Diabetes Insipidus in Children

A Pocket Guide

Craig A. Alter
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ISBN 978-3-030-83247-6 ISBN 978-3-030-83248-3 (eBook)
https://doi.org/10.1007/978-3-030-83248-3

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

I would like to thank all the authors of this book for their enthusiasm as well as their willingness to share knowledge with lucid chapters about caring for children with diabetes insipidus. I want to pay respect to the late Dr. Thomas Moshang, who encouraged me to take a deeper dive into the world of DI. I also salute all the scientists and their thirst to address the needs of these children. Finally, I would like to thank my family, who with grace and an avant-garde attitude has realized that draft does not mean a wind current, but yet another trip to the computer.

Foreword

Diabetes Insipidus is one of the most challenging conditions encountered in pediatric endocrinology. This textbook brings together experts in various aspects of diagnosing or treating this condition and represents an essential resource for all members of the healthcare team caring for children with this condition.

If approached in sequence, all aspects of diabetes insipidus are covered in chronological order. This starts with a case of primary polydipsia and then highlights the approach to diagnosis and its associated challenges. Practical protocols for performing a water deprivation test or investigating a child with a thickened infundibular stalk are presented. Given the wide array of causes of this condition, the disease-specific chapters are extremely useful references for clinicians who may encounter each of these infrequently. This includes the relatively more common etiologies of Langerhans cell histiocytosis or craniopharyngioma resection, as well as the rarer genetic causes.

This comprehensive and practical overview of this complex condition concludes with pearls for optimal clinical management. This includes even the most difficult scenarios such as neonatal diabetes insipidus, diabetes with absent thirst, and nephrogenic diabetes insipidus. This book will earn its place in every pediatric endocrinologist's library and will be a frequently used resource for all who care for children who have, or are suspected of having, this condition.

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Acknowledgments

I would like to thank the 27 authors who contributed to make this book possible. These authors include pediatric endocrinologists, pediatric nephrologists, pediatric oncologists, and neuro-radiologists from many different institutions. I also want to thank the Raymond A. Wood Foundation for supporting hypothalamic-pituitary brain tumor survivors and for including a personal piece in this book. My hope is that this book will improve the care of children with diabetes insipidus (DI) from diagnosis to treatment and as well as to determining the elusive cause of the DI.

Introduction

Taking care of children with diabetes insipidus (DI) has three challenging phases. First, is establishing the diagnosis of DI, then determining its etiology, and then working out the best treatment. A concern for excessive thirst and urination may present at various ages in childhood and often is not due to DI. The clinician must first determine whether the degree of thirst and urination is high normal or pathologic. Sometimes a child will present with excessive thirst or urination as the chief complaint, but polydipsia and polyuria may also emerge as a concern only as a result of astute clinical questioning during an encounter.

This book contains 16 case-based chapters describing the journey from making the diagnosis of DI to determining the etiology, learning more about each etiology, and obtaining pearls relating to therapy. I suggest the book to be used based on which stop the reader is on the challenging road of diabetes insipidus. If the diagnosis of DI is being entertained, then one can consult the first two chapters which focus on distinguishing children with primary polydipsia from those with DI, both central and nephrogenic. Details on how to perform the water deprivation study are provided. A special chapter focuses on the various radiological findings that may accompany a diagnosis of DI.

One of the biggest challenges in caring for a child with DI is to determine the etiology of the DI. Chapter 4 presents information on how to proceed when the MRI reveals a thickened pituitary infundibulum. We present more in-depth information in separate individual case-based chapters related to the main causes of DI

including hypophysitis, germ cell tumors, Rathkes cleft cysts, Langerhans cell histiocytosis, craniopharyngiomas, genetic causes, and from congenital malformations. We also present information about special circumstances such as DI after surgery for a craniopharyngioma, infants with DI, DI in children with an abnormal sense of thirst, and nephrogenic DI.

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Primary Polydipsia

1

Chelsi Flippo, Craig A. Alter,
and Constantine A. Stratakis

Case Presentation

A 2-year and 5-month-old boy presented for evaluation of polyuria and polydipsia. His medical history was notable for term gestation, midshaft hypospadias status post repair with orthotopic meatus at the top of the glans with no evidence of fistula or meatal stenosis, neonatal jaundice secondary to ABO incompatibility, and no neonatal hypoglycemia. Excessive thirst and urination were first noted at 14 months old, with about 150–170 mL/kg of

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C. A. Alter (ed.), *Diabetes Insipidus in Children*,
https://doi.org/10.1007/978-3-030-83248-3_1

water intake daily and multiple heavy diapers of clear urine per day. He did not wake to drink, though upon waking in the mornings he consistently requested water. His fluid preference was water, and he has no particular fluid temperature preference. He had a normal appetite, though preferred water over solid foods. There were no feeding issues in infancy, and he had appropriate growth for weight and length/height and appropriate neurologic development. Parents denied that he had frequent headache, vision changes, hearing impairment, or abnormal eye movements. He had a history of head trauma at 8 weeks old when he fell from a couch onto a hard floor with no loss of consciousness; he was seen in an ER and no imaging evaluation was indicated. He had no history of frequent urinary tract infections. He was taking no medications. Family history was negative for diabetes insipidus or renal disease. Physical exam was unremarkable.

His initial evaluation revealed a serum sodium was 136 mEq/L, serum osmolality of 280 mOsm/kg, urine osmolality of 145 mOsm/kg, and appropriate levels of serum glucose, serum potassium, serum calcium, and serum bicarbonate. A water deprivation test showed appropriate urine concentration of 845 mOsm/kg, with a corresponding serum osmolality of 303 mOsm/kg and serum sodium of 141 mEq/L. He was also evaluated by nephrology for polyuria and polydipsia, with a normal renal ultrasound. Given the appropriate urine concentration on water deprivation testing and normal renal ultrasound, central DI, nephrogenic DI, and a salt-losing nephropathy were considered unlikely. A gradual fluid restriction was recommended to address the presumed diagnosis of primary polydipsia. When fluids were withheld, his urine would decrease 6–8 h later, and he continued to not request fluids overnight despite sleeping 10 h nightly. However, parents noted that during the day he became irritable and frustrated when limiting water, resulting in return to his excess drinking patterns, and after several months of attempts at fluid restriction, the polyuria and polydipsia persisted. His serum sodium levels, which were repeated due to concern for evolving partial diabetes insipidus, remained normal or even low-normal. An MRI brain with and without contrast was obtained, showing a Chiari I malformation, presence of a posterior pituitary bright spot, upper limit of normal

pituitary size (5.1 mm), midline infundibulum, and otherwise normal pituitary and hypothalamus. Repeat MRI 6 months later showed a stable Chiari I malformation, as well as continued normal hypothalamus, infundibulum, and pituitary gland. Gradual fluid restriction to a goal of 100 mL/h/day, continued monitoring of with an intake/output log, and evaluation with a behavioral therapist were recommended for the presumed diagnosis of primary polydipsia.

Assessment and Diagnosis

When a child presents with excessive thirst (polydipsia) and urination (polyuria), one must first determine whether the child truly has polyuria. Polyuria is often defined as urine volumes greater than 2 L/m^2/24 h, which is approximately 150 mL/kg/day at birth, 60–110 mL/kg/day up to 2 years of age, and 40–50 mL/kg/day in older children and adults [1, 2]. In younger children, parents may report that the child has frequent heavy, wet diapers, whereas in older children, frequent large-volume voiding, nocturia, and enuresis may be present. Additionally, questions should focus on quantitating the amount of fluid intake in a day, as well as whether there are patterns of unusual water-seeking behaviors. Excess fluid intake is often defined as greater than 100 mL/kg/day in children under two years of age and greater than 70 mL/kg/day in those over two years of age [2]. Unlike in diabetes mellitus where the polydipsia and polyuria are usually present for several weeks, a child with a disorder of thirst and/or diabetes insipidus (DI) may have such symptoms for months to years. Young children or infants may search for water from bathtubs, faucets, toilets, puddles, and often by grabbing water bottles from others.

Primary polydipsia is due to excessive intake of solute-free fluids, which in turn results in slightly reduced plasma osmolarity and plasma sodium, thereby decreasing arginine-vasopressin (AVP) secretion. The decrease in plasma AVP reduces urine osmolarity and increases urine volume, allowing for a compensatory increase in water excretion which prevents over-hydration. Therefore, basal plasma osmolarity and plasma sodium tend to be

slightly lower than in patients with central or nephrogenic DI, though is usually within the normal range in primary polydipsia [2, 3]. Therefore, patients with primary polydipsia present with polyuria and, by definition, polydipsia. In contrast to those with DI, patients with primary polydipsia often deny nocturia or drinking overnight, and they often have a less acute onset of polyuria/polydipsia [4]. Various forms of primary polydipsia have been described, including psychogenic polydipsia, compulsive water drinking, and dipsogenic DI (see Table 1.1). Psychogenic polydipsia is often associated with psychotic psychiatric conditions, and it has been described to occur in 11% of those with chronic schizophrenia [5]. Patients with psychogenic polydipsia may provide delusional reasons for excessive fluid intake, and the cause of excess thirst is not well understood. Compulsive water drinking has been associated with health enthusiasts who believe that excess water improves health, patients with anorexia nervosa, and those with non-psychotic Axis I psychiatric conditions [6, 7]. Dipsogenic DI is due to an abnormally low thirst threshold. As the central thirst center is located in the hypothalamus, insults to the hypothalamus from neoplasia, vascular events, infiltrative diseases, infectious diseases, and traumatic or surgical injury may result in dipsogenic DI, and notably hypothalamic insults may also result in central DI [3]. Additionally, primary polydipsia is more common in those with neurodevelopmental disorders,

Table 1.1 Causes of primary polydipsia and their associations and pathophysiology

Primary polydipsia		
Types	Associations	Pathophysiology
Psychogenic polydipsia	Psychotic psychiatric illness	Unknown cause
Compulsive water drinking	Health enthusiasts; may have non-psychotic Axis I psychiatric disorders; associated with anorexia nervosa	Excess water intake due to belief water improves health or fear of dehydration
Dipsogenic diabetes insipidus	Hypothalamic lesions	Abnormally lowered thirst threshold

including autism and intellectual disability [6, 8]. It remains unclear if and the degree to which these various described forms of primary polydipsia overlap [4, 6]. In toddler-age children, primary polydipsia has been described in association with psychosocial stressors, such as social neglect or even a parent's return to work [9–11]. It has been speculated that drinking may provide comfort for these children, or that it may result from attachment to drinking if parents tend to offer a bottle whenever a child shows distress [9, 12, 13].

When a child presents with polydipsia and polyuria, a thorough history, including medications, and physical exam, must first be completed. Medications that may increase thirst (e.g., phenothiazine, tricyclic antidepressants, monoaminoxidase inhibitors, or other medications that may cause xerostomia) or increased urination (e.g., diuretics), as well as osmotic diuresis (e.g., mannitol, urea, sodium diuresis from IV saline or after treatment of bilateral urinary tract obstruction, or glucosuria due to hyperglycemia or SGLT2 inhibitors) should be excluded as the cause of polyuria/polydipsia. Once these have been ruled out, the challenge is whether a child has primary polydipsia, central DI, or nephrogenic DI. One may evaluate for certain causes of acquired nephrogenic DI, such as medications (e.g., lithium, demeclocycline, cisplatin), history of kidney disease, hypercalcemia, and hypokalemia, by obtaining a thorough history and serum electrolytes. Certain drugs may also result in acquired central DI (e.g., phenytoin, clonidine, and alcohol) [14]. Questions should also focus on whether there are any central nervous system risk factors, evidence of hypopituitarism including growth failure, and/or visual defects. If there are no signs of such systemic involvement, it can be difficult to distinguish primary polydipsia from DI. Obtaining morning serum sodium, serum osmolality, and urine osmolality after the longest period of time a family is comfortable extending a fast of both foods and fluids may determine the diagnosis. If the serum sodium and osmolality are elevated in the setting of urine osmolality less than 300 mOsm/kg (dilute urine), a diagnosis of DI is confirmed. Inversely, a low sodium and serum osmolality suggests primary polydipsia. If the distinction is unclear, a water deprivation study, typically completed as an

inpatient, is likely necessary (see Chap. 2). If the workup does not conclude the child has DI, then by exclusion, the diagnosis is primary polydipsia. However, when primary polydipsia is diagnosed, it should not be dismissed as an inconsequential disorder. Children with primary polydipsia often do not fully concentrate urine (i.e., urine osmolality of 300–750 mOsm/kg with a corresponding serum osmolality of >300 mOsm/kg) due to a diluted medullary gradient and downregulation of aquaporin-2 water channels, and their laboratory studies can be suggestive of partial CDI on diagnostic evaluation [1, 4]. Therefore, caution is merited as a diagnosis of partial DI can sometimes be diagnosed as primary polydipsia. Recently, studies have been completed in adults assessing the utility of plasma copeptin measurement in distinguishing partial DI and primary polydipsia [15, 16]. The arginine-stimulated copeptin test has shown promising results to aid in diagnosis; however, this test has not yet been validated in children [15]. Additionally, presence of the posterior pituitary bright spot on T1-weighted pituitary MRI may provide evidence to distinguish primary polydipsia from central DI [17].

Management

Treatment options for primary polydipsia are limited, and there is an even greater paucity of studies on treatment in children. The optimal treatment is reduction of water intake; however, this is often unsuccessful in adults due to non-compliance of those with compulsive water-drinking behaviors and continued thirst [4]. Treatment of primary polydipsia should be considered in conjunction with a psychologist or psychiatrist. However, behavioral therapy including biofeedback relaxation therapy, conditioning of desired behavior, and group therapy have shown variable success [4, 18–21]. Anti-psychotics medications have been studied as potential therapies for primary polydipsia, but whether they are treating excess thirst or simply treating an underlying psychiatric disorder is unclear [22–24].

