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Levodopa-refractory hyperprolactinemia and pituitary findings in inherited disorders of biogenic amine metabolism

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Abstract

Elevated serum prolactin concentrations occur in inherited disorders of biogenic amine metabolism because dopamine deficiency leads to insufficient inhibition of prolactin secretion. This work from the International Working Group on Neurotransmitter Related Disorders (iNTD) presents the results of the first standardized study on levodopa-refractory hyperprolactinemia (LRHP; >1000 mU/L) and pituitary magnetic resonance imaging (MRI) abnormalities in patients with inherited disorders of biogenic amine metabolism. Twenty-six individuals had LRHP or abnormal pituitary findings on MRI. Tetrahydrobiopterin deficiencies were the most common diagnoses ($n = 22$). The median age at diagnosis of LRHP was 16 years (range: 2.5–30, 1st–3rd quartiles: 12.25–17 years). Twelve individuals (nine females) had symptoms attributed to hyperprolactinemia: menstruation-related abnormalities ($n = 7$), pubertal delay or arrest ($n = 5$), galactorrhea ($n = 3$), and decreased sexual functions ($n = 2$). MRI of the pituitary gland was obtained in 21 individuals; six had heterogeneity/hyperplasia of the gland, five had

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adenoma, and 10 had normal findings. Eleven individuals were treated with the dopamine agonist cabergoline, ameliorating the hyperprolactinemia-related symptoms in all those assessed. Routine monitoring of these symptoms together with prolactin concentrations, especially after the first decade of life, should be taken into consideration during follow-up evaluations. The potential of slow-release levodopa formulations and low-dose dopamine agonists as part of first-line therapy in the prevention and treatment of hyperprolactinemia should be investigated further in animal studies and human trials. This work adds hyperprolactinemia-related findings to the current knowledge of the phenotypic spectrum of inherited disorders of biogenic amine metabolism.

KEYWORDS

biogenic amines, hyperprolactinemia, hypogonadism, neurotransmitter disorders, prolactinoma, tetrahydrobiopterin (BH_4) deficiency

1 | INTRODUCTION

Inherited disorders of neurotransmitter metabolism are rare neurometabolic disorders due to defects in biosynthesis, degradation, or transport of neurotransmitters or their cofactors. Disorders of biogenic amines (dopamine, serotonin, norepinephrine, and epinephrine) represent a subgroup that can be classified as follows[1]: (1) Primary disorders of biogenic amine metabolism, (2) Disorders of tetrahydrobiopterin (BH_4) biosynthesis and recycling, and (3) Co-chaperone associated disorders, as depicted in Table S1.

The patients present with a broad spectrum of phenotypes, ranging from mild hypotonia and drug-responsive late-onset movement disorders to early-onset lethal encephalopathies. Disease onset can occur at any time from the perinatal period to adulthood. While a subset of BH_4 deficiencies can be detected via newborn screening for phenylketonuria, others require a high index of clinical suspicion and disease-specific diagnostic tools, causing significant delays in treatment. The underlying disorder itself, the timing of diagnosis, initiation of disease-specific treatment, and long-term compliance to treatment influence the outcome. The treatment in general aims to correct the hyperphenylalaninemia (if present) and supplement the precursors of biogenic amines (e.g., levodopa [L-Dopa]/decarboxylase inhibitor (DCI), 5-hydroxytryptophan) to (i) correct the respective biochemical imbalance in the central nervous system, (ii) to ameliorate the related clinical symptoms (Figure 1).[2]

Inherited disorders of biogenic amine metabolism can be diagnosed by measuring biogenic amines, pterins, 5-methyltetrahydrofolate, and amino acids in the cerebrospinal fluid (CSF) and by molecular genetic analyses. In addition to clinical monitoring, repeated measurements of metabolites in CSF may also be required for individual tailoring of drug dosage.[2] Laboratory analysis of biogenic amines in CSF is expensive, requires an invasive procedure for sampling (lumbar puncture), and is not widely available. Therefore, peripheral biomarkers are appealing for clinical use. One such potential biomarker serving as an indirect peripheral marker of central dopamine deficiency is serum prolactin.[3] Normal serum prolactin concentrations vary by age, sex, physiologic state (e.g., pregnancy, lactation), and the assay used, but are generally below 25 μg/L (~500 mU/L).[4] Prolactin is unique among anterior pituitary hormones since its secretion is mainly regulated via inhibition by dopamine. Dopamine synthesized in the dorsomedial arcuate nucleus of the hypothalamus travels through the dopaminergic axons in the median eminence, is secreted into the pituitary portal veins, and acts on the D2 receptors on the lactotroph cells of the anterior pituitary, leading to tonic inhibition of prolactin secretion (Figure 1).[5,6] Thus, patients with cerebral dopamine deficiency may have elevated serum prolactin concentrations, which decrease after initiation of L-Dopa supplementation. Hence, it has been proposed that a prolactin profile can help titrate dopaminergic treatment.[7,8]

Using prolactin as a surrogate marker for central dopamine homeostasis has several drawbacks. First, approximately 15% of serum prolactin circulates as less bioactive dimers (big prolactin) or larger polymers (big big prolactin), and certain situations where these larger forms predominate (macroprolactinemia) should be differentiated from true hyperprolactinemia.[9] Polyethylene

