes in WBV and VV were calculated automatically from each registered three-dimensional scan pair using the BSI and expressed in cubic centimeters of volume change from baseline for each follow-up time point as previously described.³⁶ A group of clients with autopsy-proven CBD (5 cases) and PSP (5 cases) at the medical center (Tab. 2) who were analyzed with the same method did not participate

Table 2.

Percent Annualized Change in Brain Magnetic Resonance Imaging in the Client Described in This Case Report Compared With That of Other Clients With Progressive Supranuclear Palsy (PSP) and Corticobasal Degeneration (CBD)

Variable	Whole Brain Volume (Lowest)	Ventricular Volume (Lowest)
PSP (n=5)	-1.0% (-0.8)	10.9% (6.9)
CBD (n=5)	-2.3% (-1.9)	16.2% (11.2)
Client	-0.79%	4.6%

in exercise and served as controls for BSI measurements of brain volume change.^{24,25,37}

Functional Outcomes

The rationale for the outcome measures chosen is described in a previous case report.³² Briefly, the following functional tests of balance and walking performance were conducted: comfortable and fast gait speeds, Six-Minute Walk Test (6MWT), TUG, Berg Balance Scale (BBS), forward functional reach (FFR), backward functional reach (BFR), right functional reach (RFR), and left functional reach (LFR). These measures were chosen because they are valid and reliable measures of gait and balance functions in older adults with various diagnoses. The client was evaluated by a physical therapist in years 9 and 10 of the study. Falls

were self-reported by the client and his wife upon each visit to the class (twice a week). To improve clarity and consistency of the data, the number of falls was recalculated for the entire 10-year reporting period using the self-reported data.

Functional outcomes are presented in Table 1 (falls, attendance, and forward and backward treadmill speeds) and in Table 3 (gait speeds, 6MWT, TUG, BBS, and all functional reach test data). The client’s falls decreased over the 10-year period from an average of 1.9 falls per month to 0.3 falls per month. Most falls took place during sit-to-stand transfers or when moving from an upright position to the floor. None were serious enough to cause a fracture, head injury, or other major complication. His performance on balance measures, including the BBS, FFR, and BFR, declined slightly but were below minimal detectable change at the 95% confidence interval (MDC₉₅) criteria.³⁸ The RFR and LFR tests also showed a small decline. The client’s walking endurance (measured with the 6MWT) and general mobility (measured with the TUG) declined slightly, but the changes were below MDC₉₅ criteria.³⁸

Gait speed tests revealed decreases in both comfortable and fast gait

Table 3.

Comparison of Gait Speed, Six-Minute Walk Test, Timed “Up & Go” Test, Berg Balance Scale, and Multidimensional Reach in 4 Directions for the Client’s Initial 3 Years of the Program to the Current Time of 9 to 10 Years

Measure	Comfortable Gait Speed (m/s)	Fast Gait Speed (m/s)	Six-Minute Walk Test (m)	Timed “Up & Go” Test (s)	Berg Balance Scale	Forward Functional Reach (cm)	Backward Functional Reach (cm)	Right Functional Reach (cm)	Left Functional Reach (cm)
Years 1–3, \bar{X} (SD), n=14	0.84 (0.08)	1.0 (0.10)	247 (38)	25 (4)	31 (5)	19 (5)	10 (2)	17 (4)	11 (2)
Years 9–10, \bar{X} (SD), n=2	0.63 (0.13)	0.70 (0.18)	210 (40)	32 (4)	32 (4)	18 (0.3)	8 (1)	13 (7)	7 (2)
Mean difference	-0.21	-0.31	-37	-7	0.3	-1	-2	-5	-4
MDC ₉₅ ²⁵	0.18	0.25	86	-11	4	9	7		

⁹ Minimal detectable changes for people with PD are listed.³⁸ PD=Parkinson disease, n=number of times of testing, MDC₉₅=minimal detectable change at the 95% confidence interval.

speeds over the course of the study that were greater than the MCD₉₅ criteria.³⁸ At the end of the 10-year period, the client demonstrated a mean comfortable gait speed of 0.63 m/s (SD=0.13) and a mean fast gait speed of 0.70 m/s (SD=0.10), indicating that he was unable to vary his gait speed. Treadmill speed (Tab. 1) stayed relatively constant over the 10-year course of the program for both forward and backward walking.

Assessment of Brain Volume Change

Quantitative brain measurements indicated that this client has had a slower rate of WBV loss compared with clients with either CBD or PSP and demonstrated that his ventricular expansion has been much slower than that of clients with pathologically proven CBD or PSP who had undergone serial quantitative MRI measures at the medical center (Tab. 2). It should be noted that none of the other clients studied had a dual diagnosis of mixed features of CBD and PSP.

