

Single Case – General Neurology

Coming to Terms with a Conundrum: A Case of Primary Progressive Apraxia of Speech due to Corticobasal Degeneration?

Aristotelis Karantzoulis^a Emanuela Susani^b Carlo Ferrarese^a
Ildebrando Appollonio^a Lucio Tremolizzo^a

^aNeurology Unit “San Gerardo” Hospital and University of Milano-Bicocca, Monza, Italy;

^bNeurology Unit, “Niguarda” hospital, Milano, Italy

Keywords

Primary progressive apraxia of speech · Speech · Corticobasal syndrome

Abstract

Primary progressive apraxia of speech (PPAOS) is a progressive disorder impairing the motor speech act leaving linguistic function unattained. Although apraxia of speech frequently co-occurs with other neurodegenerative conditions, PPAOS defines a clinical syndrome where apraxia of speech is the sole or prominent symptom for much of the disease’s natural history. Mounting evidence is beginning to fully define this disease as the epiphenomenon of 4-repeat (4R) tau pathology although other pathologic signatures have been reported. Indeed, PPAOS patients generally present a parkinsonian syndrome late into their natural history mostly qualifying for either corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP). This is starting to be reflected in diagnostic criteria for PSP, namely, in the PSP speech and language (SL) subcategory; however, this inclusion is not reflected for CBS. Here, we present a single case of a patient with PPAOS and her clinical follow-up lasting 6 years, from the time she sought our attention to her death which occurred 8 years into the disease. PPAOS was the only and prominent symptom for most of the illness with extrapyramidal signs overtly presenting in the last months of its course. Clinical evaluation, imaging, genetic, and cerebrospinal fluid biomarkers all pointed toward an underlying CBD pathology, albeit the eventual anatomopathological confirmation was not performed. Had her clinical course been more suggestive of PSP, she would have qualified for criteria as PSP-SL. Our case therefore suggests the hypothetic need to discuss the broadening of the existing CBS criteria to encompass isolated PPAOS.

© 2021 The Author(s).
Published by S. Karger AG, Basel

Correspondence to:
Aristotelis Karantzoulis, aristotelis.karantzoulis@gmail.com
Lucio Tremolizzo, lucio.tremolizzo@unimib.it

Introduction

Primary progressive apraxia of speech (PPAOS) is a disorder characterized mainly by a selective and slowly progressive speech production deficit, deeply affecting word articulation. Usually, at symptom onset and for a consistent period of time into the disease, there is no impairment of any other linguistic and/or nonlinguistic neuropsychological function apart from orofacial apraxia which is almost always associated [1].

PPAOS is actually considered as the expression of a focal cortical neurodegenerative syndrome [2, 3]. Nonetheless, symptoms can also constitute a familial hallmark of broader neurodegeneration [4] and coexist with primarily impaired linguistic function [5]. Perhaps, due to this particular nature, PPAOS has been named in various ways, during the past years [2, 6–9]. However, the definition that is gaining most momentum is PPAOS [10] with other names being regarded as its synonyms [11]. Mounting accounts are defining a condition where speech production is the prominent, if not only, symptom of progressive neurodegeneration for a consistent period of time [12–19]. However, as it inevitably occurs in neurodegeneration, pathology spreads, attaining other cerebral areas and leading to the manifestation of broader symptomatology late into the disease's natural history.

In several cases, PPAOS can be the early clinical presentation of corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP) [20–22], with pathological footing being determined mostly by 4R-tau pathology [14, 15, 23, 24]. However, albeit rare, cases of PPAOS due to beta-amyloid pathology have been described [24, 25], with only one being autoptically confirmed [26]. This plausibly justifies performing a lumbar puncture to a PPAOS patient. Furthermore, cases of PPAOS have been described progressing to amyotrophic lateral sclerosis (ALS) [9, 13], some with genetic suggestion of an underlying TDP-43 pathology [27] and autoptic confirmation [28].

Although underreported, PPAOS can constitute up to around 20% of progressive higher-level language and speech disorders [29], and its chameleonic nature justifies an extensive workup for a correct pathological framing thus enabling the patient to be allocated into the right clinical trial and, where available, be eligible for symptomatic therapy. Hence, such a thorough characterization is indicated only for subspecialists or researchers working with phasic troubles in dementia or clinicians with ampler field of interests who wish to obtain diagnostic precision.

