Susceptibility-Weighted Imaging Reveals Subcortical Iron Deposition in *PLA2G6*-associated Neurodegeneration: The "*Double Cortex Sign*"

Magnetic resonance imaging (MRI) findings in *PLA2G6*-associated Neurodegeneration (PLAN), a "Neurodegeneration with Brain Iron Accumulation" (NBIA) disorder caused by autosomal-recessive mutations in the *PLA2G6* gene,[1] have been reported to show varying degrees of cerebral and cerebellar atrophy as well as basal ganglia iron deposition on susceptibility-weighted imaging (SWI), although some patients do not show any of these imaging features despite genetically proven PLAN.[2,3]

We here present a PLAN patient demonstrating a novel neuroimaging pattern.

A 43-year-old female presented with a progressive gait disorder showing spastic and parkinsonian features with onset at the age of 40. On examination predominant left-sided rigidity, bradykinesia, and reduced arm swing as well as small-stepped gait and postural instability were evident. Paraspasticity was noticed with catch-and-release of knee extensors and hipp adductors, brisk deep tendon reflexes, sustained clonus of the Achilles reflex, and contractures of both feet with pes equinus. Depression and cognitive deficits were evident. Levodopa therapy was started about 3 years prior to presentation, and parkinsonian symptoms improved following the initiation of L-dopa but motor fluctuations emerged shortly after. Medication at presentation included L-dopa with a daily dose of 400 mg and antidepressive treatment with sertraline (100 mg) daily.

Targeted genetic sequencing revealed pathogenic compound-heterozygous *PLA2G6* mutations (c.1963C > A; p.L655M and c.986G > A; p.R329H) in our patient and her sister who had also suffered from dystonia-parkinsonian syndrome until her passing at the age of 35. The parents were unaffected carriers, each carrying one of the two mutations.

Clinical routine MRI showed global cerebral atrophy and only slight cerebellar atrophy (Fig. 1A and Supplementary Fig. S1 in Appendix S1). SWI revealed a hypointense band adjacent to the entire cortical ribbon (Fig. 1A) and only a slight inhomogeneous hypointense signal in the putamen and substantia nigra (Fig. 1C,E). Quantitative susceptibility mapping (QSM) revealed increased magnetic susceptibility in representative sections of this hypointense band (median value frontal gray matter: 86 ppb vs 56 ppb in an age-matched, male healthy individual [Fig. 1G vs. H]) as well as in the basal ganglia (globus pallidus: 186 ppb vs. 136; putamen: 160 ppb vs. 106 ppb; caudate nucleus: 133 ppb vs. 88 ppb; substantia nigra: 272 ppb vs. 161 ppb; Fig. 1I,K vs. J,L), suggesting abnormal iron accumulation.

Although band-like hypointensities reflecting iron deposition in specific cortical regions have been demonstrated in aging and in various neurodegenerative diseases,[4] including Alzheimer's, Parkinson's, and motoneuron diseases, SWI in our patient revealed a pattern of hypointense signal subcortical to the entire cortex, leaving the impression of an additional cortical ribbon.

Brain iron deposition in NBIA subtypes has been shown to be mainly localized in the basal ganglia with to some extent specific patterns. However, only a few studies have applied QSM in NBIA subtypes demonstrating high iron contents.[5-7] In our patient, QSM revealed increased magnetic susceptibility values not only in the basal ganglia but predominantly adjacent to the entire cortical ribbon, indicating the underlying signal to result from iron deposition.

This previously undescribed imaging pattern, we have termed *"Double Cortex Sign,"* expands the neuroimaging

Key Words: PLAN, PLA2G6, NBIA, neurodegeneration with brain iron accumulation, SWI, QSM

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Relevant conflicts of interest/financial disclosures: B.R. receives support through the Clinician Scientist program of the Medical Faculty of the University of Tübingen (grant #478-0-0). This work was partly supported by EU-LACH grant #16/T01-0118 to GEH. L.S. is a member of the European Reference Network for Rare Neurological Diseases (ERN-RND)—Project No. 739510. B.B. has received travel expenses from Bayer Vital, consulting fees (paid to the institution) from Medtronic and is cofounder and shareholder of AIRAmed GmbH. L.Z., G.E.H., and K.S. have nothing to disclose. The authors declare that there are no other funding sources or conflicts of interest relevant to this work.

Received: 21 December 2022; **Revised:** 24 January 2023; **Accepted:** 7 February 2023