Discussion

Taken together, the functional data described here with respect to mobility, balance, walking speed, falls, and endurance, combined with the WBV and VV measurements, strongly suggest the importance of a regular and aggressive exercise program to prolong longevity, decrease falls, and promote stability of function (including balance and ambulation) for a client with CBD and PSP. Over the 10 years of regular participation in the locomotor training program, this client has reduced his fall frequency and has maintained other balance and ambulation measures. Given the progressive nature of both CBD and PSP, and because falls and associated trauma are major causes of morbidity and mortality in these disorders, this client's longevity and high quality of life are quite striking. Because this case appears to be the

only one in the literature of a client with a mixed diagnosis who has participated in exercise, it is not possible to establish with certainty that the exercise program is responsible for the slow rate of progression described here: it could be genetic and not altered by the exercise interventions. This is not possible to determine in a case report. However, it is likely that the exercise interventions did contribute to his slow rate of decline. Studies have demonstrated that exercise can slow the clinical progression of PD.^{14,39}

Evidence from the quantitative BSI measurements of WBV and VV demonstrates a very slow rate of change in brain volume compared with other clients with either CBD or PSP. It seems reasonable to expect that someone with both diagnoses might exhibit as much or more brain volume loss, rather than less, compared with a patient with CBD or PSP alone. In addition, this client has aged during the course of the study. He has lived 13 years since his original diagnosis of atypical CBD and 7 years since his diagnosis was revised to include PSP. The average life span for patients with PSP is approximately 5 to 10 years after diagnosis, whereas people with CBD typically live about 7 to 10 years after diagnosis.^{30,37} Studies have demonstrated that brain volume declines somewhat after age 70 years in people without neurological disease.²¹⁻²³ Although we cannot determine from these data that the exercise program has had a disease-modifying effect, there is evidence that exercise can be neuroprotective in animal models,³¹ in animals with PD,⁴⁰ and in aging humans.²⁷ This report suggests that further exploration of the role of exercise in maintaining both brain volume and functional mobility merits further investigation.

The physical therapist clinicians working with this client observed

that his movement appeared to become more fluid and coordinated as a result of his participation in the exercise program, especially following the addition of the hip abduction and knee extension resistance exercises. In addition, this client continued to learn new exercise tasks with the assistance of the therapist. For example, in a prone position with his upper extremity at 45 degrees above his head in flexion, abduction, and full external rotation, he used his lower trapezius muscle to stabilize the scapula to raise the upper extremity off the mat simultaneously with contralateral hip extension. It thus appeared that this client maintained some motor learning ability, although he required more repetitions to learn this activity than did other group members. It was more difficult with his left upper extremity than with his right upper extremity. Overall, the client's left side was more involved and less well-controlled than his right side, consistent with the finding that parieto-frontal cortex abnormalities were more evident on the right side of his brain. Control of his left lower extremity was especially challenging, and he had a particularly difficult time with left hip abduction. However, the client continued to ambulate with standby supervision and used a 4-wheeled walker in his home and in the community. He and his wife have been pleased with his quality of life.

The exercise program was developed and modified by the physical therapist, but it can be carried out by trained aides or volunteers. Once instructed by the physical therapist, trained assistants can monitor clients for safety, but in our experience the physical therapist must be very involved in the program to correct errors (such as using 2 hands on the treadmill or using incorrect treadmill settings), to cope with clients with special needs, and to

modify the program appropriately for clients with varied needs and diagnoses. In 2013, there were 15 of these exercise programs in Wisconsin: 12 led by physical therapists, 1 by an occupational therapist, and 2 by physical therapist assistants supervised by physical therapists.

The evidence presented in this case report supports the efficacy of a long-term (10-year) combined exercise program (including treadmill training) in maintaining overall mobility, including balance and ambulation, and in reducing falls in a client with mixed features of CBD and PSP. In addition, the client demonstrated a slower-than-expected rate of brain volume loss over time, given the diagnosis.

Dr Steffen, Dr Petersen, and Dr Dvorak provided concept/idea/project design. All authors provided writing and data analysis, including a review of the manuscript. Dr Steffen, Dr Boeve, Dr Petersen, and Dr Kantarci provide data collection. Dr Steffen and Dr Petersen provided project management and facilities/equipment. Dr Steffen and Dr Boeve provided the client. Dr Petersen and Dr Boeve provided institutional liaisons. Lina Prosser provided clerical support, and Paul Wangerin provided statistical support. All authors thank the client and his wife for their support in doing this research.

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Long-Term Exercise Training for an Individual With Mixed Corticobasal Degeneration and Progressive Supranuclear Palsy Features: 10-Year Case Report Follow-up

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