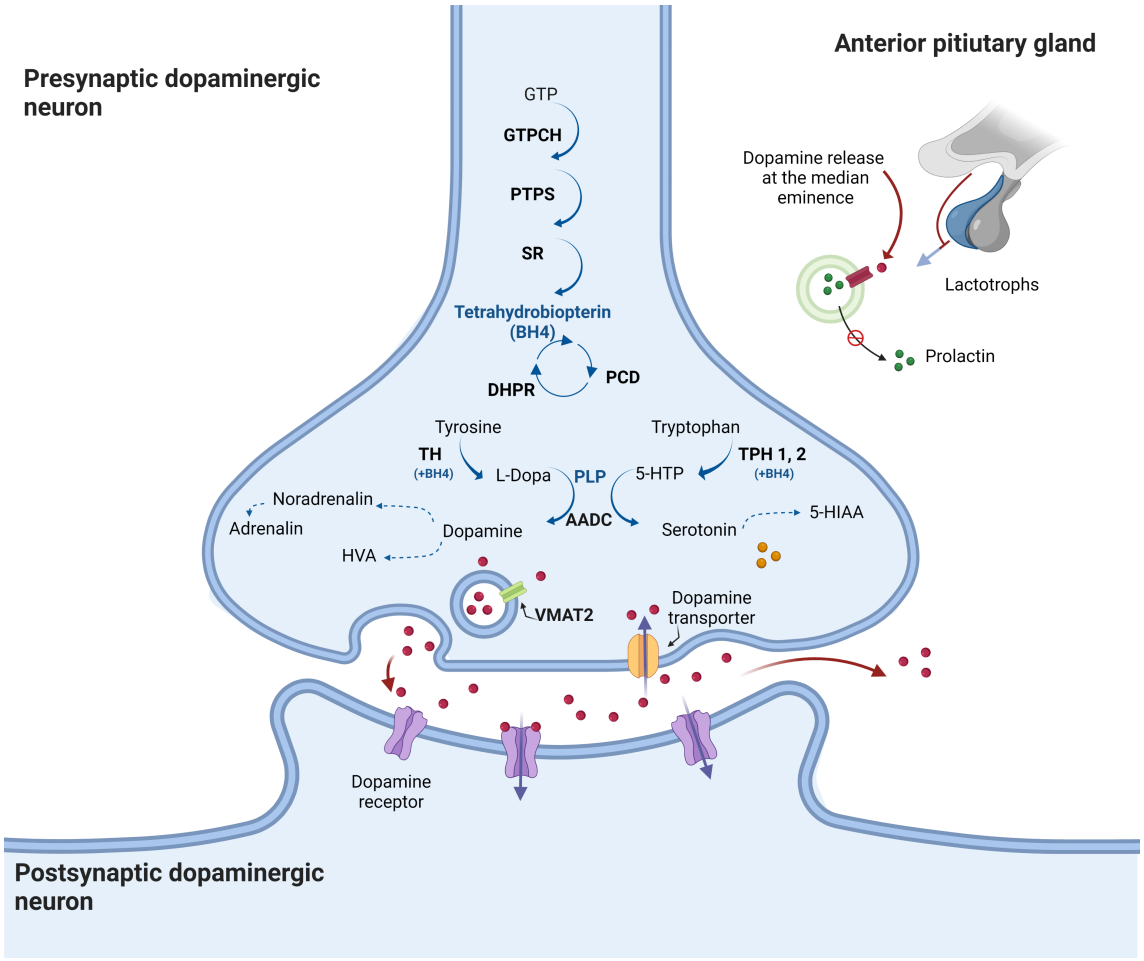

FIGURE 1 Schematic representation of biogenic amine synthesis and transport in the synapse and of dopamine action on the anterior pituitary. Figure created with BioRender.com. 5-HIAA, 5-hydroxyindoleacetic acid; 5-HTP, 5-hydroxytryptophan; AADC, L-aromatic amino acid decarboxylase; BH_4, tetrahydrobiopterin; DHPR, dihydropteridine reductase; GTP, guanosine triphosphate; GTPCH, GTP cyclohydrolase; HVA, homovanillic acid; L-Dopa, levodopa; PCD, pterin-4 alpha-carbinolamine dehydratase; PLP, pyridoxal-5-phosphate; PTPS, 6-pyruvoyltetrahydropterin synthase; SR, sepiapterin reductase; TH, tyrosine hydroxylase; TPH, tryptophan hydroxylase; VMAT2, vesicular monoamine transporter 2.

glycol (PEG) precipitates macroprolactin, and prolactin recovery rate below 40% after PEG precipitation suggests macroprolactinemia.[9] Second, although prolactin secretion is predominantly regulated by dopamine in humans,[10] prolactin concentrations may be influenced by systemic disorders, drugs, sleep disorders, epileptic seizures, venipuncture stress, pregnancy, and lactation.[4,6,11] Consequently, although hyperprolactinemia has been reported in various disorders of biogenic amine metabolism, normal prolactin concentrations may not exclude dopamine deficiency.[8,12–14] Consensus guidelines for the diagnosis and treatment of AADC and BH_4 deficiencies recommend further research on the use of prolactin for diagnosis and monitoring.[14,15]

Although elevated prolactin concentrations decrease upon initiation of L-Dopa treatment, severe hyperprolactinemia with or without prolactinoma (prolactin-secreting tumors of lactotroph cells) in patients with BH_4 deficiencies has been described in single case reports.[16,17] Hyperprolactinemia may be asymptomatic, but galactorrhea or symptoms related to hypogonadism (amenorrhea, menstrual irregularities, delayed puberty, impotence, infertility, osteoporosis, etc.) can occur. Due to the occurrence of menstruation-related symptoms, females are more likely to notice symptoms, whereas males often come to medical attention later if they have a neurologic impairment, sometimes with large adenomas causing mass effects.[4,18] Serum prolactin concentrations >1000–2000 mU/L together with a pituitary adenoma detected on magnetic resonance imaging (MRI) defines a prolactinoma.[18] Macroprolactinomas (>10 mm) may cause

additional symptoms due to their mass effect: visual field deficits or deficiencies in other pituitary hormones due to compression of the optic chiasm or the pituitary stalk, respectively. Dopamine agonists are the first-line treatment for symptomatic hyperprolactinemia and prolactinoma.[4,18]

In this work, we report the clinical, biochemical, and radiological data of individuals with inherited disorders of biogenic amine metabolism who present with moderate to severe levodopa-refractory hyperprolactinemia with or without MRI abnormalities of the pituitary gland. The results widen the spectrum of disease-related findings, and provide suggestions on implementation of prolactin measurements to improve disease monitoring.

2 | PATIENTS AND METHODS

2.1 | The International Working Group on Neurotransmitter Related Disorders

The iNTD registry (https://www.intd-registry.org) is the web-based and password-protected patient registry of the International Working Group on Neurotransmitter Related Disorders (www.intd-online.org).[19] All 42 centers in the iNTD patient registry and 5 centers in iNTD network were officially invited to contribute patients.

2.2 | Inclusion criteria of this study

Individuals fulfilling the following inclusion criteria were enrolled: patients with inherited disorders of biogenic amine metabolism, presenting with (A) persistent moderate (1000–2000 mU/L ≈ 50–100 ng/mL) or severe (>2000 mU/L ≈ 100 ng/mL) hyperprolactinemia[20,21] despite adequate doses of L-Dopa/Decarboxylase inhibitor as confirmed by the treating expert physician's clinical judgment, aided by symptoms, homovanillic acid (HVA) concentrations in CSF or guideline recommendations if available, or (B) abnormal pituitary findings on MRI together with hyperprolactinemia.

2.3 | Hyperprolactinemia-related findings

Data on prolactin measurements, and on symptoms and management of hyperprolactinemia-related findings were collected retrospectively. Galactorrhea was defined as nonlactational milk production.[22] Primary amenorrhea was defined as absence of menstruation ≥15 years in girls or absence of menarche within 3 years of thelarche[23]; secondary amenorrhea as the absence of menses for 6 months in individuals (and adolescents) with previously irregular menses, and for 3 months in individuals with previously regular menses.[24] Oligomenorrhea was defined as cycle length of ≥35 days in adult women and ≥40 days in adolescents.[25] Delayed puberty was defined as lack of pubertal development at two standard deviations above the mean age for the general population of the geographical area; arrested puberty as failure to complete puberty within approximately 4 years of its onset.[26]

Low bone mineral density is a known complication of hypogonadism,[4] but individuals on phenylalanine-restricted diet or those with neurological impairment may have low bone mineral density due to nutritional insufficiencies or poor mobility.[27,28] Due to the fact that our patient cohort could have low bone mineral density due to multiple factors, low bone mineral density, osteoporosis, or fractures were not considered as hyperprolactinemia-related findings. Since pituitary hormone deficiencies (e.g., growth hormone deficiency) are multifactorial,[29] they were regarded to be related to hyperprolactinemia only if there was a significant mass effect of a macroprolactinoma.

2.4 | MRI data

Cranial or pituitary MRI was performed in respective institutions. Pituitary glands in the MRI studies were systematically reviewed by two independent neuroradiologists (A.A.K., I.H.). Isolated stalk deviation was not rated as pathologic. MRI reports were used when the original scans were not available. The following classification was used to describe the MRI findings:

0. *normal*: No abnormality of the pituitary gland parenchyma in size and/or signal.
1. *heterogeneity/hyperplasia*: no clear adenoma with identifiable borders, but parenchymal heterogeneity with or without associated mild hyperplasia. Hyperplasia was defined using the age and gender-matched norm values for pituitary gland size.[30,31]
2. *adenoma*: circumscribed area of signal alteration compared to normal pituitary parenchyma on dynamic or standard imaging sequences.