Here, we report a single patient affected by PPAOS and her follow-up lasting 4 years, from the time she sought our attention to her death which occurred 8 years into the disease. Surprisingly enough, her condition never bloomed into a fully fledged clinical syndrome during the course of her illness, with her symptoms qualifying for possible CBD only right before her death.

Case Report

The patient was a 75-year-old right-handed female former shop owner with 5 years of formal education and a negative family history for neurodegenerative disease. She had sought our attention after a 4-year history of slowly progressive impaired articulation and mild forgetfulness that sneakily emerged after mourning for a family member. All previous specialist evaluations had framed her condition as functional and reactive to her sorrow. She had a brain MRI taken at symptom onset showing diffuse and nonspecific cerebral atrophy and a carotid ultrasonography that was normal. Moreover, she presented a past history of hypertension and dyslipidemia, for which she was taking medications, and rheumatoid arthritis that was now quiescent. On admission to our ward for an initial diagnostic workup,

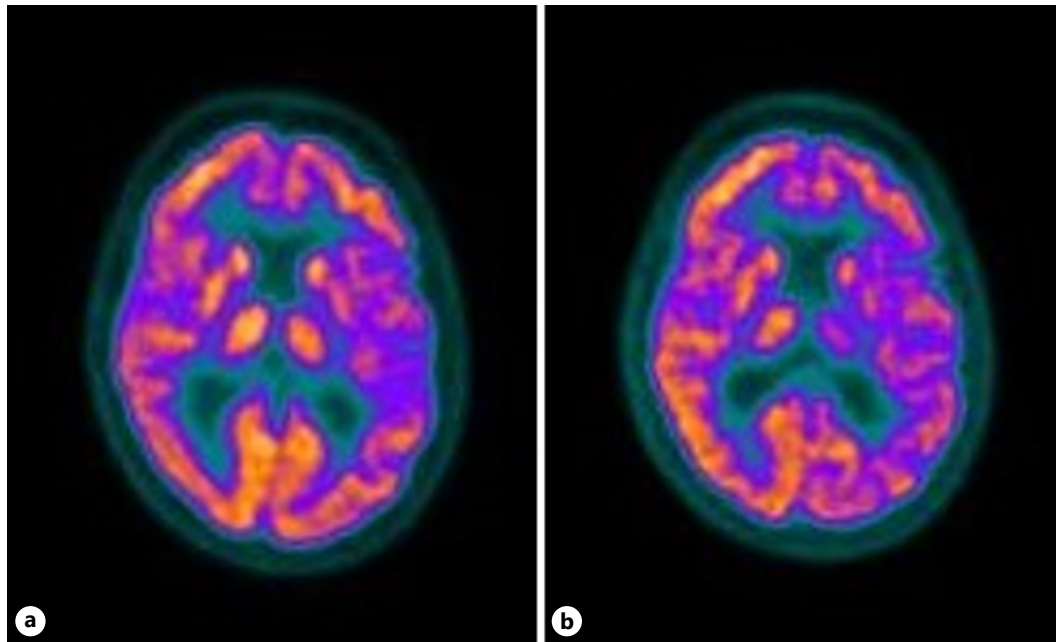


Fig. 1. Brain 18F-FDG PET. **A** Admission time, 4 years after onset. Functional imaging reveals a more marked hypometabolism of the left hemispheric precentral and postcentral gyri as well as the temporal lobe and frontal operculum in the context of a generalized cerebral hypometabolism. The latter finding being consistent with structural imaging (not shown) manifests a generalized cerebral hypotrophy. **B** Seven years later, marked cerebral hypometabolism is now evident, being more severe on the left hemisphere, namely, on the frontal, temporal, and parietal lobes.

her speech was slurred, fragmented, and presented with occasional paraphasias while neurologic examination failed to evidence further abnormalities. A brain 18F-FDG PET was taken, documenting moderate hypometabolism of precentral and postcentral gyri and temporal lobes bilaterally, although hypometabolism was more marked on the left hemisphere (Fig. 1A). After workup, she was discharged with the diagnosis of slowly progressive anarthria and mild nonamnestic cognitive impairment and was referred to our outpatient memory clinic for follow-up. Along the next years, her dysarthria slowly worsened, but no other consistent deficits emerged during repeated clinical examinations or were reported by either caregivers or the patient.