Complications

Hyponatremia due to water intoxication is the most common and severe acute complication of primary polydipsia, which occurs when water intake exceeds water excretion [4]. Hyponatremia may also occur in hypovolemic dehydration and SIADH; however, in the latter two, the urine osmolality should be elevated, whereas in primary polydipsia, the urine may be dilute. Acutely, worsening hyponatremia may result in seizures, cerebral edema, coma, and even death [7, 8]. Additionally, chronic polydipsia may result in malnutrition, bladder dilatation, hydronephrosis, osteoporosis, and central nervous system dysfunction [4, 25–28].

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2 Diagnosing DI (The Water Deprivation Test)

Priyanka Bakhtiani
and Mitchell E. Geffner

Case

A 3-year-old girl with no significant past medical history and normal development presented to the endocrinology clinic with complaints of significant and worsening polyuria and polydipsia for 10 months. She had been growing along the 75th percentile in height with her weight approximating the 90th percentile.

The child had been waking up frequently at night to drink water, and had been soaking through diapers multiple times at night. Her family reported that she would have episodes of uncontrollable screaming if fluids were not provided in a timely manner.

As part of a screening laboratory assessment after 3.5 hours of at-home fluid restriction, her serum osmolality was 289 mOsm/kg (reference range 275–295 mOsm/kg) and urine osmolality 112 mOsm/kg (reference range 50–1200 mOsm/kg). She had a normal serum sodium (143 mmol/L), hemoglobin A1c (4.8%), fasting blood glucose (87 mg/dL), TSH (1.6 uIU/mL), and corrected serum calcium (9.5 mg/dL).

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C. A. Alter (ed.), *Diabetes Insipidus in Children*,
https://doi.org/10.1007/978-3-030-83248-3_2

Because of the patient's young age, the decision was made to pursue in-hospital water deprivation testing (see Table 2.1 for details). At baseline, her serum osmolality was 295 mOsm/kg and urine osmolality 70 mOsm/kg. Plasma copeptin was <2 pmol/L (reference range 2–26 pmol/L). After 5 and 6 h of water deprivation, her serum osmolalities were 317 and 322 mOsm/kg, and concurrent urine osmolalities 76 and 83 mOsm/kg, respectively. Desmopressin at a dose of 1 mcg/m^2 was then administered subcutaneously, following which her urine osmolality increased to 478 mOsm/kg within 1 h. Thus, a diagnosis of central diabetes insipidus (DI) was established. Screening of other pituitary hormones was normal. An MRI of the brain revealed an enhancing 5-mm nodule within the pituitary infundibulum, with associated restricted diffusion, which, given the patient's age, was suspected to represent Langerhans cell histiocytosis. An oncology consultation was performed immediately, and close outpatient follow-up was recommended. The patient was started on subcutaneous desmopressin, and she was discharged home after establishment of controlled urine output and normal serum sodium levels for 24 h.

Water Deprivation Test

Concept

In healthy individuals, the release of arginine vasopressin (AVP), also known as anti-diuretic hormone (ADH), from the posterior pituitary gland is initiated concurrently with onset of a thirst response at an osmotic threshold of 282–285 mOsm/kg [1, 2]. AVP binds to the vasopressin type 2 receptor, leading to expression of aquaporin 2 channels which causes water retention. This results in increased urine osmolality to a maximum of 1200 mOsm/kg while maintaining serum osmolality within the normal reference range of 275–295 mOsm/kg.

In patients with DI, there is either a defect in vasopressin release (central) or action (nephrogenic) leading to polyuria. An intact thirst mechanism with access to water may be enough to maintain normal serum osmolality in older children and adults.

Table 2.1 Water deprivation test results

Hours of fasting	Body weight (kg)	Heart rate (bpm)	BP (mm Hg)	Serum				Plasma copeptin (pmol/L)	Urine		
				Na (mmol/L)	Osmolality (mOsm/kg)	Glucose (mg/dL)	BUN (mg/dL)		Osmolality (mOsm/kg)	Specific Gravity	Output (mL/hr)
0	16.34	99	94/81	143	295	95	12	<2	70		
1	16.31	103	94/62						<50	1.001	340
2	16.13	109	109/69	144	296	102	7		<50	1.006	210
3	16.10	92	98/65								200
4	16.00	115	96/70	147	299	71	11		91	1.001	195
5	15.92	125	90/63		317				76	1.008	210
6	15.75	122	99/72	156	322	98	14	<2	83	1.008	255
Desmopressin acetate at a dose of 0.65 mcg subcutaneously was administered.											
7	15.74	126	103/68	152	312	89	8		478	1.020	60

Heparin-locked intravenous line and urine bag were placed. Last feeding was completed at Time 0
Body surface area: 0.65 m^2
Recent medications: None

However, upon prolonged water deprivation, the urine remains dilute despite increasing serum osmolality, which is used as an indirect test of AVP function. Once a diagnosis of DI is established, concentration of urine in response to administration of an exogenous vasopressin analog will distinguish central from nephrogenic DI. Plasma AVP and/or copeptin levels measured at the beginning and end of a period of water deprivation can also assist in this regard, since these would theoretically be low in central and high in nephrogenic DI.

In contrast, in patients with primary polydipsia (PP) there is excessive consumption of fluids in the absence of physiologic stimuli that activate the thirst mechanism. This could be due to a psychiatric condition (psychogenic polydipsia), a problem in the thirst center (dipsogenic polydipsia), as a soothing mechanism in toddlers, or compulsory water drinking perceived as a health initiative in motivated individuals. The excessive fluid consumption leads to a physiologic decrease in AVP synthesis and release, resulting in polyuria with dilute urine. When the fluid intake is more than the excretory capacity of the kidney, this can lead to hyponatremia. If renal and pituitary function are otherwise intact, water deprivation leads to an increase in serum osmolality to the osmotic threshold beyond which AVP release is triggered. This in turn causes concentration of urine with resolution of polyuria.

History

Animal studies in the 1930s first demonstrated that osmotic stimulation by dehydration leads to urinary concentration, which was not seen in dogs with DI [3, 4]. In the 1950s–1960s, a high serum osmolality and dilute urine were well-established as diagnostic criteria for DI. However, multiple reports of patients with intact thirst having a normal serum osmolality despite having DI led to attempts at unmasking the disorder by inducing dehydration [5–8].

In 1970, Miller et al. described the first standardized test protocol along with detailed diagnostic criteria for the water deprivation test [9], which is very similar to what is still used today at most endocrine centers. In their small study, 36 patients with polyuria-polydipsia syndrome (central DI, nephrogenic DI, partial DI, or

PP), along with 10 healthy controls, underwent prolonged fluid deprivation. They found that healthy volunteers were able to concentrate their urine to >800 mOsm/kg after 8 hours of water deprivation. However, in patients with DI the urine osmolality remained less than serum osmolality. Urine osmolality increased by more than 50% after administration of vasopressin to patients with central DI (n = 18). This response to vasopressin was not seen in patients with nephrogenic DI (n = 2). Patients with partial central DI were able to increase urine osmolality to greater than serum osmolality after dehydration, but they further responded to vasopressin by increasing urine osmolality by more than 9%. In contrast, patients with PP (n = 5) were able to concentrate their urine osmolality to much higher maximal values, and did not respond on further injection of vasopressin (<5% rise in urine osmolality).

In 2015, deFost et al. conducted a cohort study [10] to evaluate the validity of the diagnostic criteria described by Miller et al. They noted that, after water deprivation, the sensitivity for diagnosing PP increased from 96% to 100% when the threshold for urine osmolality was decreased from 800 to 680 mOsm/kg. The specificity remained unchanged at 100%.

In 2017, one of the largest series on water deprivation tests by a single study center [11] reported that 80% of patients with DI took much longer than 8 h to meet diagnostic criteria. In addition, 26% of the patients with PP did not reach the cut-off of 800 mOsm/kg in urine osmolality, despite water deprivation for up to 48 h.

Limitations

- *Test burden*: Given the risk of dehydration, a water deprivation test generally requires hospitalization, especially in infants and toddlers. This could be a significant barrier in high-volume centers. One series showed that a combination of initial outpatient water deprivation is tolerated safely, followed by close inpatient monitoring, may be a safe alternative [12]. The effect of osmotic (hypertonic saline) and non-osmotic (nicotine, hypoglycemia, etc.) stimuli on osmolality and copeptin levels is also being studied, and may lead to a less cumbersome testing procedure [13].

- *Practicality*: Water deprivation is uncomfortable and stressful, especially for young children, often leading to termination of the test prior to attainment of maximal urine osmolality. Addition of a baseline plasma copeptin level may improve diagnostic accuracy.
- *Diagnostic validity*: More large-scale prospective trials are necessary to establish validity of currently used diagnostic criteria. The commonly used cut-off point of urine osmolality >600 mOsm/kg may theoretically increase sensitivity for PP, but could make it more difficult to distinguish it from partial DI. The route, administration, and choice of analog for AVP/desmopressin to differentiate central from nephrogenic DI require standardization across pediatric centers.
- *Confounders associated with longstanding disease*: Chronic polyuria caused by partial DI or PP can lead to downregulated synthesis of aquaporin 2 channels. Thus, the response to exogenous vasopressin analogs may be falsely diminished, secondary to this well-known "wash-out" phenomenon of the renal medullary concentration gradient. Also, many patients with partial central DI or nephrogenic DI still have a limited capacity to secrete or to respond to AVP. Therefore, an absolute distinction between PP, partial central DI, and partial nephrogenic DI may not always be possible [10].

Additional Testing

AVP

Despite the initial promise of a "direct" and less-cumbersome diagnostic test, measurement of plasma AVP by radioimmunoassay was found to have a total diagnostic accuracy of 46% when measured during water deprivation in patients with polyuria and polydipsia [14]. Furthermore, evidence suggested that plasma AVP and serum osmolality may not have a linear relationship. There were other technical limitations including a rapid plasma clearance of AVP with a half-life of 10–30 min, a high preanalytical instability [15], and a

historical long turn-around time (4–10 days). At present, AVP assays are no longer offered at major commercial laboratories.

Copeptin

Recently, copeptin, the C-terminal glycoprotein of the AVP prohormone, has been established as an easy-to-measure, fast, reliable, and stable surrogate for endogenous plasma AVP [16]. In 2011, a prospective study demonstrated that adding copeptin measurements at baseline and after water deprivation significantly increased diagnostic accuracy of the water deprivation test [14]. It was proposed that in adult patients, a baseline copeptin level <2.6 pmol/liter could differentiate patients with complete central DI from those with PP. A follow-up study revealed that a single baseline copeptin value >21.4 pmol/L in adult patients with polyuria and polydipsia had 100% sensitivity and specificity for diagnosing nephrogenic DI [17]. A copeptin value of >4.9 pmol/L after osmotic stimulation with hypertonic saline (administered until serum sodium is >150 mmol/L) has also been shown to have a diagnostic accuracy of 95% in separating PP from partial DI [18].

The following reference ranges for the pediatric population are suggested based on a study comparing plasma copeptin values after 6–10 h of water deprivation in healthy children to those with diabetes insipidus or primary polydipsia [19]:

- <2.2 pmol/L: Complete central DI
- 2.2–5 pmol/L: Overlapping levels between central DI and PP; when copeptin level is 2.2–3.5 pmol/L, the probability to have central DI is 75%, whereas if plasma copeptin level is 3.5–5, the probability lowers to 25%.
- >5–20 pmol/L: Primary polydipsia
- >20 pmol/L: Nephrogenic DI

The immunofluorescence assay for copeptin is now available at most commercial laboratories.

Patient Selection and Testing Protocol and Interpretation

- Polyuria with or without polydipsia (either >2 liters/m^2/day) has been confirmed.
- Other confounding disorders (e.g., diabetes mellitus, hypercalcemia, hypokalemia, hyperthyroidism, protein-energy malnutrition, UTI) and effect of medications (e.g., diuretics and lithium) have been ruled out.
- Screening laboratory tests after the longest period of routinely tolerated overnight water deprivation and fasting at home are inconclusive (serum osmolality <300 mOsm/kg, with urine osmolality <600 mOsm/kg).
- In-hospital water deprivation testing should be considered in high-risk patients for whom any period of fasting at home may impose a significant threat to well-being.

Preparation Prior To Admission

- Ensure availability of staff for continuous observation of the patient.
- Provide and review the testing protocol with nursing staff.
- Consider sealing taps/bathroom access in older patients.
- If the patient is already on desmopressin, stop its administration 24 h prior to the test.
- Ensure normal hydration and stable weight during this pre-test 24-h period.

On Admission

- Place patient on cardio-respiratory monitor.
- Place large-bore intravenous line (heparin-locked) and urine collection device (catheter/bag).
- Obtain baseline weight (after bladder-emptying), vital signs, serum and urine osmolalities, serum and urine sodium, serum BUN, plasma copeptin, and urinalysis.

- Note time and start fluid restriction. No solids or liquids permissible after time 0.
- Every 1 hour: measure weight, vital signs, and total urine output.
- Every 2 hours: measure serum sodium, BUN, and osmolality, plasma glucose, and urine osmolality.
- Given risk of ketotic hypoglycemia in toddlers and young children, consider obtaining bedside blood glucose levels hourly after 18 hours of fasting.

At Any Time During the Test (See Fig. 2.1)

1. If the serum osmolality is <300 mOsm/kg and urine osmolality <600 mOsm/kg, continue the test if the patient is clinically stable.
2. If the serum osmolality is >300 mOsm/kg and urine osmolality is <300 mOsm/kg, this establishes a diagnosis of complete DI.
3. If the urine osmolality is >800 mOsm/kg once or more than 600 mOsm/kg at two consecutive time-points (normal response), stop the test. The diagnosis would be PP in this case.