2.5 | Statistical analysis

Statistical analyses were performed in R (version 1.2.5042). Numeric variables were compared between two independent groups with Kruskal–Wallis test.

Wilcoxon rank-sum test was used to compare numeric variables between more than two groups. Correlations between numerical variables with non-normal distributions were analyzed using Spearman's rank correlation. Categorical variables were compared using Fisher's exact test and pairwise Fisher's exact test as post hoc test. $p < 0.05$ was set as statistically significant.

3 | RESULTS

3.1 | Study population

Out of 320 individuals with inherited disorders of biogenic amine metabolism from 34 iNTD registry centers, 34 individuals were reported to have hyperprolactinemia. Eighteen individuals from iNTD registry centers and eight from two iNTD network centers (26 in total) fulfilled the inclusion criteria of the study. Clinical summaries of the individuals are presented in Table S2.

Out of 26 patients (15 females), 14 had 6-pyruvoyltetrahydropterin synthase (PTPS), six had dihydropteridine reductase (DHPR), three had tyrosine hydroxylase (TH) deficiency, and one each had autosomal recessive guanosine triphosphate cyclohydrolase (arGTPCH), sepiapterin reductase (SR), and DNAJC12 deficiency. The median age at onset of the underlying neurotransmitter disease was 3 months (range: 0–240 months, 1st–3rd quartiles: 1–6 months, $n = 22$). The median age at diagnosis of the neurotransmitter disease was 6 months (range: 0.27–252 months, 1st–3rd quartiles: 3–24 months, $n = 26$, Figure 2).

3.2 | Clinical and biochemical findings

The median age at diagnosis of LRHP was 16 years (range: 2.5–30 years, 1st–3rd quartiles: 12.25–17 years, $n = 26$; Figure 2, Table S2). At the time of LRHP diagnosis, the median serum prolactin concentration was 2539 mU/L (range: 926–31 914 mU/L, 1st–3rd quartiles: 1331–5225 mU/L, $n = 25$). PEG precipitation of serum prolactin was performed in 15 individuals at least once during the disease course, and prolactin recovery rates were all >40%, excluding macroprolactinemia. CSF HVA concentration at the time of LRHP was available in five individuals (Patient_01-04, and 20), and was below the age-dependent reference range only in Patient_02 (200 nmol/L; normal: 313–824 nmol/L).

Past and concomitant neurological findings attributable to their underlying neurotransmitter disorder were diverse, and are presented in Table S2. Fourteen individuals (six females) did not have any symptoms related to hyperprolactinemia. Twelve individuals (9 females [75%]) had symptoms attributed to hyperprolactinemia-related hypogonadism: menstruation-related abnormalities were the most common ($n = 7$, including irregular menses/oligomenorrhea, and primary or secondary amenorrhea) followed by pubertal delay or arrest in five individuals (two females), and decreased libido and sexual functions in two (both male). Three individuals (all female) reported galactorrhea. Some individuals had more than one symptom (Table S2). Symptoms occurred predominantly in females (9/15 females [60%], 3/11 males [27%]; Table S2).

Median serum prolactin concentrations (not under treatment with any dopamine agonists) did not differ significantly between individuals with or without hyperprolactinemia-related findings (Kruskal–Wallis test, p-value > 0.05, Figure 3A).

3.3 | MRI findings

MRI was performed in 21 of 26 individuals. Twenty-five MRI studies of 17 patients were reviewed by experienced neuroradiologists (A.A.K. or I.H.; pituitary MRI in 11, cranial MRI in 2, both in 3 patients). The radiologic report was used due to the unavailability of six original MRI scans. MRI findings are presented in Table 1.

The age range at the time of MRI scans was 4.6–35 years. Ten patients had normal MRI scans. Heterogeneity/hyperplasia of the pituitary gland was described in six patients, and a clearly identifiable pituitary microadenoma in five. Representative magnetic resonance images are presented in Figure 4. The sizes of detected microadenomas ranged from 1 to 7.5 mm. Pituitary stalk deviation was observed in five cases. No macroadenoma, invasion of the cavernous sinus, or compression of the optic chiasm was observed. Follow-up MRI scans were available in seven patients. Only two patients (Patient_11 and 13) with microadenomas had follow-up MRI (3 and 2 years after initiation of cabergoline, respectively), not demonstrating a significant reduction in adenoma size. These two patients also reported poor compliance with cabergoline (Figure 5, Table S2) and presented fluctuating prolactin concentrations.

Median serum prolactin concentrations (not under treatment with any dopamine agonists) in patients with heterogeneity/hyperplasia of the pituitary gland were slightly significantly higher than in patients with normal pituitary MRI findings (Wilcoxon test, $p < 0.05$; Figure 3B). MRI findings and hyperprolactinemia-related symptoms did not reveal a significant association ($p > 0.05$, Fisher's exact test).