Seven years into the disease, her MRI profile was markedly asymmetrical between hemispheres with a more severe involvement of the left structures in particular involving the left parietal and temporal lobes (Fig. 2) without involving brainstem structures such as the midbrain. In addition, also a second brain 18F-FDG PET showed frontal, parietal, and temporal hypometabolism that was more marked on the left (Fig. 1B), and a DaTSCAN SPECT evidenced dopaminergic degeneration mostly involving the left putamen. Clinically, her most prominent impairment was speech production, which left her almost mute, and she also presented marked orofacial apraxia. At this stage of the disease, her muscle tone was still normal, no falls were reported either by the patient or the caregivers, and her eye movements showed no abnormalities. However, she now exhibited also a marked reduction of mental flexibility and started to unexplainably flee from home. Nonetheless, she was self-sufficient in daily life activities. Her comprehension was intact, and she could still express herself in written form although her writing was littered with marked phonemic errors mainly in the form of substitutions and omissions with slight notes of agrammatism (Fig. 3). A lumbar puncture was performed with normal glucose, protein, and cells. CSF beta-amyloid was 655 pg/mL (normal values

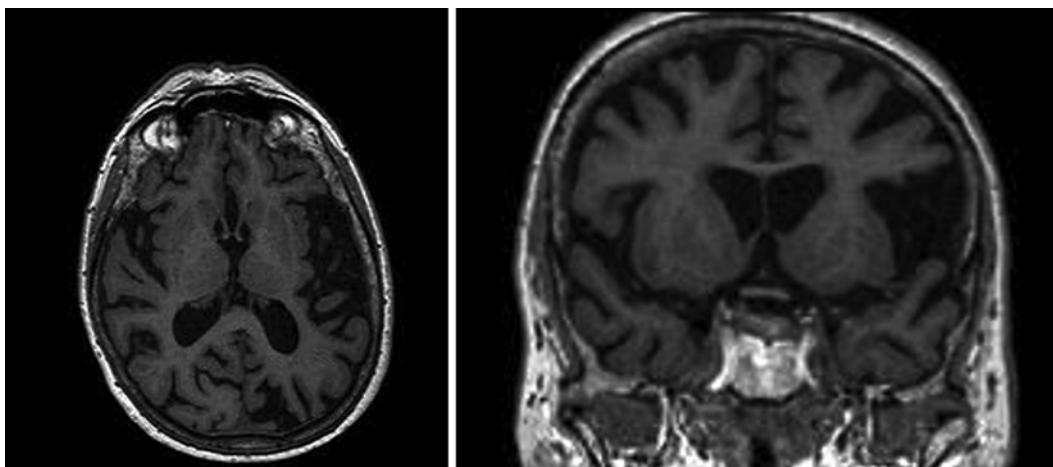


Fig. 2. T1W brain MR image taken 7 years into the disease. Structural imaging confirms what was suggested by brain 18F-FDG PET: on a diffusely atrophic background, a dramatic atrophy on the left frontotemporal and parietal lobes can be observed.

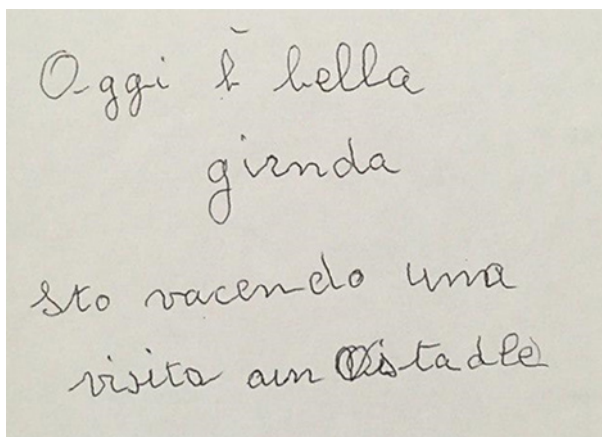


Fig. 3. Writing sample obtained 7 years after onset. Correct sentence (Italian): “Oggi è una bella giornata. Sto facendo una visita in ospedale” (“Today is a nice day. I am having a visit at the hospital”).