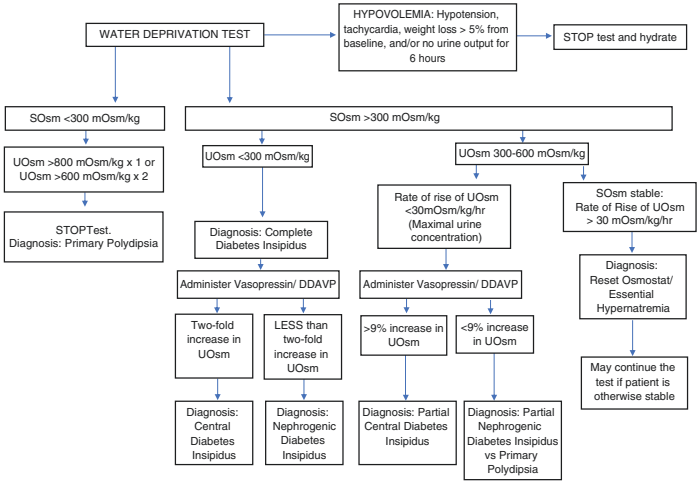

Fig. 2.1 Interpreting the water deprivation test

4. If the serum osmolality is >300 mOsm/kg and stable, but the urine osmolality is >300 mOsm/kg and continuing to rise by more than 30 mOsm/kg with each sample, the patient may have an altered threshold for vasopressin release, also termed a "reset osmostat/essential hypernatremia" [20, 21]. This may occur after head trauma, neurosurgery, or brain tumors. If the patient is otherwise stable, the test may be continued to establish normal urine concentrating ability.
5. If the serum osmolality is >300 mOsm/kg and the urine osmolality is between 300 and 600 mOsm/kg and stable (<30 mOsm/kg rise between two consecutive time-points indicating maximal urine concentrating ability), this could indicate partial DI.
6. Stop the test if the patient is showing signs of significant hypovolemia (hypotension, tachycardia, weight loss >5% from baseline, and/or no urine output for 6 h).

Measure weight, serum sodium, BUN, and osmolality, plasma copeptin, urine osmolality, and total amount of urine output at the termination point of the test.

Assessment of Response to Vasopressin

Once the diagnosis of DI is established, the delineation of central from nephrogenic DI may be made by assessing the response to vasopressin.

- Give vasopressin at a dose of 1 U/m^2 subcutaneously (SQ) and measure the following parameters at 0, 30, and 60 minutes: serum sodium, BUN, and osmolality, and urine osmolality and urine output. Alternatively, desmopressin (deamino-8-d-arginine vasopressin or DDAVP, the synthetic analog of AVP) can be used for older children and adult-sized patients. Formulations of desmopressin acetate commonly used in conjunction with water deprivation testing include subcutaneous (1 mcg/m^2) and intranasal (0.25 mcg/kg, up to a maximum of 10 mcg). The response can vary and should be monitored hourly for up to 4 hours after administration. The administration of desmopres-

sin in very young children is generally considered safe when used carefully. However, there is a small controversy surrounding its use given the potential risk of water intoxication.
- The patient should not be allowed to drink. In select cases, urine volume replacement may be considered with increasing sodium levels or behavioral intolerance of further water deprivation.
- If the patient has complete central DI, urine volume should fall and osmolality should at least double during the next hour, compared with the value before vasopressin therapy. If there is less than a two-fold increase in urine osmolality after vasopressin administration, the patient likely has nephrogenic DI.
- In case of partial DI (maximal urine concentration of 300–600 mOsm/kg), a rise in urine osmolality by more than 9% is considered indicative of central etiology. In addition to the response to vasopressin, a low copeptin level, history of CNS surgery/injury and/or positive response to a therapeutic trial of DDAVP can also be used to confirm partial central DI [22].

Our Patient

Our case illustrates that patients with DI may present with normal baseline serum and urine osmolality values in the presence of adequate fluid intake. In our patient, a hospital admission was necessary since at-home fasting did not lead to conclusive results and attempts at prolonged water deprivation testing could put the patient at risk of significant dehydration. When our patient was deprived of fluid intake, her serum osmolality rose to above 300 mOsm/kg after 5 h, with a urine osmolality of <300 mOsm/kg. The urine osmolality did not increase significantly on persistent withholding of water for the next hour. Thus, the diagnosis of diabetes insipidus was confirmed. After administration of desmopressin, her urine osmolality increased by more than two-fold. This was considered a positive response, thus establishing a diagnosis of central DI.

The hospital setting was also conducive to safely assess the patient's response to desmopressin, followed by careful dose titra-

tion to prevent dehydration and water intoxication in this young child. An undetectable baseline copeptin (the level of which took 48 h for processing) was also paramount in substantiating the diagnosis of severe central DI.

Summary

A water deprivation test along with the assessment of response to the administration of an exogenous AVP analog is the key tool to help identify the cause of polyuria/polydipsia. Diagnostic accuracy can be increased by obtaining plasma copeptin levels at baseline and at the end of the test. However, the final diagnosis should be based on a comprehensive assessment of patient and family history, clinical and biochemical data, imaging of the hypothalamic-pituitary region, and a therapeutic trial with desmopressin.

Clinical Pearls and Pitfalls

- If a child is able to concentrate urine to an osmolality of >800 mOsm/kg once or stable urine osmolality >600 mOsm/kg, DI is ruled out.
- Serum osmolality >300 mOsm/kg with stable urine osmolality <300 mOsm/kg is diagnostic of complete diabetes insipidus.
- Urinary concentration by more than twofold in response to vasopressin or desmopressin in a patient with DI is indicative of a central etiology. Conversely, lack of response is characteristic of nephrogenic DI.
- Discerning the diagnosis can be onerous despite an appropriately performed water deprivation test in cases of partial DI, reset osmostat, or chronic primary polydipsia.

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3 MRI Lesions in Diabetes Insipidus

Karuna Shekdar

Abbreviations

CP	Craniopharyngioma
DI	Diabetes insipidus
GCT	Germ cell tumor
LCH	Langerhans' cell histiocytosis
MRI	Magnetic resonance imaging
RCC	Rathke cleft cyst
SOD	Septo optic dysplasia

Introduction

A wide spectrum of disease processes can result in central diabetes insipidus in children [1]. Disease processes affecting the neurohypophysis, the pituitary stalk/infundibulum, and the pituitary hypothalamic axis are some of the common causes of central DI [1]. The clinical symptoms from these above-mentioned lesions

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C. A. Alter (ed.), *Diabetes Insipidus in Children*,
https://doi.org/10.1007/978-3-030-83248-3_3

can be varied and present a diagnostic challenge to the pediatricians and the endocrinologists. The characteristic MR imaging findings of common conditions that can result in central DI in children have been described in this chapter.

Magnetic resonance imaging (MRI) of the pituitary and the pituitary hypothalamic axis offers excellent soft tissue detail with multiplanar imaging capability which is much superior than CT [2]. MRI offers significant benefits (over CT) such as high signal-to-noise ratio, high spatial resolution, and lack of ionizing radiation which make MR imaging the imaging modality of choice. In some cases both MRI and CT may need to be performed and the information obtained from MRI and CT is complementary.

When evaluating a case of central DI, a pituitary protocol MRI should be performed, which provides thin slices through the pituitary-hypothalamic area, to provide visualization and detailed evaluation. The use of contrast enhancement in MRI is necessary in evaluation of pituitary mass lesions and infectious and inflammatory disorders. For certain indications, it is necessary to image the entire brain. For example, certain tumors (i.e., germinomas) may disseminate and require imaging of the brain and spine, and some developmental pituitary anomalies can be associated with other midline congenital defects such as septo-optic dysplasia [3, 4].

Normal MRI Appearance of the Pituitary Gland (Fig. 3.1)

The pituitary gland is in the sella turcica, within the central skull base. The pituitary gland consists of two lobes, the anterior pituitary (adenohypophysis) and the posterior pituitary (neurohypophysis). The adenohypophysis is isointense to the brain parenchyma, and the neurohypophysis is brighter/hyperintense compared to the brain parenchyma on T1-weighted images. The T1 hyperintensity of the neurohypophysis is attributed to the protein hormone granules within. The pituitary stalk is the inferior continuation of the hypothalamus inserting to the superior aspect of the pituitary gland in the midline. The pituitary stalk is broader superiorly and gradually tapers inferiorly.

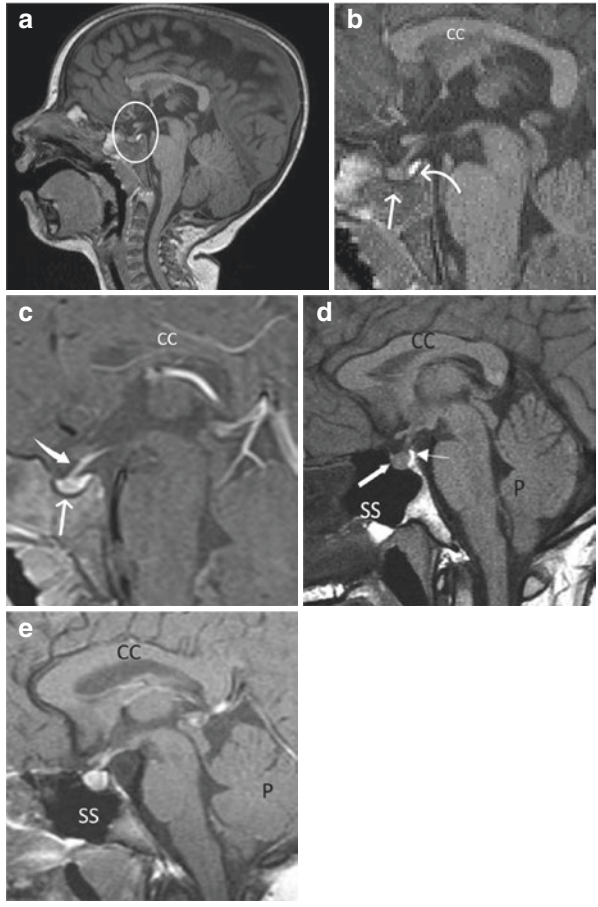

Fig. 3.1 Normal appearance of pituitary gland on MRI. (**a**) Sagittal T1 images through the brain in a 2-year-old boy with white circle marking the area of the sella and the pituitary gland. (**b**) Magnified unenhanced sagittal T1 image demonstrating the pituitary gland (straight arrow) and posterior pituitary bright spot of the neurohypophysis (curved arrow). (**c**) Postcontrast sagittal T1 image shows homogeneously enhancing pituitary gland (straight arrow) with normal enhancing pituitary stalk/infundibulum (thick white arrow). (**d**) Unenhanced T1 sagittal and (**e**) postcontrast T1 sagittal through the pituitary gland in a pubertal 13-year-old female demonstrating the pituitary gland (straight arrow) and posterior pituitary bright spot of the thin white arrow) and homogeneous enhancement. CC corpus callosum, SS sphenoid sinus, P cerebellum

It is important to identify the presence and location of the T1 hyperintensity ("bright spot") of the neurohypophysis. The bright spot may be found in an ectopic location when there is a pituitary developmental abnormality, or it may be absent if there is vasopressin, also known as anti-diuretic hormone (ADH), deficiency due to mass effect or infiltration from space-occupying lesions [2].

A normal pituitary gland enhances diffusely and homogeneously following administration of intravenous gadolinium. There is also enhancement of the pituitary stalk, but the hypothalamus does not show any enhancement.

The MRI imaging protocol for diabetes insipidus at our institute typically includes evaluation of the whole brain. The following sequences are obtained: 3-D volumetric T1 sagittal with axial and coronal reformations obtained pre and postcontrast, axial TSE T2, axial FLAIR, postcontrast spin echo T1 sagittal and coronal with fat suppression through the pituitary gland, axial spin echo T1 with fat saturation through the brain and axial diffusion.

MRI Findings in a Child with Diabetes Insipidus

Most children have a nonspecific finding of non-visualization of the posterior pituitary bright spot. Thickening of either the entire pituitary stalk or just the proximal portion is the second most common abnormality on MRI scans [5]. When present, the thickening suggests infiltration. The most common diagnoses which are associated with DI pituitary stalk thickening are hypophysitis, Langerhans cell histiocytosis (LCH), and germ cell tumors (e.g., germinoma) [5].

If the pituitary stalk is not thickened, follow-up scans should be done, as there can be progression of disease, especially of germinoma; progression is generally seen by 6 months but can occur years later [6].

The common findings on MR imaging in patients with DI are listed in Table 3.1.

When a child is diagnosed with central DI, the endocrinologist's and/or oncologist's goal is to determine whether the child

Table 3.1 Common findings seen on MRI in children with DI

	Common findings on MRI seen in DI	DI causes
1	Non-visualization of the posterior pituitary bright spot	LCH, LH, GCT, CP post-surgery, TB, sarcoidosis
2	Thickening of the pituitary stalk	LCH, LH, GCT, TB, sarcoidosis
3	Mass lesions	GCT, CP, RCC, gliomas
4	Thin pituitary stalk or disruption of pituitary-hypothalamic axis	SOD, other developmental causes, post-surgery, trauma

has hypophysitis or one of the more aggressive conditions (LCH or germ cell tumors).

Langerhans Cell Histiocytosis (LCH)

Studies on the causes of central diabetes insipidus show approximately 5–20% prevalence of Langerhans' cell histiocytosis as the cause [7]. LCH in children commonly affects bones, skin, and the pituitary gland. Central diabetes insipidus is the most frequent central nervous system manifestation of LCH, occurring in 10–50% of all LCH patients [7].