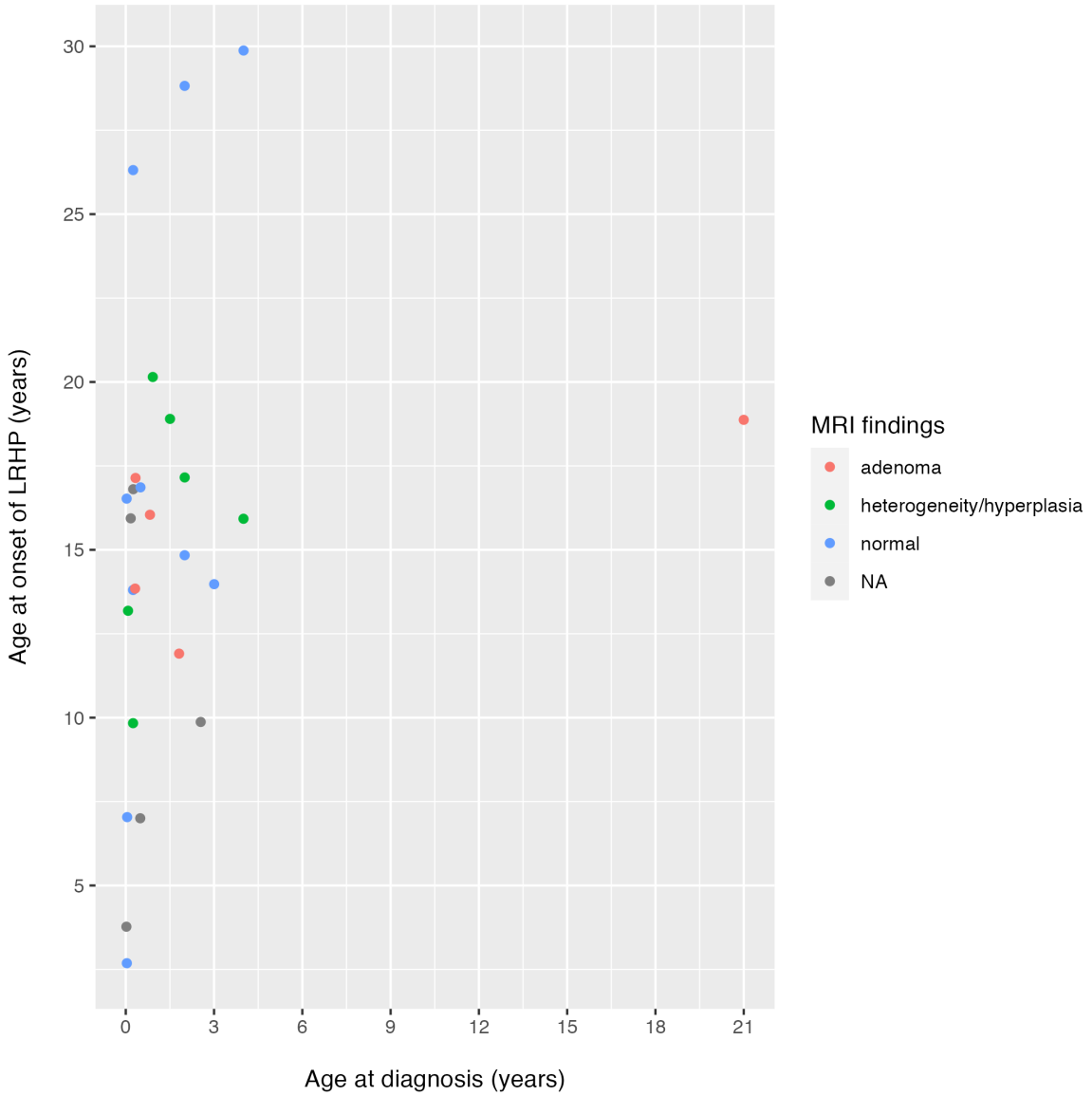

FIGURE 2 Distribution of the age at diagnosis of underlying neurotransmitter diseases versus the age at diagnosis of levodopa-refractory hyperprolactinemia (LRHP). There was a weak significant correlation between the age at diagnosis of underlying neurotransmitter disorder and the age at diagnosis of LRHP (Spearman $\rho = 0.39$, $p = 0.049$. The patient with DNAJC12 deficiency diagnosed at the of 21 years was considered an outlier and excluded from this analysis). NA, not available.

3.4 | Treatment and clinical follow-up

Serum prolactin concentrations before and after the detection of LRHP in each patient are presented in Figure 5. Thirteen individuals did not receive specific treatment for LRHP. Among the remaining 13 individuals, one was offered a dopamine agonist but has not yet started to take it (Patient_21). Increasing the dose of L-Dopa/DCI was the only treatment in one patient (Patient_20), resulting in fluctuations in prolactin concentrations. The remaining 11 patients received the dopamine agonist cabergoline (with doses ranging from 0.125 to 1.25 mg/week), including Patient_11, who failed to respond to increasing L-Dopa doses before the addition of cabergoline, and Patient_15, who had previously used another dopamine agonist (bromocriptine) before switching to cabergoline. A transient increase in involuntary movements was observed in Patient_26 during the first few days after the initiation of cabergoline, which resolved spontaneously. None of the other patients reported any change in neurological symptoms or other adverse events related to cabergoline or bromocriptine. Serum prolactin concentrations decreased in all of the 11 patients

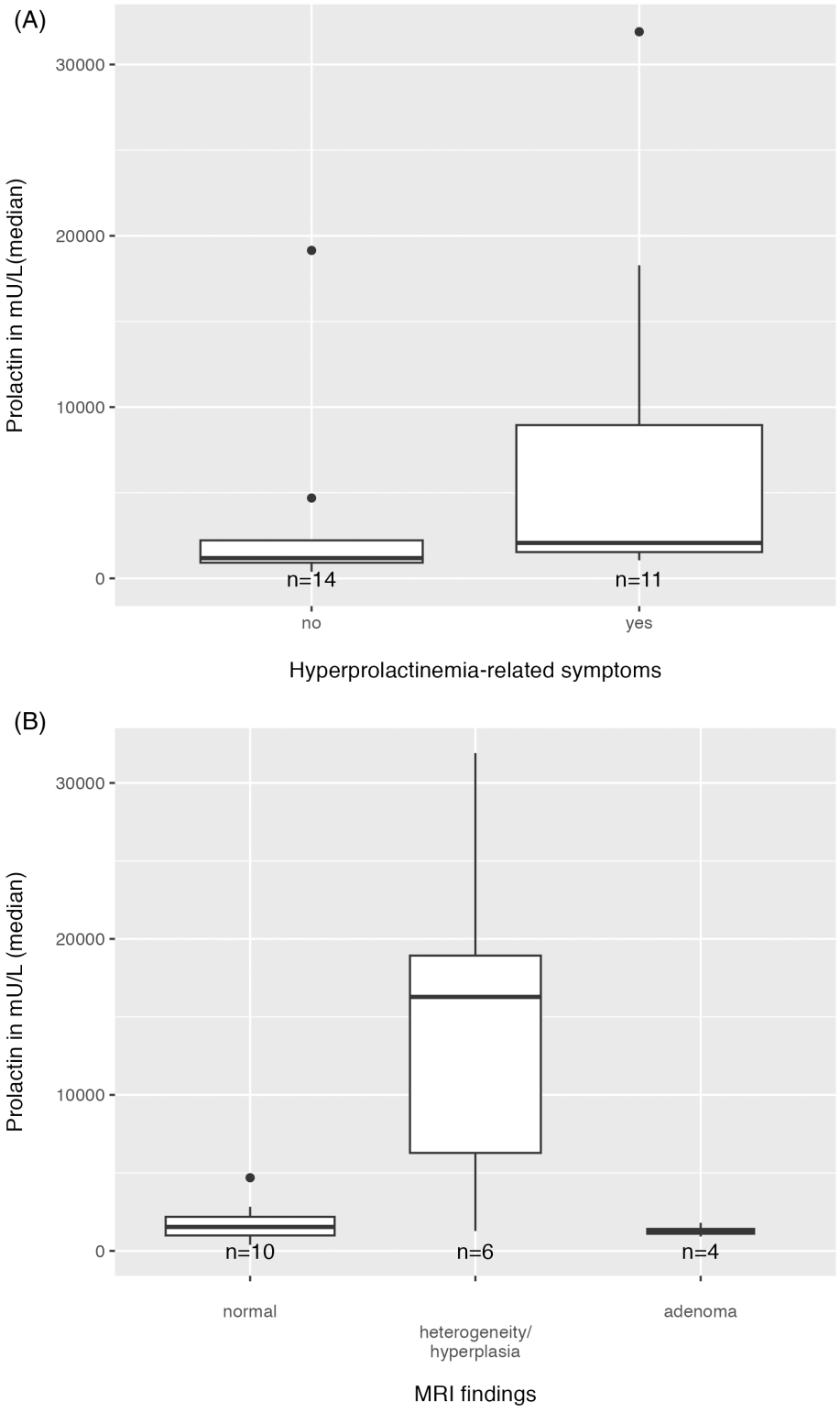

FIGURE 3 (A) Individuals with hyperprolactinemia-related symptoms did not have significantly higher prolactin concentrations than those with no symptoms (Kruskal–Wallis test, p-value > 0.05), but their prolactin concentrations had a wider distribution. (B) Serum prolactin concentrations were higher in individuals with heterogeneity/hyperplasia of the pituitary gland than in those with normal MRI findings (Wilcoxon test, $p < 0.05$). Median prolactin concentrations in patients with adenoma did not differ significantly from those with heterogeneity/hyperplasia or with normal pituitary magnetic resonance imaging (Wilcoxon test, $p = 0.07$ and 0.6, respectively).

under this treatment (five with adenoma, four with heterogeneity/hyperplasia, and two with normal pituitary gland finding, Table S2).