>500 pg/mL), total tau was 153 pg/mL (normal values <500), and phospho-tau was 28 pg/mL (normal values <61 pg/mL). Genetic testing was performed: *GRN*, *C9ORF72*, and *TARBDP* were all negative for mutations.

Her last visit at the outpatient clinic was more than 7 years into the disease, and she evidenced extinction upon double touch, notes of limb apraxia, ideomotor slowing, pronounced mental inflexibility, and perseveration. The last time she was assessed, 8 years into the disease, she was at home for she was bedridden due to marked postural instability and asymmetric limb rigidity. The patient had to be fed and helped with daily life activities. Eventually, she developed dysphagia and died of ab ingestis pneumonia.

Discussion

The condition presented by our patient appears to be consistent with PPAOS. In line with most accounts, hindrance in word articulation was the main and only symptom for a substantial part of disease duration (7 years in our case) [9, 13, 19, 27, 30, 31]. Orofacial apraxia appeared

until very late into the disease, while frank language impairment failed to develop until the very end. Structural and functional imaging showed a marked posterior frontal and temporal degeneration that was preponderantly lateralized to the left side. Although most cases seem to show a prevalent frontal anterior involvement [30], others [17, 19] depose for a more posterior one, emphasizing the heterogeneous nature of this disease. Neatly, the DaTSCAN was in line with substantial evidence marking basal ganglia involvement [19, 32]. In comparison with other accounts [13, 19, 21, 22, 33], our case presented limited signs of a significant parkinsonian syndrome only very late into the disease. Indeed, the patient's clinical condition satisfied criteria for possible CBD pathology [34] (asymmetric rigidity/akinesia and cortical sensory loss) only right before her death.

In summary, we reported the natural history of a single case of PPAOS who unlike already described cases did not overtly progress into an evident parkinsonian syndrome. Furthermore, although the majority of PPAOS cases seem to be due to PSP [21, 22] and diagnostic categories for PSP now comprise a speech and language variant [35], our case, with good probability, was due to an underlying CBD, which in itself constitutes a less common phenomenon. At present, there are only 3 single case reports of PPAOS due to CBD [18, 19, 33], but CBD is also the final diagnosis in a minority of patients in published case series [13, 21, 22]. In particular, if follow-up is sufficiently long (i.e., >6 years), a Parkinson plus syndrome appears to inevitably develop supporting PPAOS as an early presentation of a Parkinson plus disorder [36]. Obviously, the lack of a pathological confirmation represents the major eventual limit to our diagnostic hypothesis, thus posing a limitation to the scientific scope of this study, for a portion of the conclusions lacks backing by pathological evidence. However, it should also be noted that due to different intrinsic variables that may be due to consent by the family, ethical issues, institutional practice, or national custom, histopathologic confirmation is difficult to obtain in tantamount occurrences, marking the same aforementioned limitation for other studies in this topic as well. Finally, a minor limit is that the patient somehow could not completely satisfy criteria for probable CBD. However, evidence is pointing toward cognitive manifestations of the frontal type as preponderant in early stages of CBS (a key criterion for antemortem diagnosis of CBD) with parkinsonian signs emerging later into the disease [37], suggesting that a broadening of the existing criteria might perhaps be needed.

Indeed, although diagnostic criteria for antemortem CBD diagnosis encompass apraxia of speech, they regard it as a component of nonfluent/agrammatic primary progressive aphasia [34], which in its own terms can be misleading, for apraxia of speech proper is not a disorder of language but rather of speech. We therefore may propose a new subcategory for the in vivo diagnosis of CBD, akin to the SL category already established for PSP [35], comprising cases of early and predominant PPAOS. Further case reports and series with neuropathological confirmation will be unquestionably needed in order to establish if this interesting hypothesis could be validated.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki, and the patient gave written informed consent to this publication, including to the use of the images. Due to the article type, no ethics committee approval was needed.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

Funding Sources

The authors did not receive any funding.