MRI of the pituitary gland in a child with LCH may demonstrate absent T1 hyperintensity of the posterior pituitary/neurohypophysis and a thickened pituitary stalk [8, 9] (Fig. 3.2). In some cases of LCH the posterior pituitary signal may initially be detectable but may disappear over time, hence follow-up MRI may need to be obtained in some cases of LCH. Other MR imaging findings of LCH such as calvarial lesions, foci of T2 hyperintensity in the basal ganglia, thalami, and cerebellum may be noted in some cases [7] (Figs. 3.2 and 3.3).

In children with a new diagnosis of DI, LCH should be considered [10]. Clues might include associated skin lesions and bone lesions.

Typical MRI features are an absent posterior pituitary bright spot and a thickening of the stalk [9]. Additional pituitary hormone deficiencies may be present, such as GH deficiency, or may develop several years later.

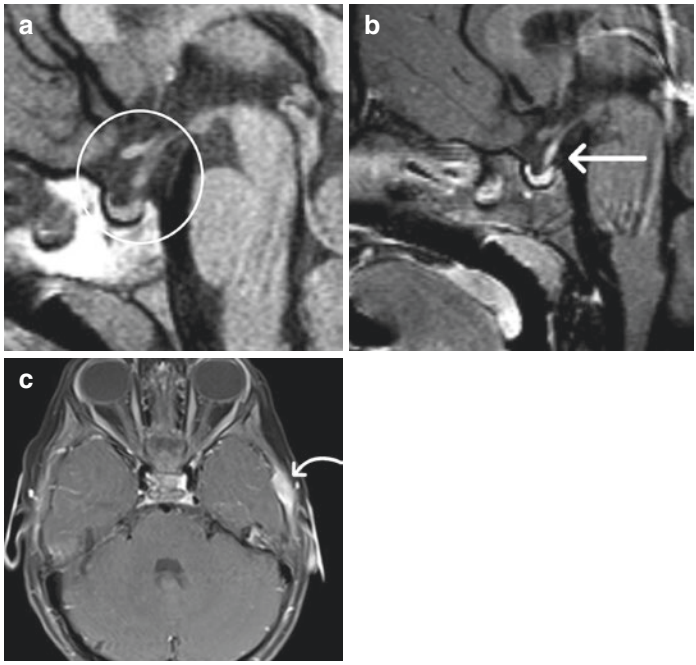

Fig. 3.2 Langerhans' cell histiocytosis (LCH) MRI images of a 5-year-old boy with LCH. (**a**) Unenhanced T1 sagittal image showing absence of the normal posterior pituitary bright spot. (**b**) Postcontrast sagittal T1 with fat saturation demonstrate thickened enhancing pituitary stalk(straight arrow). (**c**) Postcontrast axial T1 with fat saturation shows enhancing left temporal bone lesion of LCH (curved arrow)

Hypophysitis

When there is autoimmune destruction of the pituitary, like what occurs in Hashimoto's thyroiditis, it is termed hypophysitis. Hypophysitis may be associated with both anterior and posterior pituitary deficits. It is presumed that when there is idiopathic diabetes insipidus, it is likely due to hypophysitis [11]. Follow-up MRI scans of patients with hypophysitis as the cause of DI and a

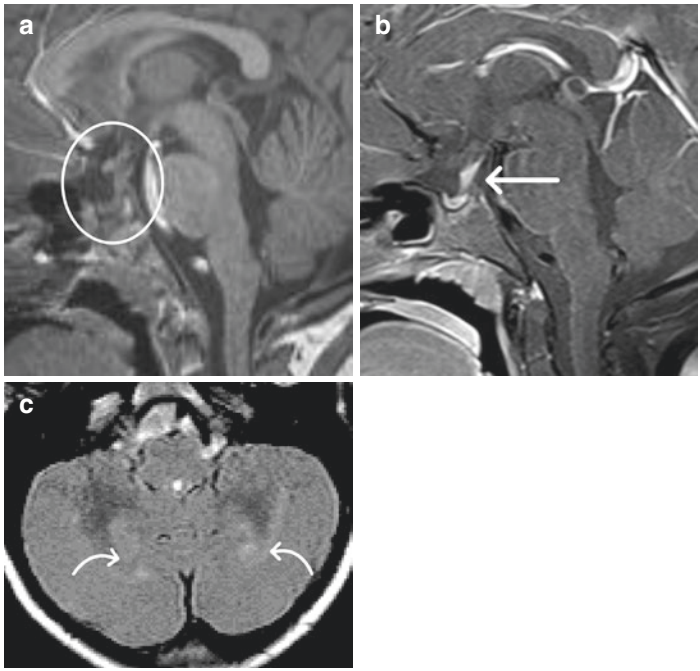

Fig. 3.3 Langerhans' cell histiocytosis (LCH) MRI images of a 9-year-old boy with LCH. (**a**) Unenhanced T1 sagittal image showing absence of the normal posterior pituitary bright spot. (**b**) Postcontrast sagittal T1 with fat saturation demonstrate thickened enhancing pituitary stalk (straight white arrow). (**c**) Axial FLAIR shows hyperintense lesions in the cerebellum (curved arrows)

thickened pituitary stalk show a range of changes, from a spontaneous resolution of the abnormality to no change (Fig. 3.4). Caution must be made as germ cell tumors and hypophysitis have similar presentations. Follow-up MR imaging and other investigations including germ cell tumor markers and, in some cases genetic testing for LCH may need to be performed before arriving at this diagnosis [8].

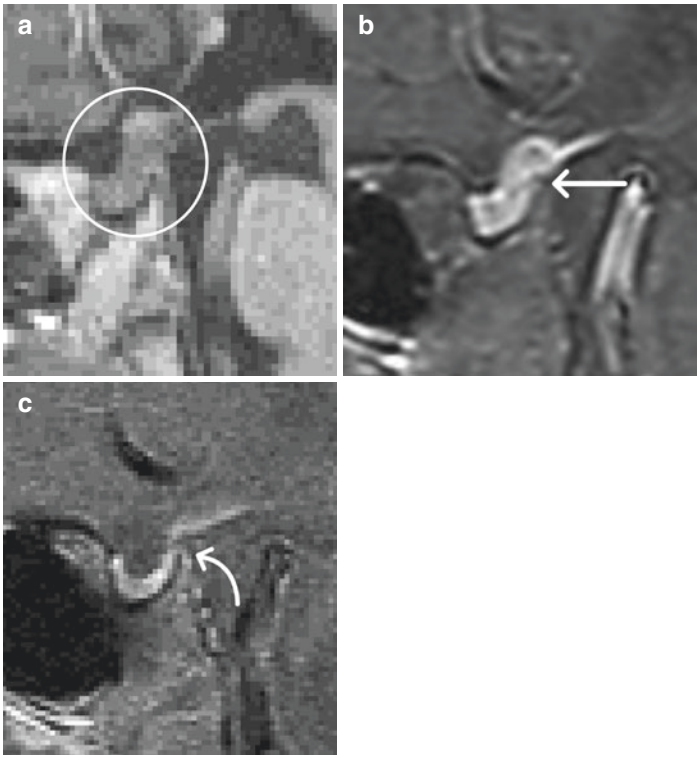

Fig. 3.4 Lymphocytic hypophysitis (LH) MRI images of a 11-year-old girl with LH. (**a**) Unenhanced T1 sagittal image showing absence of the normal posterior pituitary bright spot and thickened pituitary stalk. (**b**) Postcontrast sagittal T1 with fat saturation demonstrate thickened enhancing pituitary stalk (straight white arrow) MRI image three years following treatment. (**c**) Postcontrast sagittal T1 with fat saturation demonstrates resolution of the previously noted pituitary stalk thickening (curved arrow)

Germ Cell Tumors (GCT)

Germ cell tumors include germinoma, as well as non–germinomatous tumors such as teratoma, yolk sac tumor, and embryonal carcinoma. Central nervous system (CNS) germ cell tumors (GCTs)

represent approximately 3% of primary pediatric brain tumors. The clinical presentation varies by location and size, and it frequently includes endocrine abnormalities including central DI, visual changes, and signs of increased intracranial pressure [12]. A small percentage of those with germ cell tumors have tumor markers alpha-feto protein and/or human chorionic gonadotropin (HCG) in the serum and/or CSF, and both blood and CSF should be evaluated [12]. In this group of germ cell tumors the MR imaging findings along with the tumor marker elevation may be diagnostic in themselves without the need for tissue confirmation [13].

Essentially, when a child is diagnosed with central DI, the endocrinologist's and/or oncologist's goal is to determine the cause and to assess if the child has any of the more aggressive conditions which includes germ cell tumors [14].

MR imaging findings in suprasellar GCTs include absent posterior pituitary bright spot and thickened pituitary stalk with enhancement [3] (Fig. 3.5).

DI can present for extended period prior to MR abnormalities which become evident in cases of suprasellar germinomas. Some of the GCTs have a tendency for dissemination through the CSF; therefore, it is essential to scan the whole brain and the entire spinal axis to exclude dissemination. It is not possible by MR imaging to differentiate between the different types of germ cell tumors.

Majority of the GCTs are noted to be very sensitive to radiation treatment. Serial MR imaging is useful in assessing response to treatment [12] (Fig. 3.5).

Rathke Cleft Cysts (RCC)

Rathke cleft cysts (Fig. 3.3) are incidental pituitary cysts that arise from the non-obliterated intrasellar lumen of Rathke pouch. RCCs are benign, sellar region endodermal cysts lined by ciliated, mucus-producing epithelium [15]. When RCCs are large, they become symptomatic, because of the exerted mass effect. Larger RCCs can result in pituitary dysfunction (70%) and central diabetes insipidus [16].

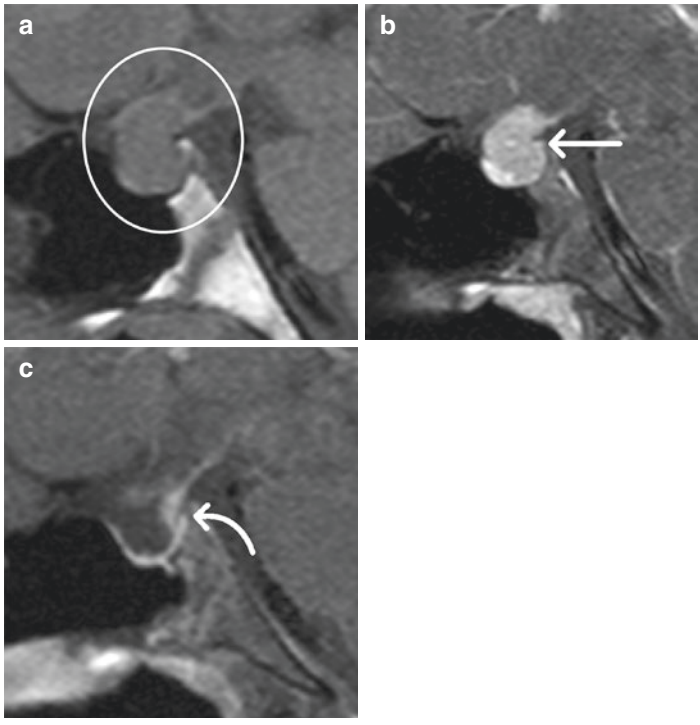

Fig. 3.5 Suprasellar germinoma (SG) MRI images of a 12-year-old boy with SG presenting with new-onset diabetes insipidus and panhypopituitarism. (**a**) Unenhanced T1 sagittal image showing absence of the normal posterior pituitary bright spot and thickened pituitary stalk. (**b**) Postcontrast sagittal T1 with fat saturation demonstrate thickened enhancing pituitary stalk (straight white arrow) MRI image two years following treatment. (**c**) Postcontrast sagittal T1 with fat saturation demonstrates resolution of the previously noted pituitary stalk thickening (curved arrow)

RCCs are smoothly lobulated well-delineated intrasellar/suprasellar cystic masses, typically without enhancement. MR imaging findings of RCCs depend on the cyst content (Fig. 3.6). Typically, RCCs with proteinaceous content are hyperintense on T1 and hypointense on T2 in 50% of cases and the remainder may be T1 hypointense and T2 hyperintense [17]. Small non-enhancing intra-cystic nodule is seen in 75% of cases [17]. When they are T1 bright no enhancement is appreciated.

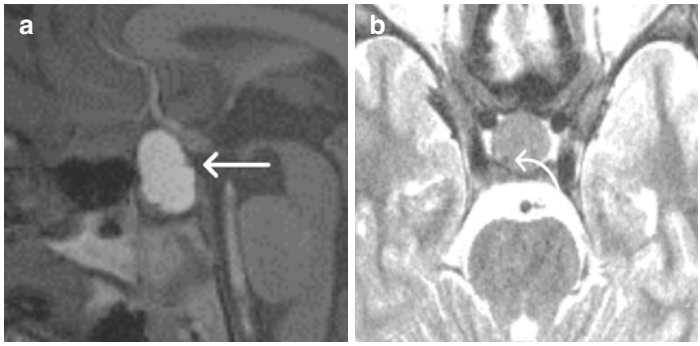

Fig. 3.6 Rathke cleft cyst (RCC) MRI images of a 10-year-old boy with RCC presenting with new onset diabetes insipidus. (**a**) Unenhanced T1 sagittal image showing hyperintense cyst in the sella and suprasellar region (straight white arrow). (**b**) Axial T2-weighted imaging showing hypointense / dark content within the cyst with a peripheral hypointense/dark nodule (curved arrow)

Craniopharyngioma

Craniopharyngiomas (CP) (Fig. 3.4) account for 1.2–4.6% of all central nervous system tumors and about 6% of pediatric brain tumors [18, 19]. Childhood CP almost always have an adamantinomatous pathology, may be cystic and may have calcifications (Fig. 3.4B) [20].