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29364

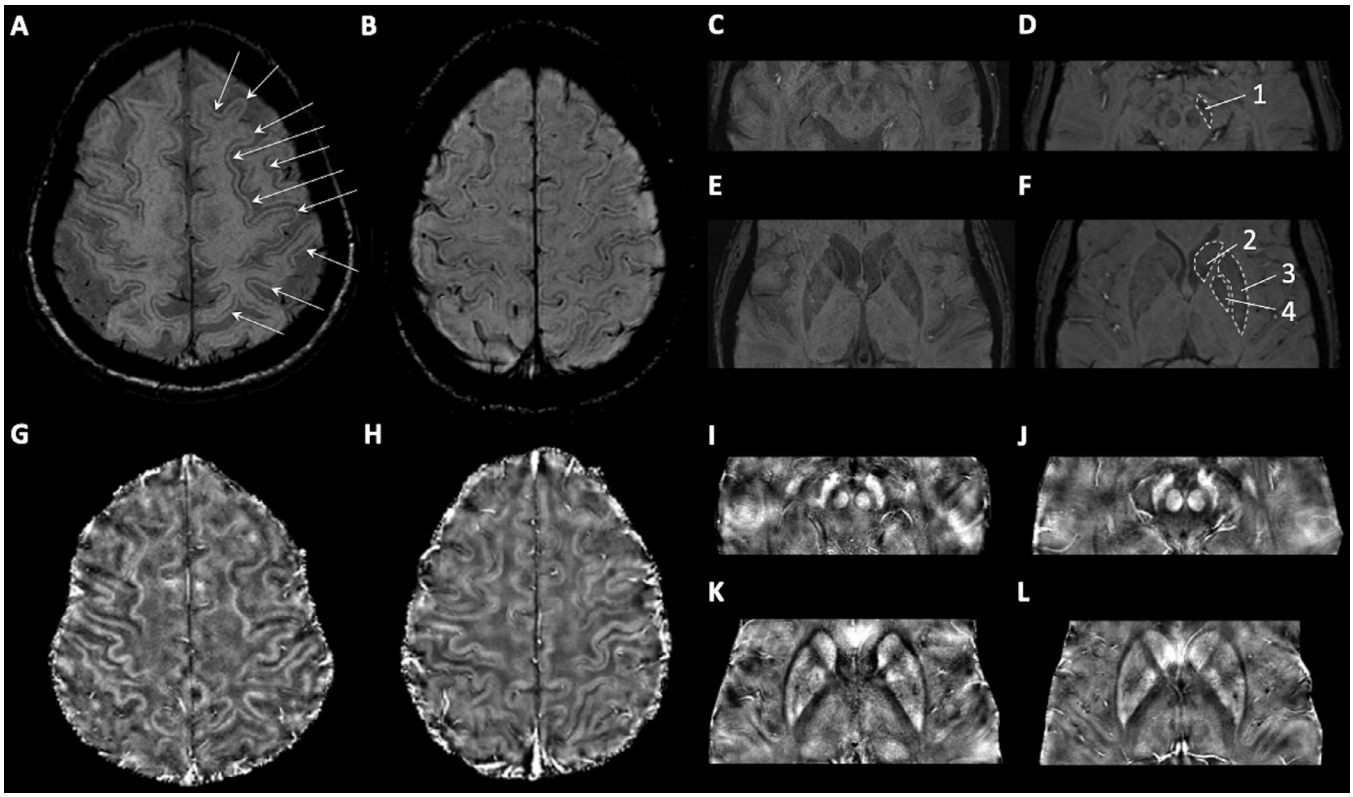

FIG. 1. "Double Cortex Sign" in PLAN. Susceptibility-weighted images (SWI) reveal a subcortical hypointense band adjacent to the entire cortical ribbon (**A**; arrows), while showing only slight and inhomogeneous iron accumulation in the basal ganglia (**C** and **E**; healthy control **B, D & F**). Cerebral atrophy is overt (A), whereas there was only slight cerebellar atrophy (see Supplementary Fig. S1 in Appendix S1). Quantitative susceptibility mapping (QSM) demonstrates increased magnetic susceptibility values in our PLAN patient (**G**) indicating increased subcortical iron contents compared to an age-matched healthy control (**H**). Regions of interest for QSM are encircled with dotted lines as follows: substantia nigra (1), caudate nucleus (2), putamen (3) and globus pallidus (4).

spectrum of PLAN. Quantification of brain susceptibility alterations, for example, using QSM, may provide novel imaging biomarkers, which are of high relevance given the variability and heterogeneity of imaging findings reported so far in PLAN and other NBIA subtypes. ■

Acknowledgment: We thank the patient and her family for participating in this study. Open Access funding enabled and organized by Projekt DEAL.

Ethical Statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. We confirm that the approval of an institutional review board was not required for this work. We also confirm that informed consent from the patient was obtained.

Financial Disclosures for the Previous 12 months.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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(1) Research project: A. Conception, B. Organization, C. Execution. (2) Data analysis: A. Design, B. Execution, C. Review and critique. (3) Manuscript preparation: A. Writing of the first draft, B. Review and critique.

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Author Contributions

Benjamin Roeben contributed to the conception, organization and execution of the study, designed and executed the data analysis and wrote the first draft of the manuscript. Lena Zeltner contributed to the organization and execution of the study, reviewed and provided critique to the final version of the manuscript. Gisela E. Hagberg designed, executed, reviewed and critiqued the data analysis, and reviewed and provided critique to the final version of the manuscript. Klaus Scheffler contributed to the execution of the study, and reviewed and provided critique to the data analysis and the final version of the manuscript. Ludger Schöls contributed to the organization and execution of the study, and reviewed and provided critique to the data analysis and the final version of the manuscript. Benjamin Bender contributed to the conception, organization and execution of the study, designed and executed the data analysis, and reviewed and provided critique to the data analysis and the final version of the manuscript.