Author Contributions

All authors were involved in the direct management of the case and ongoing extensive discussion; A.K., E.S., and L.T. wrote the manuscript.

References

- 1 Tyrrell PJ, Kartsounis LD, Frackowiak RS, Findley LJ, Rossor MN. Progressive loss of speech output and orofacial dyspraxia associated with frontal lobe hypometabolism. *J Neurol Neurosurg Psychiatry*. 1991;54(4):351–7.
- 2 Cohen L, Benoit N, Van Eeckhout P, Ducarne B, Brunet P. Pure progressive aphemia. *J Neurol Neurosurg Psychiatry*. 1993;56(8):923–4.
- 3 Broussolle E, Bakchine S, Tommasi M, Laurent B, Bazin B, Cinotti L, et al. Slowly progressive anarthria with late anterior opercular syndrome: a variant form of frontal cortical atrophy syndromes. *J Neurol Sci*. 1996;144(1–2):44–58.
- 4 Duffy JR, McNeil MR, Chapey R. Primary progressive aphasia and apraxia of speech. *Language intervention strategies in adult aphasia*. Baltimore: Wolters Kluwer/Lippincott, Williams and Wilkins; 2008. p. 543–64.
- 5 Mesulam MM. Slowly progressive aphasia without generalized dementia. *Ann Neurol*. 1982;11(6):592–8.
- 6 Alajouanine T, Ombredane A, Durand M. *Le syndrome de disintegration phonetique dans l'aphasie*. Paris: Masson; 1939.
- 7 Bay E. Aphasia and non-verbal disorders of language. *Brain*. 1962;85:411–26.
- 8 Silveri MC, Cappa A, Salvigni BL. Speech and language in primary progressive anarthria. *Neurocase*. 2003;9(3):213–20.
- 9 Lucchelli F, Papagno C. Is slowly progressive anarthria a “pure” motor-speech disorder? Evidence from writing performance. *Neurocase*. 2005;11(3):234–41.
- 10 Duffy JR. Apraxia of speech in degenerative neurologic disease. *Aphasiology*. 2006;20(6):511–27.
- 11 Ogar J, Slama H, Dronkers N, Amici S, Gorno-Tempini ML. Apraxia of speech: an overview. *Neurocase*. 2005;11(6):427–32.
- 12 Santens P, Van Borsel J, Foncke E, Meire V, Merckx H, De Bleecker J, et al. Progressive dysarthria. Case reports and a review of the literature. *Dement Geriatr Cogn Disord*. 1999May;10(3):231–6.
- 13 Soliveri P, Piacentini S, Carella F, Testa D, Ciano C, Girotti F. Progressive dysarthria: definition and clinical follow-up. *Neurol Sci*. 2003;24(3):211–2.
- 14 Josephs KA, Boeve BF, Duffy JR, Smith GE, Knopman DS, Parisi JE, et al. Atypical progressive supranuclear palsy underlying progressive apraxia of speech and nonfluent aphasia. *Neurocase*. 2005;11(4):283–96.
- 15 Josephs KA, Duffy JR, Strand EA, Whitwell JL, Layton KF, Parisi JE, et al. Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. *Brain*. 2006;129(6):1385–98.
- 16 Papagno C, Lucchelli F, Vallar G. Phonological recoding, visual short-term store and the effect of unattended speech: evidence from a case of slowly progressive anarthria. *Cortex*. 2008;44(3):312–4.
- 17 Limousin N, Rimbaux S, Mondon K, Hommet C, Corcia P, De Toffol B, et al. Anarthrie progressive: une entité propre (Progressive anarthria: an individual entity). *Rev Neurol*. 2008;164:444–51.
- 18 Assal F, Laganaro M, Remund CD, Ragno Paquier C. Progressive crossed-apraxia of speech as a first manifestation of a probable corticobasal degeneration. *Behav Neurol*. 2012;25(4):285–9.
- 19 Ruggeri M, Blundo C, Gerace C, Ricci M. Primary progressive dysarthria as the initial presentation of corticobasal degeneration: A case report. *Rev Neurol*. 2019;175(5):336–8.
- 20 Josephs KA, Duffy JR. Apraxia of speech and nonfluent aphasia: a new clinical marker for corticobasal degeneration and progressive supranuclear palsy. *Curr Opin Neurol*. 2008;21(6):688–92.
- 21 Josephs KA, Duffy JR, Strand EA, Machulda MM, Senjem ML, Gunter JL, et al. The evolution of primary progressive apraxia of speech. *Brain*. 2014;137(10):2783–95.
- 22 Seckin ZI, Duffy JR, Strand EA, Clark HM, Utianski RL, Machulda MM, et al. The evolution of parkinsonism in primary progressive apraxia of speech: a 6-year longitudinal study. *Parkinsonism Relat Disord*. 2020;81:34–40.
- 23 Deramecourt V, Lebert F, Debachy B, Mackowiak-Cordoliani MA, Bombois S, Kerdraon O, et al. Prediction of pathology in primary progressive language and speech disorders. *Neurology*. 2010;74(1):42–9.
- 24 Utianski RL, Whitwell JL, Schwarz CG, Senjem ML, Tosakulwong N, Duffy JR, et al. Tau-PET imaging with (18F) AV-1451 in primary progressive apraxia of speech. *Cortex*. 2018;99:358–74.