Craniopharyngiomas are thought to arise from neoplastic transformation of ectopic embryonal remnants along the hypophyseal duct through which the Rathke pouch migrates to form the anterior pituitary gland [18]. Because they arise along the hypophyseal duct, they may be in an infradiaphragmatic location (below the dura mater through which the pituitary stalk passes) and/or a suprasellar location above the pituitary gland to the floor of third ventricle. Because craniopharyngiomas are located close to and can invade the pituitary gland, pituitary stalk, and the hypothalamus, they can present with pituitary hormone deficiencies; and when suprasellar, they are more likely to present with hypothalamic dysfunction including DI [21].

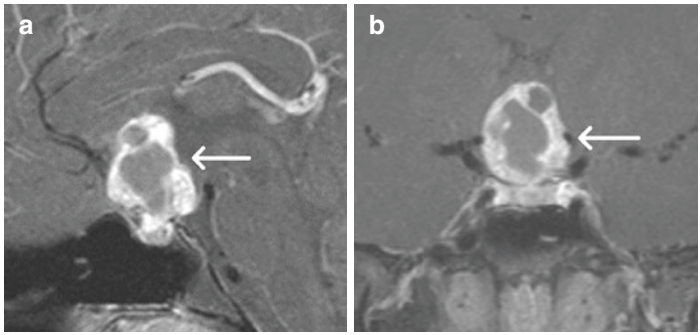

Fig. 3.7 Craniopharyngioma (CP) MRI images of a 6-year-old girl with CP. (**a**) Postcontrast sagittal T1 with fat saturation image. (**b**) Postcontrast coronal T1 with fat saturation showing mixed cystic and solid mass with heterogeneous enhancement extending to the suprasellar region (straight white arrow)

On MR imaging typically the craniopharyngiomas are a heterogeneous solid and cystic mass in the sellar and suprasellar region with heterogeneous enhancement of the solid components. The appearance of the cysts on MRI is variable depending on the content and can be hyperintense on T1. The presence of calcifications is a hallmark of craniopharyngioma and can be identified easily on CT scan compared to MRI (Fig. 3.7).

Major morbidity can occur during surgical resection of the craniopharyngioma with injury to the surrounding structures, as well as due to scarring and reactive changes after resection and radiation therapy (Fig. 3.8). These complications include DI in addition to hypopituitarism, hypothalamic (morbid) obesity, visual, and neurological deficits [22].

Other Tumors

Gliomas and lymphoma are tumors that may rarely grow in the region of the pituitary [23]. Gliomas are sometimes seen in children with neurofibromatosis type 1 (NF1). Large hypothalamic-chiasmatic gliomas (seen in NF1) and meningiomas (seen in NF2) can cause DI [24].

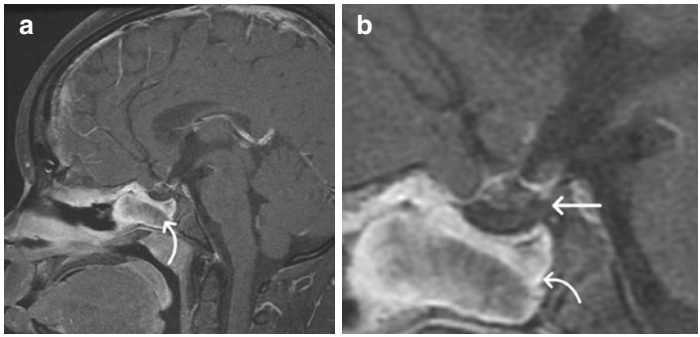

Fig. 3.8 Posttreatment craniopharyngioma (CP) MRI images of a 13-year-old boy with recurrent craniopharyngioma with pan hypopituitarism and central DI. (**a**, **b**) Postcontrast sagittal T1 with fat saturation showing post-surgical distortion in the sella following endoscopic endonasal resection and radiation therapy. The pituitary gland, posterior pituitary bright spot, and the pituitary stalk are not well visualized (straight white arrow). There is enhancement of the mucosal flap in the sphenoid sinus (curved arrow)

Rarely, large pituitary adenomas can surround and compress the pituitary stalk, resulting in DI.

Metastases to the pituitary-hypothalamic axis can present clinically, with DI as the main presenting symptom mainly in adults. DI of a transient nature may occur from metastases to the posterior lobe of the pituitary.

Congenital Abnormalities in the Pituitary/Hypothalamic Region Causing DI

Ectopic Posterior Pituitary (EPP)

Occasionally, in the workup for a child with a new diagnosis of GH deficiency, an MRI that shows the bright spot is located either on the stalk or even above the stalk (Fig. 3.9). The presence of an EPP is usually associated with anterior pituitary hormone deficiencies, and occasionally DI [14, 25].

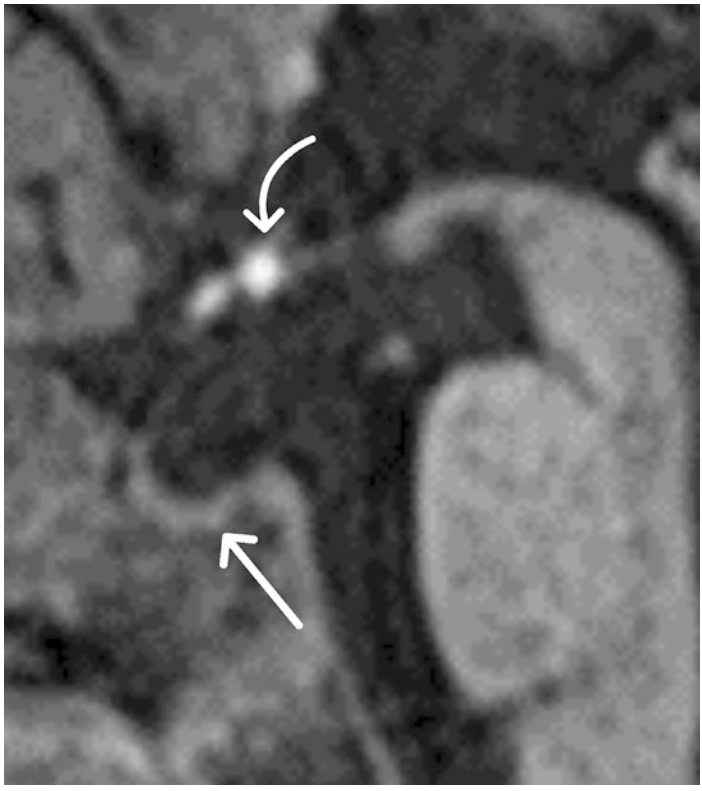

Fig. 3.9 Ectopic neurohypophysis in a 7-month-old boy with DI. Unenhanced sagittal T1 image showing diminutive pituitary gland (straight arrow). The pituitary stalk cannot be identified and note ectopic location of the neurohypophysis (curved arrow)

Septo-optic Dysplasia (SOD)

SOD is a congenital malformation where there is a small pituitary, underdevelopment of the optic nerves, and absence of midline brain structures such as the septum pellucidum and corpus callosum. Children with SOD may present with features secondary to anterior and posterior hormone deficiencies including DI [4]. SOD is diagnosed by MRI identification of small pituitary

gland and an absent infundibulum in addition to absence of septum pellucidum and other midline and optic nerve anomalies [25, 26] (Figure included in the chapter on pituitary causes of short stature).

Inflammatory and Infectious Conditions

Granulomatous diseases like sarcoidosis can involve the hypothalamic-pituitary axis, and result in central DI. MR imaging reveals a smooth thickening of the pituitary stalk, with occasional involvement of the adjacent hypothalamus or pituitary gland [27, 28].

Among infectious causes of central DI, the most common infection is tuberculosis [28]. MR imaging reveals a smooth thickening of the pituitary stalk, like sarcoidosis, associated with diffuse leptomeningeal enhancement, especially in the basal cisterns [29].

Rarely trauma and following surgery disruption of the pituitary–hypothalamic axis result in DI. The MRI findings would reflect changes related to trauma and pituitary findings include non-visualization of the T1 hyperintensity of the neurohypophysis with or without imaging evidence of disruption of the pituitary infundibulum [16].

Summary

A wide spectrum of disease processes can result in central diabetes insipidus. MR imaging plays an important role in the assessment of pituitary-hypothalamic axis and in identifying lesions that can cause central DI. The high spatial resolution, multiplanar imaging capability, and lack of ionizing radiation make MR imaging the investigation of choice in the workup of diabetes insipidus in children.

Disclosure Statement No relevant financial disclosures.

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4 Central Diabetes Insipidus with Pituitary Stalk Thickening

Ahsan Uddin and Shabana Kalladi Puthanpurayil

Case Description

A 7-year-old female was evaluated by her pediatrician for complaints of intermittent headaches, polydipsia, polyuria, and new onset nocturnal enuresis. Her symptoms persisted despite bedtime water restriction. Workup initiated by her pediatrician showed a serum sodium of 147 mmol/L and they were referred to pediatric endocrinology. At repeat evaluation, studies showed sodium of

In the interest of full disclosure – the illustrative case in this chapter was presented in a poster presentation at Endo 2020 Conference [March 2020], however the images were not used.
Citation below for your reference:
Puthanpurayil SK, Uddin A, Gerrits PM. SUN-282 transient infundibulohypophysitis in a child with central diabetes insipidus. J Endocrine Soc. 2020;4(Supplement_1): SUN-282. https://doi.org/10.1210/jendso/bvaa046.693

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C. A. Alter (ed.), *Diabetes Insipidus in Children*,
https://doi.org/10.1007/978-3-030-83248-3_4

147 mmol/L, creatinine of 0.65 mg/dl, serum osmolality of 291 mOsm/kg, and urine osmolality of 137 mOsm/kg. Antidiuretic hormone (ADH) level was undetectable. An inpatient water deprivation test was recommended to rule out diabetes insipidus.

Water deprivation testing was conducted approximately 4 weeks following onset of symptoms. The study confirmed central diabetes insipidus (CDI), with doubling of urine osmolality in response to desmopressin administration, and the patient was started on treatment with 0.05 mg of desmopressin twice daily by mouth. Magnetic resonance imaging (MRI) of brain with and without gadolinium was performed to evaluate for an underlying cause of CDI. The study showed markedly thickened and homogeneously enhancing pituitary stalk (17 mm × 10 mm) (Fig. 4.1a) suggestive of Langerhans cell histiocytosis (LCH). This prompted scheduling of a pituitary stalk biopsy and skin biopsy. The skin biopsy report was normal. During the endoscopic procedure for pituitary stalk biopsy, which was performed 7 weeks after the initial MRI, direct visualization of the pituitary stalk did not show any abnormalities and therefore no tissue sample was taken. A repeat brain MRI performed at this time (i.e., 7 weeks after the initial MRI) showed complete resolution of the previously demonstrated pituitary stalk thickening (PST). Follow-up MRIs at 5

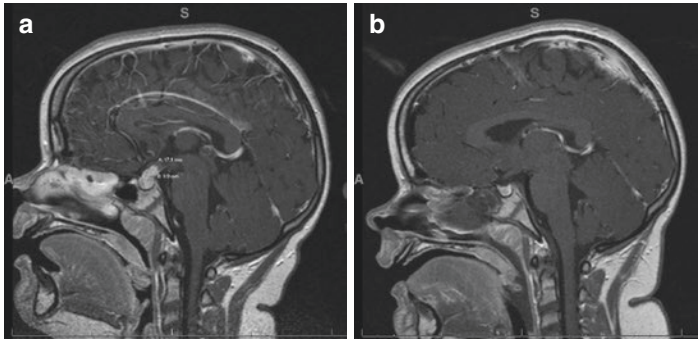

Fig. 4.1 (**a**) MRI of the pituitary with gadolinium contrast demonstrating marked thickening of the pituitary stalk. (**b**) MRI of the pituitary in the same patient 7 weeks later showing complete resolution of previously demonstrated pituitary stalk thickening

and 15 months after initial diagnosis continued to demonstrate complete resolution of the infundibular mass (Fig. 4.1b) suggesting transient inflammation as the likely cause. Alpha-fetoprotein (AFP) and beta human chorionic gonadotropin (hCG) were normal in blood and cerebrospinal fluid (CSF), and CSF cytology was also negative.

At a follow-up visit in clinic 1 year later, she presented with new papular, scaly appearing skin lesions on left thumb, forearm, and fourth digit of right hand. Given these new findings, she was referred to dermatology for a repeat skin biopsy and to oncology for re-evaluation of possible histiocytic disease. A repeat MRI of the pituitary gland performed 28 months after initial diagnosis continued to demonstrate absence of the posterior pituitary bright spot with no other structural abnormalities.

Assessment and Diagnosis

Diabetes insipidus usually presents with a combination of polydipsia and polyuria along with decreased urine osmolality and increased serum osmolality. Diabetes insipidus may be classified as central or peripheral, caused by ADH deficiency or resistance, respectively. They can be differentiated based on response to administration of ADH at the end of a water deprivation study (see Chap. 2 for making the diagnosis of central diabetes insipidus). Once the diagnosis of central diabetes insipidus (CDI) has been established, it is important to identify the underlying etiology, which in children can be due to infectious, neoplastic, traumatic, or genetic processes that disrupt the hypothalamus or pituitary stalk. In particular, identifying neoplasia is critical to determine the best approach to therapy, with germinoma (or other germ cell tumors), craniopharyngioma, and Langerhans cell histiocytosis all being important causes of CDI. Other infiltrative lesions such as lymphoma, although rare, should also be considered [1]. These should ideally be identified early to avoid the pitfall of empiric treatment of presumed hypophysitis (See Chap. 5).