Among these patients, follow-up data on hyperprolactinemia-related symptoms was available in eight, all demonstrating clinical improvement (progression of pubertal stages in four, emergence or regulation of menses in three individuals, and cessation of galactorrhea in one individual); galactorrhea persisted in one female (Patient_14; see below). The symptoms recurred in three individuals who had discontinued cabergoline due to poor compliance, drug

TABLE 1 Magnetic resonance imaging findings.

Patient_ID, Gender, and NT disease	Age at Dx of hyper-PRL (year)	Age at MRI (year)	Protocol of assessed MRI	General description of the pituitary gland	Details and notes
01—F, PTPSD	26.4	26.4	pMRI	Normal	Slight left shift of the pituitary stalk. Some asymmetric signal in dynamic sequence at level of carotid artery, suggesting phase encoding artifact. No unequivocally measurable microadenoma, signal changes not clearly different from phase encoding artifact
03—M, PTPSD	16.5	16.5	pMRI	Normal	Slightly oblique coronal sections depict slightly asymmetric adenohypophysis lateral to posterior pituitary (bilateral less enhancement); but no correspondence on other sequences. No unequivocal microadenoma, signal changes not clearly different from phase encoding artifact
		16.9	pMRI	Normal	Same findings as previous MRI
04—F, THD	14.0	15.0	pMRI	Normal	Pulsation artifact on the right on coronal postgadolinium images. Gland height 7 mm (normal)
		20.7	pMRI	Normal	Gland height 7.5 mm (normal)
05—M, arGTPCHD	2.5	4.6	cMRI, pMRI	Normal	Slightly convex upper contour of the gland. No T2 or postcontrast images dedicated to the pituitary gland. Gland height 6 mm (normal upper limit for age)
09—F, PTPSD	14.0	14.0	pMRI	Normal	Gland height 7 mm (normal)
10—M, DHPRD	12.0	12.0	2 consecutive pMRI	Adenoma	Cystic multiseptated well-circumscribed T1-hypointense, T2-hyperintense lesion (7.5 mm TV × 6 mm SI × 6 mm AP) within the right side of the gland, without an apparent solid component, suggestive of a cystic adenoma, hypoenhanced on post-contrast dynamic and delayed images. Left deviation of the pituitary stalk.
11—F, PTPSD	16.0	18.0	pMRI	Adenoma	T1-hypointense, T2-hyperintense lesion (2.5 mm TV × 3 mm SI × 2 mm AP) within the left inferior aspect of the gland, suggestive of an adenoma, hyperenhanced on post-contrast delayed images, but not on dynamic images (possibly due to its small size). Gland height 8.5 mm (normal)
		21.0	pMRI	Adenoma	Stable compared to prior MRI
12—M, DHPRD	15.0	17.0	Data from report	Normal	
		23.0	pMRI	Normal	Subtle questionable hypointensity only seen on dynamic images not seen on other planes/images, attributed to motion artifacts. Suboptimal study due to extensive motion artifacts
		25.0	pMRI	Normal	Questionable hypointensity on coronal T1 postcontrast images, not seen on other planes (likely representing artifact)

TABLE 1 (Continued)

Patient_ID, Gender, and NT disease	Age at Dx of hyper-PRL (year)	Age at MRI (year)	Protocol of assessed MRI	General description of the pituitary gland	Details and notes
13—F, DHPRD	14.0	14.0	pMRI	Adenoma	Punctate (<1 mm) T1-hypointense, T2-hyperintense signal abnormality within the right-superior aspect of the gland. Enhancement could not be evaluated due to its small size. Gland height 8.5 mm (normal)
		15.0	pMRI	Adenoma	Interval increase in size of the lesion (2 mm), with hyperenhancement on dynamic study, isoenhancement on delayed images
		18.0	pMRI	Adenoma	Stable microadenoma (2 mm), isoenhancing on both dynamic and delayed images
14—F, DNAJC12D	19.0	21.0	Data from report	Adenoma	Pituitary microadenoma (4 mm)
15—F, DHPRD	17.0	23.0	Data from report	Adenoma	Microadenoma
		26.0	pMRI	Adenoma	Likely adenoma (4 mm) with slight hypointensity within the right side of the gland on dynamic images. Gland height 5 mm (normal)
16—M, PTPSD	20.0	20.0	pMRI	Hyperplasia, heterogeneity	No well-defined adenoma, but the pituitary gland is heterogeneous, and it has upper contour convexity (uncommon in males). Gland height 8 mm (slightly above the upper limit of normal)
		21.0	pMRI	Heterogeneity	Stable findings
		22.0	pMRI	Heterogeneity	Stable findings
17—M, PTPSD	13.0	13.5	pMRI	Hyperplasia, heterogeneity	Gland height 11 mm (slightly enlarged), very mild parenchymal heterogeneity. Slight right deviation of pituitary stalk
18—F, PTPSD	10.0	10.0	pMRI	Hyperplasia	Slightly enlarged pituitary gland (height 11 mm), no significant heterogeneity or adenoma
20—M, DHPRD	7.0	6.0	cMRI	Normal	Gland height 3.5 mm (normal)
21—F, SRD	16.0	16.0	Data from report	Heterogeneity	Heterogeneous enhancement of the gland without an adenomatous lesion
22—F, THD	17.0	17.0	pMRI	Heterogeneity	Mild gland heterogeneity without an apparent adenoma. Gland height 9 mm (normal). Slight left deviation of pituitary stalk
23—F, THD	17.0	17.0	Data from report	Normal	
24—M, PTPSD	30.0	35.0	cMRI, pMRI	Normal	Gland height 7 mm (normal)
25—F, PTPSD	2.0	29.0	cMRI, pMRI	Normal	Punctate (1 mm) right paramedian T1 hyperintensity (may represent tiny Rathke cleft cyst versus hemorrhagic adenoma); pituitary stalk deviated slightly to the right. Gland height 6 mm (normal)
26—M, PTPSD	25.6	25.0	Data from report	Hyperplasia	

Abbreviations: AP, anteroposterior; arGTPCHD, autosomal recessive guanosine triphosphate cyclohydrolase deficiency; cMRI, cranial MRI; DHPRD, dihydropteridine reductase deficiency; DNAJC12D, DNAJC12 deficiency; Dx, diagnosis; hyper-PRL, hyperprolactinemia; MRI, magnetic resonance imaging; NT, neurotransmitter; pMRI, pituitary MRI; PTPSD, 6-pyruvoyltetrahydropterin synthase deficiency; SI, superior to inferior; SRD, sepiapterin reductase deficiency; THD, tyrosine hydroxylase deficiency; TV, transverse.