- 25 Josephs KA, Duffy JR, Strand EA, Machulda MM, Senjem ML, Lowe VJ, et al. Syndromes dominated by apraxia of speech show distinct characteristics from agrammatic PPA. *Neurology*. 2013;81(4):337–45.
- 26 Gerstner E, Lazar RM, Keller C, Honig LS, Lazar GS, Marshall RS. A case of progressive apraxia of speech in pathologically verified Alzheimer disease. *Cogn Behav Neurol*. 2007;20(1):15–20.
- 27 Praline J, Vourc'h P, Guennoc AM, Veyrat-Durebex C, Corcia P. Co-occurrence of progressive anarthria with an S393L TARDBP mutation and ALS within a family. *Amyotroph Lateral Scler*. 2012;13:155–7.
- 28 Otsuki M, Nakagawa Y, Mori F, Tobioka H, Yoshida H, Tatezawa Y, et al. Progressive anterior operculum syndrome due to FTLD-TDP: a clinico-pathological investigation. *J Neurol*. 2010;257:1148–53.
- 29 Wicklund MR, Duffy JR, Strand EA, Machulda MM, Whitwell JL, Josephs KA. Quantitative application of the primary progressive aphasia consensus criteria. *Neurology*. 2014;82:1119–26.
- 30 Josephs KA, Duffy JR, Strand EA, Machulda MM, Senjem ML, Master AV, et al. Characterizing a neurodegenerative syndrome: primary progressive apraxia of speech. *Brain*. 2012;135:1522–36.
- 31 Didic M, Ceccaldi M, Poncet M. Progressive loss of speech: a neuropsychological profile of premotor dysfunction. *Eur Neurol*. 1998;39:90–6.
- 32 Seckin ZI, Whitwell JL, Utianski RL, Botha H, Ali F, Duffy JR, et al. Ioflupane 123I (DAT scan) SPECT identifies dopamine receptor dysfunction early in the disease course in progressive apraxia of speech. *J Neurol*. 2020;267:2603–11.
- 33 Tetzloff KA, Duffy JR, Strand EA, Machulda MM, Boland SM, Utianski RL, et al. Clinical and imaging progression over 10 years in a patient with primary progressive apraxia of speech and autopsy-confirmed corticobasal degeneration. *Neurocase*. 2018;24:111–20.
- 34 Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, et al. Criteria for the diagnosis of corticobasal degeneration. *Neurology*. 2013;80:496–503.
- 35 Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, et al. Movement disorder society-endorsed PSP study group. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. *Mov Disord*. 2017;32:853–64.
- 36 Respondek G, Compta Y. Primary progressive apraxia of speech: a further piece in the progressive supranuclear/corticobasal degeneration spectrum jigsaw. *Parkinsonism Relat Disord*. 2020;81:219–20.
- 37 Mathew R, Bak TH, Hodges JR. Diagnostic criteria for corticobasal syndrome: a comparative study. *J Neurol Neurosurg Psychiatry*. 2012;83:405–10.