MRI with gadolinium contrast is indispensable in the evaluation of these children as imaging with CT is unable to identify

many pituitary abnormalities [2] leading to incorrect classification of many cases as "idiopathic". Some patients with CDI may present with obvious lesions such as tumors or midline malformations that explain the development of CDI and suggest the underlying diagnosis. One of the most common, albeit non-specific, findings on MRI is absence of the normal pituitary bright spot on T1-weighted imaging [3]. Thus, the absence of the posterior pituitary bright spot is consistent with CDI, but gives no information regarding its underlying etiology. One-third of children with CDI present with pituitary stalk thickening (PST) on initial evaluation with MRI. The normal size of the pituitary stalk is dependent on age. Therefore, the definition of pituitary stalk thickening also changes with the age of the patient. Some authors define stalk thickening in children to be >2.5 mm [2, 4, 5], in the largest cross-section on imaging while most use >3 mm [6]. In patients older than 8 years, the adult definition of >3.5 mm [4] may be used. The thickening may be seen in the proximal, middle, or distal portion of the stalk and this location may have an impact on management as thickening closer to the optic chiasm may warrant more aggressive intervention [7] given the higher likelihood of visual impairment. Given the size changes under consideration, consultation with a neuroradiologist for optimal MRI parameters, including slice thickness, is recommended where the resources are available. Previous studies have shown that the degree of PST is variable depending on the underlying etiology [8] and a significant number of cases are associated with neoplasm of which CDI may be the initial presentation. Furthermore, regression of PST has been observed in many cases of CDI with PST which is attributed to idiopathic or autoimmune process.

In addition to focused MRI examination of the pituitary gland, patients with thickened stalk should have MRI imaging of the brain and spinal cord to seek other abnormalities. Other imaging findings can include abnormal size of the anterior pituitary gland and lesions in the pineal gland, the presence of which may be more suggestive of infiltrative/neoplastic diagnoses such as germ cell tumor (GCT) or less commonly LCH.

MRI findings with CDI are dynamic and it is important to serially follow these patients for changes. Most authors recommend

following patients with CDI with MRI every 3–6 months for at least 2–3 years to identify changes suggestive of neoplasm [9, 10]. In particular it has been demonstrated that frequent neuroimaging follow up can reduce time delay in diagnosis of germinoma from 2.5 years to 1 year [11]. The optimal timing may vary based on patient factors with some authors advocating for more frequent scans [2]; conversely, it may be reasonable to have less frequent follow up in individuals with normal initial imaging or stable imaging beyond the first 2 years. Increasing stalk size is more frequently associated with eventual diagnosis of neoplastic process and may be an indication for pituitary stalk biopsy whereas decreasing size is more suggestive of transient inflammatory process. In cases where stable or resolving PST is noted, routine neuroimaging follow up may be discontinued after 3–5 years. For those patients with persistent or progressive PST, at least annual neuroimaging may be recommended along with consideration of biopsy and investigation of extracranial sites with suspicion of underlying LCH [9].

Our suggested algorithm, based on available literature, for evaluation of a child with central diabetes insipidus and PST, has been outlined in Fig. 4.2. In cases where CDI is present without PST, we recommend following MRIs every 6 months for one year and then annually thereafter. In those where PST is present, follow-up MRI every 3–6 months during the first year, 6–12 months during the second year, then annually up to 5 years is suggested.

In addition to deficiency of ADH, some patients may have associated abnormalities of other pituitary hormones. Anterior pituitary hormone deficits (APDs) can present at any point through the course of CDI associated with structural pituitary abnormalities. There may be a single deficit or multiple deficits. Overall, the most common hormone affected tends to be growth hormone (GH) (60%) followed by thyrotropin (TSH), then adrenocorticotropin (ACTH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). When PST is present, nearly all cases may demonstrate an associated APD at some point during the disease. The number and rate at which APDs develop may also be predictive of underlying malignancy. Most APDs develop within the first 24 months of diagnosis, particularly GH deficiency. However,

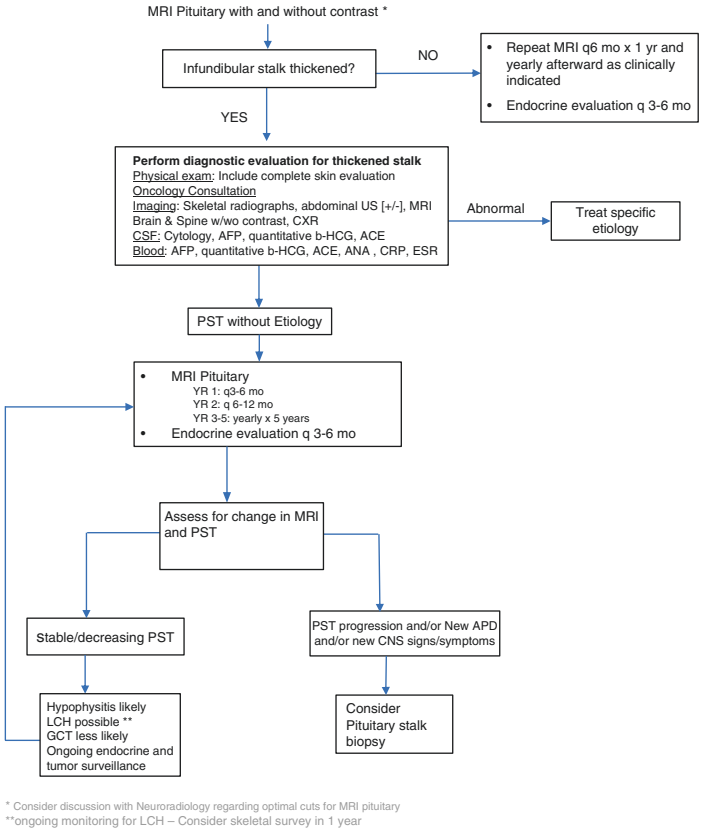

Fig. 4.2 Suggested algorithm for evaluation and follow up of a child with central diabetes insipidus

TSH and ACTH deficiency may develop up to 12 years after initial diagnosis. Therefore, it would be prudent to monitor pituitary function clinically and biochemically every 3–6 months during the initial 2–3 years and annually thereafter [12]. Identification of APDs would warrant appropriate treatment by the endocrinologist. Some authors advise caution when approaching patients with CDI and associated GH deficiency as some evidence has suggested that treatment with GH replacement may cause progression

of the underlying infiltrative disease due to its mitogenic properties [1].

Specific testing to help establish an underlying etiology must be undertaken at the time of CDI diagnosis. This typically involves obtaining cytology and tumor markers, including quantitative beta hCG and AFP, in both serum and cerebrospinal fluid. If these are non-diagnostic initially, the presence of abnormalities on MRI may warrant a biopsy to establish a tissue diagnosis (Fig. 4.2). Negative initial GCT workup in combination with progressive MRI findings may necessitate repeating these assessments at a later point in the patients' clinical course. Another common cause of CDI with imaging abnormalities is LCH which warrants specific testing including anti-nuclear antibodies, C-reactive protein, erythrocyte sedimentation rate (ESR), and serum and CSF angiotensin-converting enzyme (ACE) (See Chap. 14). Extracranial imaging (skeletal radiographs looking for lytic lesions, abdominal ultrasound looking for organomegaly, and chest radiography) and detailed skin examination [7] are also useful in the workup of potential LCH. It is recommended to collaborate with an oncologist (or neuro-oncologist) when the initial findings are suggestive of neoplastic etiology.

Tissue diagnosis remains the gold standard to identify the underlying etiology for CDI with PST. Where abnormalities of the pituitary stalk exist, pituitary stalk biopsy often has the greatest likelihood of establishing the diagnosis. Due to the invasive nature of pituitary stalk biopsies, particularly through craniotomy, previous authors have advocated for a more conservative approach, recommending to biopsy only if there is a large (>7 mm) degree of thickening [2, 6], demonstration of progressive lesion growth [11], or development of new APDs. Significant change on serial MRI may be defined as a change in dimension of 15% [13], 20% [5], or 25% [7]. We advise discussion with neuroradiology on the threshold of change depending on available resolution at your institution. Conversely, some patients with initial PST can show spontaneous regression and even complete resolution. Most authors advise against biopsy should this be the case [2, 11] given the higher likelihood of transient inflammation being the cause. There is limited data on the safety of performing pituitary stalk

biopsy in pediatric patients. A 2020 study with a limited cohort of 9 patients comments on the safety of endoscopic trans-sphenoidal biopsy compared with open craniotomy [14]. They report a diagnostic yield of 77% despite presence of compelling radiographic evidence suggestive of underlying GCT. In the case of LCH the first choice for biopsy may be an extracranial site particularly in cases where systemic symptoms are suggestive of the diagnosis. A retrospective review of 54 patients with CDI found to be due to LCH had diagnosis made on extracranial biopsy in 91% of the patients [15].

One case describes a 9-year-old girl in which after diagnosis of CDI and PST, LCH was highly suspected from history and empiric therapy was started. However, biopsy of the pituitary lesion itself confirmed diagnosis of germinoma [16]. These examples underscore the importance of histologic confirmation of diagnosis prior to initiation of empiric therapy. Despite best practice, the diagnosis of intracranial GCT can be missed in up to 60% of cases as initial biopsies can show inflammatory changes consistent with hypophysitis, which itself may be secondary to GCT. GCT should remain part of the differential despite initial imaging and tumor marker results and is one of the reasons that serial MRIs are indicated in patients with CDI.

Germ cell tumor (GCT) is a significantly concerning etiology associated with CDI and PST, which is why the evaluation of these patients is designed around early identification of this potential diagnosis. The prevalence of GCT in cases of CDI with PST has been reported to range from 15% [2] to 60% [17]. Initial evaluation with tumor markers from serum and CSF are helpful when positive but too insensitive to be able to exclude the diagnosis when negative [11]. Multiple MRI findings are predictive of GCT including bifocal disease involving the pituitary gland and pineal gland [7], decreased size of adenohypophysis, presence of PST >6.5 mm at any point, and progressive increase in PST on serial imaging [2, 10, 18]. Biochemically, there is correlation between the presence of multiple and early presenting APDs and the eventual diagnosis of GCT [2, 19]; however, this association is strongly demonstrated with degree of PST as well [12]. Therefore, the association between germinoma and multiple APDs may be

modified by PST rather than being an independent association. The absence of the above predictive factors does not rule out germinoma and it should always be considered in the differential, particularly if there is a lack of response to initial therapy [19].

Langerhans cell histiocytosis (LCH) is a common cause of CDI with prevalence reported from 7% [20] to 19% [2] and CDI, usually with PST, is often the first presentation of the disease [7]. Diagnosis of LCH is challenging both because of similarity in presentation with GCT and due to its prolonged and unpredictable course. Initial imaging findings can include PST (70%) which may be moderate or large and can increase or decrease in size on follow up [6, 7]. The presence of symmetry and unifocality on MRI are more suggestive of the LCH diagnosis [7] but in many cases the diagnosis relies on identification of extracranial manifestations such as bone, skin, or lung lesions which are present at CDI diagnosis in 18% of patients and may present in another 51% within 1 year follow up [15]. APDs are uncommon on initial presentation and less likely to develop early; however, extended follow up shows a higher likelihood (~80%) of patients with LCH having at least one APD develop within 8 years compared with "idiopathic" CDI cases [11, 20]. LCH must be kept in the differential long-term as the diagnosis may only be apparent 8 or more years after CDI diagnosis.

Not all cases of CDI with PST have an independent disease process. These cases are considered to be "idiopathic". Previously the prevalence of "idiopathic" CDI was reported as 30–50% [11] but this has recently been challenged as an underlying diagnosis is more commonly found, particularly in those patients with abnormal imaging, and so the prevalence of idiopathic cases in recent series is lowered to 12% [8]. Nevertheless, cases of idiopathic CDI with PST do occur, though generally the degree of PST is small or moderate and tends to remain stable (30%) or regress (30–50%) in most individuals [2, 11]. Due to this response, pituitary biopsy is usually not indicated and the diagnosis of presumed transient lymphocytic inflammation is extrapolated from adult studies [6]. Along with PST, these patients may also demonstrate decreased anterior pituitary size along with a single APD (usually GH) [12]. Development of multiple APDs is less common. Some

patients may have the finding of specific antibodies directed against vasopressin cells [21]. In adult series, other factors that may suggest idiopathic inflammation are personal or family history of autoimmune conditions and female sex. However, the same risk factors have not been seen in pediatric patients with lymphocytic neurohypophysitis [5].

Management

Most patients with CDI and associated PST continue to require long-term ADH replacement therapy regardless of underlying diagnosis or resolution of imaging findings. Those who are found to have GCT, LCH, or other infiltrative processes should be managed in cooperation with an oncologist to determine additional disease treatments and surveillance. As mentioned above, a significant proportion of patients with CDI and PST will develop an additional APD on follow up that may warrant replacement therapy. The consideration of treatment of isolated GH deficiency remains controversial due to the theoretical risk of promoting CNS lymphoma in the long term.

Clinical Pearls and Pitfalls

- Diabetes insipidus diagnosed in infancy or childhood can be due to infectious, neoplastic, traumatic, or genetic processes that disrupt the hypothalamus or pituitary stalk.
- Recognizing and understanding the underlying cause of the patient's presentation is critical to treating the patient effectively.
- A histopathological diagnosis may pose a challenge, given lack of data on safety of pituitary stalk biopsy in pediatric population.
- Germ cell tumors and LCH should remain on the differential and warrant surveillance regardless of initial findings.

Outcome

A definitive underlying diagnosis for why this patient had CDI with a high degree of PST has not been established. With recent development of a scaly skin rash, it was recommended that the family have a dermatology consultation for a skin biopsy, to evaluate for LCH. Based on the biopsy report, the skin lesions were diagnosed as verruca vulgaris (common warts).

With disappearance of pituitary stalk thickening, a histopathologic diagnosis via pituitary stalk biopsy could not be achieved. She was initiated on treatment with oral desmopressin for management of CDI. Her other pituitary hormones are being serially monitored and have thus far remained normal. Follow-up MRI scans at 1 year and 28 months after initial presentation have not demonstrated recurrence of PST, although the pituitary bright spot remains absent. Given that PST has completely resolved without recurrence on subsequent MRIs, and surrounding structures are normal, we will repeat MRI in 1 year, sooner if clinically indicated (development of new APDs, new central nervous system signs or symptoms).