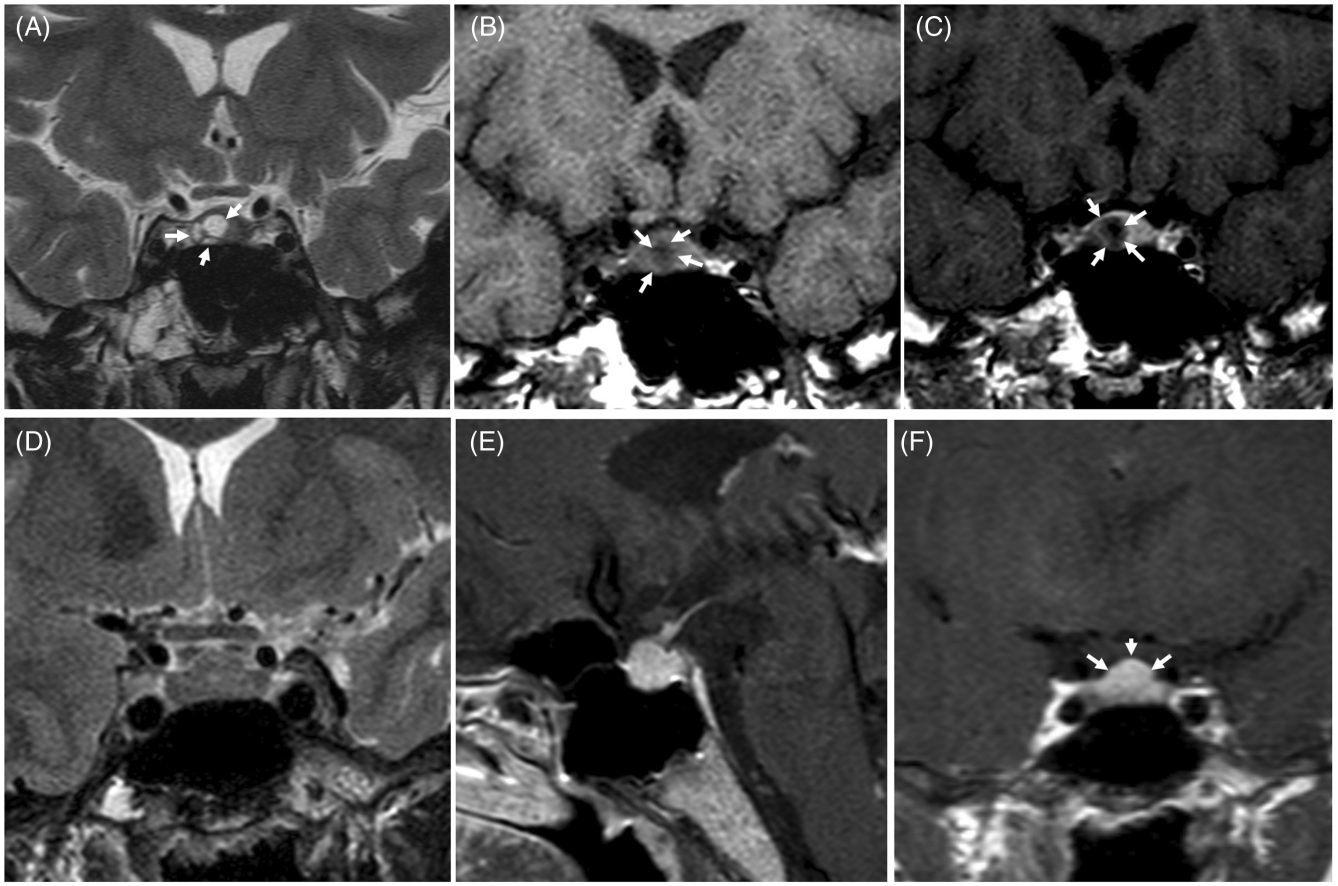

FIGURE 4 *Top panel*: Twelve-year-old male with DHPRD (Patient_10). Pituitary MRI demonstrated a predominantly cystic multiseptated well-circumscribed lesion centered within the right lateral aspect of the pituitary gland, suggestive of a cystic adenoma. In coronal sections, this lesion (shown with arrows) appears (A) hyperintense on T2-weighted images, (B) hypointense with thin septations internally on T1-weighted images, and (C) with linear enhancement of its septae on post-contrast images. Prior MRI study obtained 7 years earlier revealed no apparent lesions within the pituitary gland (data not shown). *Bottom panel*: 20-year-old male with PTPSD (Patient_16). On pituitary MRI, (D) there is central parenchymal heterogeneity of the pituitary gland, particularly apparent on T2-weighted images, with no evidence of a well-defined adenoma on (E) sagittal and (F) coronal post-contrast T1-weighted images. There is increased convexity of the upper contour of the gland (arrows, F) with maximal height of the pituitary gland measuring 8 mm (slightly above the upper limit of normal for the patient's age and sex). DHPRD, dihydropteridine reductase deficiency; PTPSD, 6-pyruvoyltetrahydropterin synthase deficiency.

unavailability, or physician's recommendations, and re-subsided when cabergoline was restarted (Table S2, Figure 5).

The youngest individual diagnosed with LRHP (at 2.5 years) has arGTPCH deficiency and remains asymptomatic with regards to his hyperprolactinemia currently at the age of 5.8 years without treatment with dopamine agonists (Patient_05, Table S2). The oldest individual in our study is a 43-year-old male diagnosed with PTPS deficiency at the age of 4 years and hyperprolactinemia at 30 years, when he had hypogonadotropic hypogonadism with small testes, sparse facial and axillary hair, decreased sexual functions, and osteoporosis. Cabergoline was started at the age of 37 years, titrated according to prolactin concentrations, and resolved the hypogonadism symptoms while osteoporosis persisted (Patient_24, Table S2). Patient_14 was initially diagnosed with hyperphenylalaninemia due to assumed phenylalanine hydroxylase deficiency. She was lost to follow-up. At the age of 19 years, she presented with oligomenorrhea and galactorrhea. She was diagnosed with hyperprolactinemia and pituitary adenoma and received cabergoline. Additional neurological symptoms, namely mild tremor, chorea, and dystonia, led to the diagnosis of DNAJC12 deficiency at the age of 21 years. The treatment was then adjusted with L-Dopa/carbidopa, 5-hydroxytryptophan, and pramipexole.