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Hypophysitis

5

Christopher Gibson

Vignette

SJ is a 9-year-old male presenting with a 6-week history of polyuria and polydipsia, and 4 months of intermittent headaches alleviated with vomiting. He denies any appetite, visual, skin, or stooling changes. There has been no weight gain in the past 6 months, but his height has consistently tracked the 55th percentile over the past 7 years. Laboratory investigations are notable for a urine specific gravity of 1.000 and he is referred to Endocrinology. Overnight fasting evaluation shows morning urine and blood work consistent with diabetes insipidus (elevated sodium and serum osmolality with inappropriately low urine osmolality). Anterior pituitary hormone investigations are normal. Magnetic resonance imaging of the brain and pituitary demonstrates homogeneous enhancement of a thickened pituitary stalk, measuring 5 mm in antero-posterior dimension, abutting the optic chiasm without compression, and a T1 hyperintensity of posterior pituitary representing the neurohypophysis bright spot. Nightly oral desmopressin therapy is started, 0.05 mg, with resolution of

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C. A. Alter (ed.), *Diabetes Insipidus in Children*,
https://doi.org/10.1007/978-3-030-83248-3_5

polyuria and polydipsia, and concentrated urine osmolality and normalized serum osmolality.

His neuro-oncologic evaluation shows a normal skeletal survey, normal serum and cerebrospinal fluid (CSF) alpha-1-feto protein (AFP), beta-human chorionic gonadotropin (β-hCG), and angiotensin converting enzyme levels, and a normal CSF immunoglobulin G level. He undergoes pituitary stalk biopsy, which demonstrates an inflammatory infiltrate consisting of mainly T and B lymphocytes, and histiocytes. No Langerhans or germ cells are identified. A comprehensive solid tumor panel (tumor/normal pair) analysis of the biopsy shows no clinically significant variants, and *BRAF* analysis is negative. He recovers in the intensive care unit without incident and is discharged on oral desmopressin therapy.

About 2 weeks after biopsy, he develops fatigue and bradycardia, with a decreased morning cortisol of 5.5 mcg/dL and a low free thyroxine on direct analysis and equilibrium dialysis (0.6 and 0.7 ng/dL, respectively). He is started on hydrocortisone therapy followed several days later by thyroxine replacement, with clinical and laboratory improvements. Follow-up MRIs over the next 12 months show no new lesions or changes in pituitary stalk thickening, and no changes in serum tumor markers.

However, he experiences growth failure with decreasing insulin-like growth factor-1 levels. Subsequent stimulation testing with arginine and glucagon agents, off hydrocortisone therapy for several days, demonstrates a peak cortisol of 8.7 mcg/dL and peak growth hormone of 1.89 ng/mL. Hydrocortisone is restarted, and growth hormone is started soon thereafter.

Chapter Write-Up

The first case of hypophysitis was described in 1962 and became increasingly recognized throughout the 1980s as a cause of hypopituitarism, mostly in women with an intrasellar mass or hypopituitarism symptoms during late pregnancy or the postpartum period [1, 2]. Histologic study of this first case showed lymphocytic infiltration of the anterior pituitary without giant cells or

granulomas. These findings were felt to be different than the more commonly reported phenomenon of Sheehan's syndrome seen in post-partum women: healed pituitary necrosis and acellular fibrosis, typically found in a part of the pituitary susceptible to ischemia. Some of the reports described the degree of hypopituitarism as out of proportion to the pituitary mass size seen on imaging or intra-operatively, suggesting cellular pituitary destruction as the cause of pituitary destruction, rather than compression [2]. Although these early adult studies could not elucidate a precise hypophysitis etiology, autoimmunity was felt to play a role as many of the subjects were female with concurrent autoimmune disorders [1–3]. This hypothesis was further supported by animal model studies demonstrating that lymphocytic hypophysitis could be induced in rats injected with both homologous and heterologous pituitary tissue [4]. While most of the first hypophysitis cases were described in post-partum or pre-menopausal females, subjects outside of this demographic were reported more frequently over the next 30 years in the medical literature, including children.

Description/Incidence

Hypophysitis is an uncommon disorder in children with less than 100 cases reported to date [5, 6]. Both acute and chronic inflammation of the pituitary gland has been described in these cases, which can lead to hypopituitarism. Dysfunction or deficiency of the adenohypophysis, neurohypophysis, and hypothalamus, or a combination of the three, can be seen in adults and children [7]. A comparison of these three subtypes in adults has proven challenging as the classifications in the literature have been heterogeneously derived from an endocrinological, pathological, and radiological standpoint [8]. The cause can be primary (isolated to the pituitary gland) which is often idiopathic, or secondary to infiltration, local tumor extension, distant metastases, medications, infection, or systemic inflammatory disorders [9, 10]. The diagnosis of hypophysitis is not always certain during the first several months or years of a subject's presenting complaints, and other etiologies, such as germinoma and histiocytosis, have to be monitored for vigilantly. An

annual incidence of 2.4 in 10 million has been reported for adult surgical and conservative hypophysitis cases, and 1 in 9 million for surgical cases [11, 12]. Given the rarity of hypophysitis in children, and a dearth of studies reporting such cases, ascertaining the true incidence of pediatric hypophysitis is difficult.

Classifications

There have been five histologic types of hypophysitis described to date: (1) lymphocytic, (2) granulomatous, (3) xanthomatous, (4) IgG4-related, and (5) necrotizing. Of these five sub-types, lymphocytic is the most common in children, with the latter four rarely reported in children. Adult lymphocytic hypophysitis typically occurs in adult females, associated with pregnancy or autoimmune disorders such as Hashimoto's thyroiditis, Graves' disease, type I diabetes, and systemic lupus erythematosus. In children, no gender predisposition has been established [6]. Whether or not these autoimmune conditions put a child at greater risk for hypophysitis has not yet been determined.

Difference from Adults

In children, symptoms of diabetes insipidus and signs of growth hormone deficiency (GHD) are typically the most common presenting complaints or concerns, both prior to hypophysitis diagnosis and any surgical procedures or interventions [6, 13]. While many adults with hypophysitis often report to visual disturbances and headaches, this is seldom seen in the pediatric population [6]. Many of the adults described in earlier studies suffered from partial or panhypopituitarism at some point prior to surgical interventions, including adrenocorticotrophic hormone (ACTH), gonadotropin (luteinizing and follicle-stimulating hormones), and thyrotropin (TSH) deficiencies [2, 6]. Symptoms of neurohypophysis dysfunction (polydipsia and polyuria) and permanent diabetes insipidus were less seldom seen, with the first case not reported until 1991 [14]. Growth hormone deficiency occurs less often in

adults. This has led some authors to speculate that anterior pituitary hormone deficiencies (APHDs) develop in reverse order in hypophysitis when compared to the timeline of deficiencies seen in pituitary adenomas (ACTH and TSH deficiencies first in hypophysitis, followed by GH and gonadotropin deficiencies) [11]. Total hypophysectomies performed on adults with hypophysitis resulted in permanent hypopituitarism for most; however, several who underwent partial hypophysectomies continued to have hypopituitarism if they had significant pre-operative pituitary deficiencies [2, 15]. This would suggest that ongoing pituitary inflammation develops over time in subjects with hypophysitis, both pre-operatively and post-operatively, regardless of the surgical pituitary procedure they undergo. Children are therefore likely at a greater hypopituitarism risk post-surgical interventions, particularly those with one or more APHDs at the time of initial presentation.

Laboratory and Imaging Studies

A stepwise approach should be taken in pediatric hypophysitis investigations, with a goal to promptly and definitively establish the diagnosis, combining the utility of clinical assessment, and laboratory and imaging studies, prior to biopsy. Anterior pituitary hormone levels should be analyzed first, along with serum and urine osmolality. The timing of pituitary MRI with and without contrast is often done concomitantly or after initial blood and urine tests. Tumor markers (AFP, β-hCG) and angiotensin-converting enzyme (ACE) level can be drawn next, along with complete blood count, metabolic panel, erythrocyte sedimentation rate, and C-reactive protein. Skeletal survey, or cranial X-ray, should be obtained to rule out extra-cranial lesions, seen typically in LCH. Serologic studies for syphilis, tuberculosis-specific testing, and bacterial and fungal cultures can also be considered [13]. Upon collaboration with Neuro-Oncology specialists, bone marrow aspirate can be considered as well.

MR imaging at the time of preliminary workup is often beneficial and sometimes diagnostic. One large-scale prospective study

of children and young adults in Italy showed a yield of 28% of etiologic diagnosis in 85 patients with central diabetes insipidus [16]. Pituitary stalk thickening and enlargement has been shown to be the hallmark of hypophysitis imaging [8, 14, 17, 18]. A marked contrast enhancement of the hypophysitis is also typically seen, as well as an area of ring-like enhancement, in line with central necrosis [19, 20]. Normal-sized or slightly enlarged pituitary fossa is also often observed [18, 21, 22].

Histologic Findings

Many of the first adult subjects described were noted to have pituitary glands depicted as unusually firm. Lymphocytic infiltration was often noted on adenohypophysis microscopy, along with a small number of plasma cells, and varying degrees of edema and fibrosis [2]. In children, lymphoid follicles with coinciding plasma cells are the characteristic histologic finding in lymphocytic hypophysitis, throughout part of, or the entire, pituitary gland. Eosinophils, neutrophils, and macrophages are occasionally observed. Fibrosis typically replaces normal pituitary tissue [23]. Current literature on adult lymphocytic hypophysitis cases has shown two entities, both demonstrating a preponderance for T lymphocytes over B lymphocytes [24, 25]. In the first pattern, Th17+ lymphocytes are found in greater numbers than T reg cells, with pituitary infiltration characterized by higher numbers of macrophages, monocytes, granulocytes, and natural killer cells. CD20+ B cell production of lymphocytes is seen in the second entity, surrounded by CD3+ T cells and numerous T reg cells, taking on a lymphoid tissue pattern similar to the types seen in the immune tolerant phase of chronic infections [25].

Natural History

The natural history of this condition in children is often unpredictable: sometimes with spontaneous recovery and complete resolution of clinical, laboratory, and radiological abnormalities; and

other cases resulting in permanent hypopituitarism with or without neurologic impairment. It had previously been suggested that the pituitary typically enlarges with inflammation and edema early in the course. This stage can be subclinical for some individuals, while others might suffer from mass-effect symptoms or partial APHDs. Fibrosis then occurs as previous pituitary tissue atrophies, with resolution of pituitary growth or mass and subsequent hypopituitarism. However, some regain pituitary function, suggesting that certain individuals with prior symptoms of pituitary deficiencies suffered compression of surrounding pituitary tissue from their respective inflammatory lesion [2].

Differential

The differential for those with suspected hypophysitis includes: primary hypophysitis, germinoma, histiocytosis (Langerhans, and non-Langerhans), lymphoma, craniopharyngiomas, pituitary adenomas, other tumors, metastases, medications, sarcoidosis, abscesses, syphilis, Tuberculosis, fungal, viral, and bacterial infections (e.g., group B streptococcus, *Haemophilus influenza*). New onset diabetes insipidus with or without pituitary stalk thickening is generally the presenting symptom within the pediatric age group. As the germinomas and histiocytosis can progress over time, an early diagnostic certainty of hypophysitis is not always straightforward and is often a diagnosis of exclusion over time. Children should be followed closely for several years as a germinoma can be diagnosed up to 3 years after initial hypophysitis diagnosis, and sometimes even after longer periods, particularly those in the prepubertal age range [6, 26]. Pituitary stalk biopsies are typically reserved for those with progressive or worsening stalk thickening, evolving APHDs, or increased intracranial pressure or optic chiasm compression (see Chap. 4) [26–30].

Preliminary investigations to help exclude germinoma should include serum and CSF AFP and β-hCG analyses. Serum and CSF ACE levels should also be considered to rule out sarcoidosis. Pituitary MRI findings seen on germinoma and LCH can be unique among children, with the former group showing a more

proximal thickening, and the latter demonstrating a central thickening [31, 32]. Of those children presenting with diabetes insipidus, the exact time to oncologic diagnosis varies: germinoma diagnosis within the first 1–18 months, and an LCH diagnosis typically within the first through twelfth months, but sometimes not until several years later [27, 33]. Pituitary stalk biopsy is often the gold standard in differentiating the conditions, although germinomas can show lymphocytic infiltrate with local inflammation, without a visible pituitary mass, making the diagnosis more challenging [34].

Treatment

Pituitary hormone replacement is the mainstay of treatment for children in both the acute and chronic phases of hypopituitarism secondary to hypophysitis. As mentioned previously, surgical exploration is reserved with those manifesting signs of optic nerve compression or increased intracranial pressure. Corticosteroids have been used for treatment at some adult centers with mixed results. A recurrence of symptoms while on corticosteroid therapy, or during a taper, has also been reported [14, 19, 35–37]. Since the inflammatory process is typically self-limited in hypophysitis, corticosteroids are unlikely going to provide any curative benefit. The treatment benefits of corticosteroid therapy in children with hypophysitis outweighs the risks has not been proven to date.

Immunosuppressants (azathioprine, methotrexate, and cyclosporine) have been used in several adult cases of corticosteroid-resistant hypophysitis, but their long-term benefits and effectiveness have yet to be fully studied [7]. Certain immunotherapies are now being trialed in adults, including infliximab and rituximab treatments, as well as stereotactic radiosurgery and fractionated radiotherapy in select patients with corticosteroid-resistant cases [7, 38, 39]. These novel treatments are still reserved for select adults with challenging hypophysitis cases and are not yet standard of care in children.