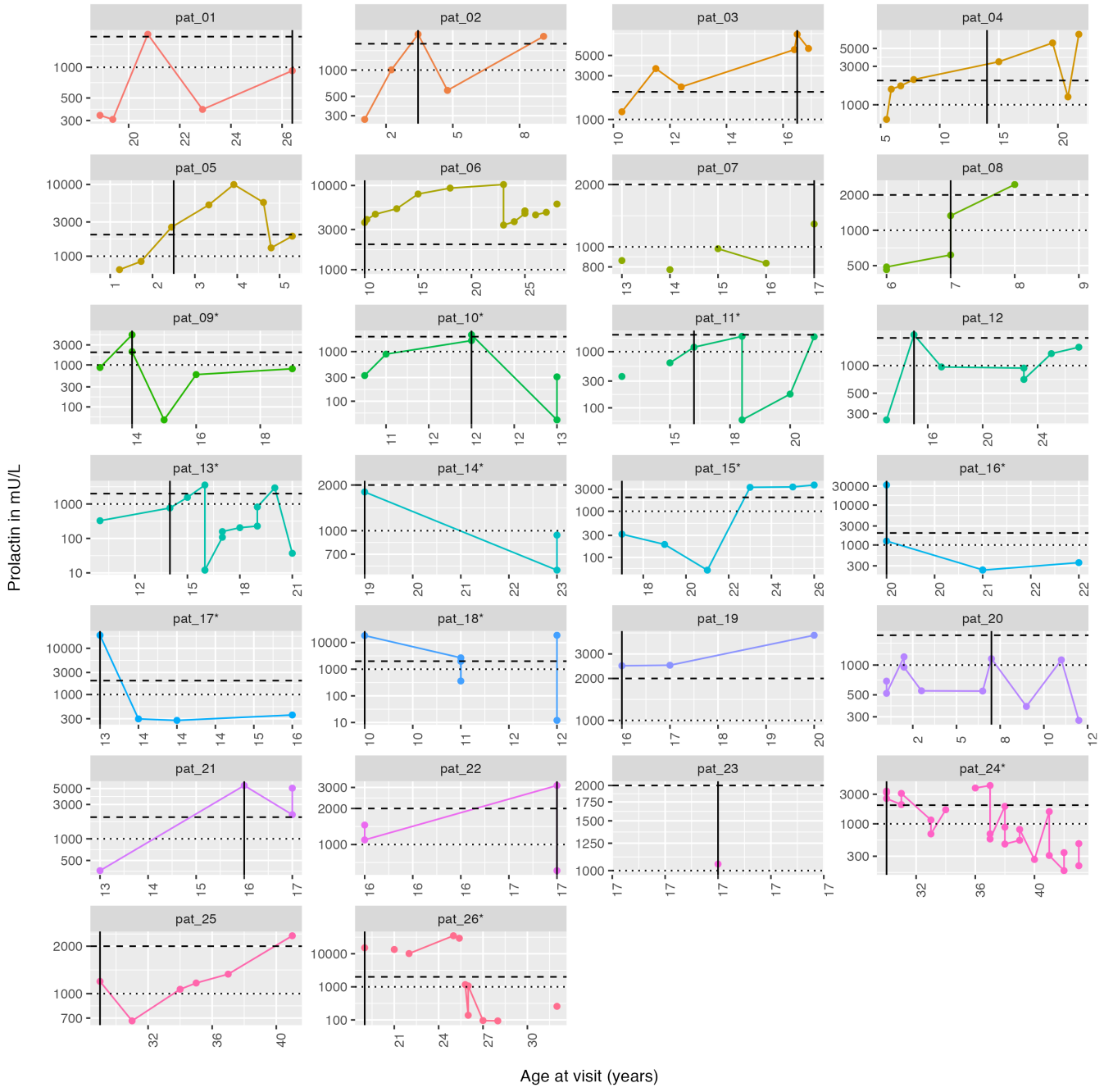

FIGURE 5 Serum prolactin concentrations on a logarithmic scale before and after detection of levodopa-refractory hyperprolactinemia in each patient. The age at detection is represented by the vertical black lines. Following the detection date, prolactin concentrations decline in patients receiving dopamine agonists (Patient_09, 10, 11, 13–18, 24, and 26; as indicated by "*" in the facet labels) and fluctuate depending on the continuity of drug intake and dose. Dopamine agonist was introduced 2, 6, and 7 years after LRHP onset in Patients_13, 24, and 26, respectively. Serum prolactin concentrations of 1000–2000 mU/L and >2000 mU/L denote moderate and severe hyperprolactinemia, respectively. Limits between these ranges are indicated by horizontal dotted (1000 mU/L) and dashed (2000 mU/L) lines.

4 | DISCUSSION

This study comprises the first standardized description and evaluation of 26 patients with inherited disorders of biogenic amine metabolism presenting with LRHP, 11 of them with abnormal pituitary MRI findings. The age at the diagnosis of LRHP had a wide range, but 50% of patients were diagnosed between the ages of 12 and 17 years, and only four (15.4%) before the age of 10 years. MRI findings, especially pituitary gland heterogeneity/hyperplasia, and

hyperprolactinemia-related findings were associated with higher serum prolactin concentrations. The most common symptoms, predominantly occurring in females, were menstrual irregularities, delayed or arrested puberty, and galactorrhea.

The results of this study may have multiple clinical implications. First and foremost, our data adds hyperprolactinemia-related findings to the current knowledge of the phenotypic spectrum of inherited disorders of biogenic amine metabolism. Therefore, careful assessment of these symptoms (galactorrhea, hypogonadism, and its manifestations) should be incorporated as part of standard of care. Symptoms such as decreased libido, impotence, dyspareunia, and subfertility may be overlooked unless specifically addressed. Since prolactin measurement is easily applicable, monitoring prolactin concentrations in patients with dopamine deficiency can be utilized to screen for hyperprolactinemia as a possible comorbidity itself. Elevated serum prolactin concentrations in patients with worsening neurological symptoms may reflect inadequate dopaminergic treatment. Poor compliance with recommended drug treatment should be ruled out as an underlying reason. In neurologically stable patients, autonomous prolactin secretion should be considered and the causes of hyperprolactinemia (macroprolactinemia, medications, renal or thyroid dysfunction, pregnancy, lactotroph hyperplasia, pituitary adenoma, etc.) should be thoroughly investigated. Symptomatic hyperprolactinemia or detection of a pituitary abnormality on MRI warrant consultation with an endocrinologist.

Our data challenge the use of prolactin as a peripheral marker of dopamine deficiency. The decision to adjust L-Dopa/DCI dose should not be based solely on elevated prolactin concentrations, especially after the first decade of life, based on our observation that most patients were adolescents or adults at the time of diagnosis of LRHP. This is consistent with the principle that autonomous secretion leading to hyperplasia or adenoma is a gradual process. One patient in our report, being diagnosed with DNAJC12 deficiency because of hyperprolactinemia-related symptoms after a period of lost to follow-up, reflects this assumption.

The results of this study could also lead to a reconsideration of the treatment recommendations for TH, DNAJC12, and BH_4 deficiencies. Hyperprolactinemia in these patients becomes resistant to L-Dopa/DCI while it is evident that the lactotroph cells retain the capacity to decrease prolactin secretion in response to activation of D2 receptors by dopamine agonists. This may be explained by the differential action of dopamine and its synthetic agonists on D2 receptors: D2 receptors inhibit not only prolactin secretion, but also cellular signal transduction pathways that mediate lactotroph proliferation,[5] preventing hyperplasia and adenoma formation.[32,33] In healthy individuals, binding of dopamine to D2 receptors inhibits the release of secretory granules containing prolactin within seconds, but it takes persistent dopamine action and days before inhibition of lactotroph proliferation.[34] The notoriously short half-life of L-Dopa, even if administered together with a DCI, is responsible for the fluctuation of symptoms in patients with Parkinson's disease and inherited neurotransmitter disorders treated with L-Dopa/DCI, and may necessitate 3–6 daily doses.[15] A single case study from 1998 clearly demonstrated that even with 6-time dosing of L-Dopa during daytime, prolactin concentrations remain high during the night, but the peaks are markedly ameliorated just by switching to 3-time dosing of a slow-release formulation.[3] Additionally, the use of a low-dose dopamine agonist (pramipexole, with a longer half-life of 8–12 h) in combination with L-Dopa/DCI and other dopaminergic treatment modalities including monoamine oxidase and catechol-*O*-methyltransferase inhibitors, has been shown to effectively suppress prolactin over a long period of 34–100 months in patients aged 7–31 years.[35] However, serious adverse effects of pramipexole in this cohort were impulse control disorders,[35] which can occur with other dopamine agonists as well, and may be a significant issue if used long-term, especially in adolescents and adults.[15] Although L-Dopa/DCI is the first-line therapy in BH_4, TH, and DNAJC12 deficiencies,[2,15,36,37] it may be insufficient to provide sustained stimulation of D2 receptors to suppress lactotroph hyperplasia, eventually leading to LRHP.

While cabergoline and bromocriptine (both ergot derivatives with dose-dependent risk of cardiac or retroperitoneal fibrosis)[38] are the first-line drugs recommended for the treatment of symptomatic hyperprolactinemia,[4] nonergot dopamine agonists such as pramipexole or ropinirole may also treat hyperprolactinemia and neurotransmitter disorder simultaneously. These dopamine agonists are first-line agents in aromatic L-amino acid decarboxylase deficiency (AADCD),[14] which could explain why no AADCD patients are represented in the current study cohort. Therefore, the use of dopamine agonists or slow-release L-dopa formulations could be considered not only due to neurological symptoms, but also in the treatment and prevention of hyperprolactinemia and prolactinoma. Long-term outcome studies with data from the iNTD patient registry can help validate this hypothesis. TH-deficient mice, which present with hyperprolactinemia and female infertility,[39] and animal models of BH_4 deficiencies[40,41] may also serve as directions of study.

Limitations of the present study include its retrospective nature, and missing or nonuniformly collected data for several included individuals. Different follow-up regimens in respective countries preclude the estimation of the incidence of hyperprolactinemia or prolactinoma in disorders of biogenic amine metabolism. Considering the relationship between dopamine and prolactin secretion[3] and relative rarity of prolactinomas in the general population (~100–500 per million in adults[42] and 0.1 per million in children[43]), it is reasonable to conclude that dopamine deficiency is central to the pathogenesis of hyperprolactinemia and prolactinoma in these patients. The preponderance of BH_4 deficiencies in our cohort may stem from selection bias, as most patients are from centers that follow relatively more patients with BH_4 deficiencies and monitor prolactin concentrations on a routine basis.[44] Furthermore, it cannot be excluded that LRHP may have occurred at an earlier age than recognized in patients whose prolactin concentrations were not monitored on a routine basis in different centers. Cross-sectional or prospective studies on all inherited disorders of biogenic amine metabolism with dopamine deficiency may reveal more patients with prolactinomas or LRHP.

Another limitation of the study is that the unequivocal differentiation between adenoma and hyperplasia is only possible by histopathological examination. Whether lesions responding to medical treatment should be called hyperplasia whereas adenomas should be defined with irreversible growth is a matter of debate.[45] It should be recognized that increased prolactin secretion, lactotroph hyperplasia, microprolactinoma, and macroprolactinoma represent a continuum and may be difficult to differentiate. This is reflected in our observation of higher prolactin concentrations in pituitary gland heterogeneity/hyperplasia compared to adenomas and normal findings. Throughout this article, we have defined "pituitary adenomas" by radiological terms, and acknowledge that overlap with histopathological hyperplasia is possible. It should also be noted that imaging protocols have varied across the participating centers, and different MRI protocols, especially studies performed solely with brain MRI may alter the sensitivity of detection of smaller pituitary adenomas.

In conclusion, this study demonstrates the occurrence of L-Dopa-refractory hyperprolactinemia as a possible comorbidity in individuals with inherited disorders of biogenic amine metabolism. Routine monitoring of hyperprolactinemia-associated symptoms and prolactin concentrations should be taken into consideration during follow-up evaluations, especially after the first decade of life. Long-term observational studies, prospective clinical trials, and studies on animal models may help evaluate the use of slow-release L-Dopa formulations and low-dose nonergot dopamine agonists (e.g., pramipexole) as part of first-line therapy in preventing hyperprolactinemia-associated comorbidities.

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CONFLICT OF INTEREST STATEMENT

Yılmaz Yıldız has received travel and meeting attendance support from BioMarin and PTC Therapeutics. Roser Pons has received speaker and advisory board honoraria from PTC Therapeutics, Novartis Gene Therapies, Ardius Pharma, Genesis Pharma, Roche Hellas, and BioMarin, and travel and meeting attendance support from Genesis Pharma and Ardius Pharma. Eduardo López-Laso has received honoraria for lectures, grant for an investigator-initiated study on selective screening for aromatic L-amino acid decarboxylase (AADC) deficiency in Andalusia, Spain from PTC Therapeutics, and has been an advisory board member. Natalia Alexandra Julia Palacios has received meeting attendance support from PTC Therapeutics. Marisela E. Dy-Hollins has received honoraria and symposium attendance scholarship from the American Academy of Neurology, and is a member of its clinical research subcommittee. Angeles García-Cazorla has received research support and honoraria for lectures from PTC Therapeutics, she has received honoraria for lectures from BioMarin, Immedica, and Recordati Rare Diseases Foundation, meeting attendance support from BioMarin, PTC Therapeutics, and Eisai, is a co-founder of the Hospital Sant Joan de Déu start-up "Neuroprotect Life Sciences," and has a pending patent for "Neuroprotect" P2021130532. Serap Sivri has received travel and meeting attendance support from BioMarin and PTC Therapeutics, and speaker honoraria from BioMarin. Thomas Opladen has received speaker honorarium from PTC Therapeutics (on newborn screening or AADC gene therapy), Recordati Rare Disease Foundation, and from Verein für medizinische Fortbildung; meeting attendance or travel support from ÖGKJ Academy and Recordati Rare Disease Foundation; and his institution has received research grants from PTC Therapeutics. Oya Kuseyri Hübschmann, Ayça Akgöz Karaosmanoğlu, Filippo Manti, Meryem Karaca, Ida Vanessa D. Schwartz, Francesco Porta, Ivana Kavecan, Mehmet Cihan Balcı, Suet-Na Wong, Mari Oppebøen, Leonardo Simão Medeiros, Leila Cristina Pedroso de Paula, Georg F. Hoffmann, Kathrin Jeltsch, Vincenzo Leuzzi, Gülden Gökçay, Daniel Hübschmann, Inga Harting, and Z. Alev Özön declare no conflicts of interest. The authors confirm independence from the sponsors; the content of the article has not been influenced by the sponsors.

DATA AVAILABILITY STATEMENT

Raw data and the MRI images are not publicly available due to data protection laws. Data is available from the corresponding author (Thomas Opladen) within the limitations of informed consent upon reasonable request. Data ownership is maintained by the members of the iNTD centers. All participating iNTD members approved this study. All data requests will be reviewed by the corresponding author, iNTD executive board, and iNTD members within 72 h.

ETHICS STATEMENT

iNTD registry study was approved by the Institutional Research Ethics Board (IRB) of Heidelberg University Hospital (S-471/2014, registered German Clinical Trials Register, https://www.drks.de, DRKS00007878) on December 22, 2014, and subsequently by all contributing centers. All procedures were in accordance with the Helsinki Declaration of 1975, as revised in 2013. Written informed consent was obtained from all study participants or their legal guardians enrolled in the registry. The enrollment of all patients from centers that are in the iNTD network but not in the iNTD registry was carried out anonymously.

PATIENT CONSENT STATEMENT

Informed consent was obtained from all patients or their legal guardians prior to being included in the study. No informed consent was required for anonymized data acquisition.

ANIMAL RIGHTS

This article does not contain any studies with animal subjects performed by any of the authors.

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