Utility of Autoantibodies

The usefulness of antipituitary and antihypothalamus antibodies (APA, AHA) is still disputed in light of conflicting results obtained with varying laboratory assays, and low sensitivity and specificity [10, 40–42]. The timing of APA and AHA measurement may also play a role in their utility as they are unlikely to be produced after pituitary gland destruction secondary to an autoimmune attack [23]. Positive APAs can be found in healthy subjects as well, and other pituitary disorders, such as pituitary adenomas, Sheehan's syndrome, and empty sella syndrome [10, 23, 40]. Lastly, the pathogenic role of these antibodies has not been studied extensively in children with idiopathic hypopituitarism [43, 44].

Imaging Findings Over Time

Pituitary stalk thickening is the classic finding in pediatric hypophysitis. The precise timing of onset, persistence, and resolution of this finding on serial MRI scans has not been well defined. One retrospective study in Belgium looked at nine children, ages 3–14, over a 15-year time span, who initially presented with signs of diabetes insipidus and pituitary stalk thickening on imaging, with subsequent MRI studies. The stalk thickening resolved in 6, regressed in 2, and persisted in 1 over a mean follow-up of 5.4 (1.5–15) years, with a change in stalk thickness defined by at least 20% variation on larger axis on two consecutive examinations [45]. An earlier retrospective pediatric study from 2000 looked at 79 subjects with central diabetes insipidus. Fifty percent of these subjects had idiopathic DI, and the authors suggested these children did not have hypophysitis given their young age, presence of APHDs, and progressive stalk thickening over time. The remainder had intracranial tumor (23%), LCH (15%), familial disease (6%), skull fracture (3%), and autoimmune polyendocrinopathy (1%). Twenty-nine of these 79 subjects demonstrated pituitary stalk thickening at some point on MRI. Six of these showed normalization of stalk size (median time span 1.3, range 1.0–

5.7 years), one with a decrease in thickness size (over 2.1 years of follow up), seven with further thickening (median 1.6, range 0.8–10.3 years), and four with new onset thickening (median 0.8, range 0.2–3.0 years) [46].

MRI studies can also sometimes provide more information regarding ongoing tumor development, and prospective anterior pituitary hormone deficiency (APHD) risks. It has been proposed that increased anterior pituitary size on surveillance MRI screening more strongly supports the diagnosis of neoplastic and infiltrative disorders (e.g., germinoma, histiocytosis), while reduction in anterior pituitary size supports a hypophysitis diagnosis [26]. For those subjects in the 2000 retrospective review with idiopathic DI, there was a statistically significant greater risk of APHD development with a smaller than expected anterior pituitary on MRI [46].

The precise timing of pituitary MRI surveillance has not been clearly defined for children with suspected hypophysitis based on diabetes insipidus diagnosis and imaging studies. Some groups advocate for every 3 months early on, while others recommend every 6 months during the first 2 years of diagnosis, and then yearly for the next 3 years [26]. More studies are needed to gain the necessary clinical information on how to best follow children with pituitary stalk thickening and suspected hypophysitis. Most institutions with pituitary centers follow these children 2–4 times annually during the initial years of presentation.

Anterior Pituitary Hormone Deficiency (APHD) Over Time

With regard to the development of anterior pituitary hormone deficiencies (APHDs) over time, studies have shown conflicting results. The retrospective Belgian study looking at 9 children with DI and pituitary stalk thickening at presentation demonstrated one subject with an APHD (central hypothyroidism) at DI onset, with only one patient developing APHDs over the mean follow-up of 5.4 years, with subsequent resolution of stalk thickening (and it is not explicitly stated if the patient with hypopituitarism was the

one with central hypothyroidism at onset). DI remained in all subjects [45].

Of the 79 pediatric subjects with central diabetes insipidus analyzed in the 2000 retrospective study, 48 displayed anterior pituitary hormone deficiencies (APHDs) with median onset of 0.6 (range 0.1–18.0) years after DI diagnosis, with GH deficiency being the most common, followed by TSH, gonadotropin, and ACTH deficiencies. Of the idiopathic DI patients in this study, 49% developed APHDs, with a median onset of first deficiency at 0.6 (range 0.1–18) years after DI diagnosis, and the median onset of final deficiency at 7.7 (range 0.1–18) years. Growth hormone deficiency was the most common finding. Seventy-five percent of the patients with LCH developed APHDs with the median onset of 3.5 (range 0.1–6.0) years after DI diagnosis. The mean estimated probability of developing one anterior pituitary hormone deficit within 6 years of DI diagnosis was 81% in LCH patients and 49% in those with idiopathic DI, with no difference of developing additional deficiencies between the two groups. The study further explores the association of stalk thickening with the development of APHD between the LCH and idiopathic DI groups. Seventeen of the eighteen idiopathic DI patients with thickened stalk developed APHDs, while only 2 of the 19 idiopathic cases without stalk thickening developed APHDs. The risk of APHDs in LCH patients was independent of the pituitary stalk size [46]. Demonstration of the precise timing and definitive risk of single or multiple APHDs in children with hypophysitis has yet to be studied in depth.

Conclusion

Lymphocytic hypophysitis is an uncommon disorder in children but carries a significant clinical risk of hypopituitarism. There are differences in both clinical presentation and laboratory findings between adults and children, and the approach to the differential also requires special consideration in children. Recognizing the signs of this disorder and establishing a thorough differential with appropriate preliminary investigations is essential prior to the

gold standard of pituitary biopsy. Frequent follow-up and MRI surveillance is needed in children, with prompt attention to MRI changes. Endocrinologic follow-up is necessary as anterior pituitary hormone deficits are often already occurring at presentation in some children or develop over time. Further studies of hypophysitis are needed to devise a more thorough clinical guideline for the pediatric population.

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Germ Cell Tumors

6

Kavita Desai and Michael J. Fisher

Key Clinical Concepts

- Diabetes insipidus can be present for months to years prior to definitive diagnosis of a germ cell tumor mandating serial follow-up with MRI and tumor markers.
- The diagnosis and management of germ cell tumors requires a multidisciplinary approach.
- Germ cell tumors are divided into two major subgroups: germinomas and nongerminomatous germ cell tumors (NGGCT).
- The treatment for germ cell tumor subtypes differs and remains a topic of investigation with the goal of maximizing overall survival while limiting the long-term consequences of treatment.

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C. A. Alter (ed.), *Diabetes Insipidus in Children*,
https://doi.org/10.1007/978-3-030-83248-3_6

Case Presentation #1

A 12-year-old male was referred to the pediatric endocrinologist due to a four-month history of polyuria, polydipsia, enuresis, fatigue, and loss of 10 pounds over 8 months. Just prior to presentation, he had new onset of headaches occurring late in the day and not awakening him at night. He denied visual disturbance, abdominal pain, constipation, dry skin, or galactorrhea. He recently presented to his primary care physician with rash and was started on doxycycline for Lyme disease. His growth rate had slowed over the last 2 years; otherwise, his physical exam at presentation was unremarkable. His case presentation was concerning for a diabetes insipidus (DI) and central hypothyroidism. The initial endocrinology work-up demonstrated a low free T4 (0.67 ng/dL), elevated prolactin (37 ng/mL), and low IGF-1 (86 ng/mL) supporting the diagnosis of DI and central hypothyroidism. Given his ongoing treatment for Lyme disease, the decision was made to re-evaluate at the completion of therapy. At his follow-up visit with the endocrinologist, he was noted to have persistent polyuria and worsening polydipsia. Repeat blood work confirmed central hypothyroidism (T3 uptake 15%, free T4 0.53 ng/dL), central DI, and concern for adrenal insufficiency. The diagnosis of panhypopituitarism prompted a brain and pituitary MRI with and without contrast which revealed an absent posterior pituitary signal and a 1.4 cm solid enhancing sellar mass with suprasellar extension causing compression and elevation of the optic chiasm (Fig. 6.1).

After initiation of hormone replacement, he was referred to Neuro-oncology, Neurosurgery, and Neuro-Ophthalmology for further work-up. The neuro-ophthalmology evaluation revealed no visual acuity or visual field deficits, though there was concern for pale optic discs. Germ cell tumor markers of alpha fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG) were sent from both serum and CSF and found to be negative. CSF cytology was also normal. He underwent an endonasal biopsy of the pituitary mass by neurosurgery, and pathology confirmed a pure germinoma germ cell tumor. He was treated with proton radiation to

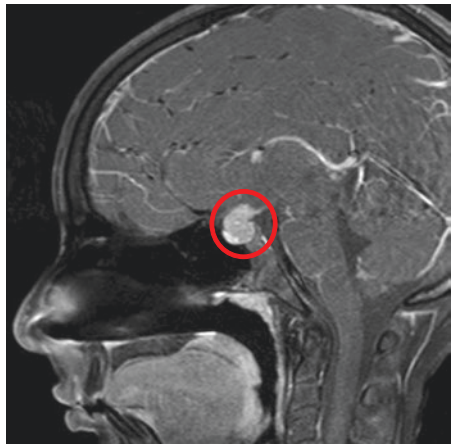

Fig. 6.1 Sagittal, post-contrast, T1-weighted MRI brain showing an enhancing suprasellar mass

the whole ventricles to a dose of 2340 cGy with an additional tumor bed boost of 2160 cGy. His course was uncomplicated, and 3 years after treatment MRI reveals no evidence of recurrent disease. He remains on growth hormone, desmopressin, thyroxine, and prednisolone to manage his panhypopituitarism.

Case Presentation #2

A 13-year-old male with no significant past medical history presented to a pediatric endocrinologist with a prolonged history of polyuria and polydipsia. For the previous 6–10 months, he was noted to drink about 200 ounces daily and would wake during the night to drink an additional 50 ounces. He also had nocturia with voiding 2–3 times every night. He reported no associated symptoms of headache, nausea, vomiting, or vision changes. He was developmentally appropriate for age, tanner 3–4 on exam, and had no focal neurological deficits. A five-hour water deprivation test confirmed the diagnosis of diabetes insipidus (DI). His anterior pituitary function was unremarkable. At the time of diagnosis, MRI of the brain and pituitary reported a normal pituitary gland in size and enhancement, no intrasellar, parasellar, or suprasellar

mass, and a missing bright spot of the posterior pituitary (Fig. 6.2). He was started on desmopressin for DI and was closely followed by the endocrinologist.

He remained stable for approximately 2 years until routine screening labs revealed new onset with hypothyroidism and adrenal insufficiency. This prompted a repeat brain and pituitary MRI which demonstrated new thickening of the pituitary stalk (Fig. 6.2). He was referred to neurosurgery and neuro-oncology for further evaluation. Tumor markers (AFP and β-HCG) were obtained and elevated in both the serum and CSF (Table 6.1).

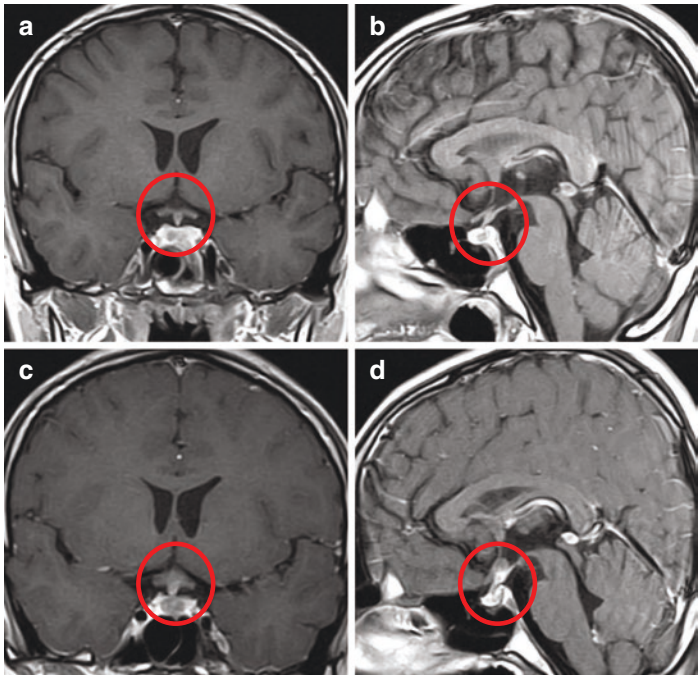

Fig. 6.2 Initial MRI of the pituitary and pituitary stalk: (**a**) coronal, post-contrast, T1-weighted image; (**b**) sagittal, post-contrast, T1-weighted image. Repeat imaging performed two years after initial MRI showing interval thickening of the pituitary stalk: (**c**) coronal, post-contrast, T1-weighted image; (**d**) sagittal, post-contrast, T1-weighted image

Table 6.1 Tumor Markers in serum and CSF

Tumor Marker	Level
Serum β-HCG	50.9 ↑
Serum AFP	8.3 ↑
CSF β-HCG	78 ↑
CSF AFP	<1

Abbreviations: *CSF* cerebrospinal fluid, *β-HCG* β-human chorionic gonadotropin, *AFP* alpha fetoprotein

Staging work-up, including MRI spine and CSF cytology, was negative for metastatic disease. The diagnosis of nongerminomatous germ cell tumor (NGGCT) was made based on the elevated tumor markers, thus eliminating the need for biopsy. He was treated with six cycles of chemotherapy followed by proton radiation to the craniospinal axis to a dose of 3600 cGy with an additional boost to the tumor bed of 1800 cGy. Since treatment, he has remained in remission and continues on endocrine replacement therapy with desmopressin, levothyroxine, and hydrocortisone.

Discussion

Central nervous system germ cell tumors (GCT) are rare brain tumors that typically occur in adolescents and young adults. GCTs represent approximately 2–3% of all pediatric CNS tumors in the United States, but 8–15% in far east Asia. The cause of this geographic variation of frequency remains unknown. The peak incidence of GCTs occurs during adolescence and is seen more often in males than females. It is proposed that the abnormal migration of primitive germ cells during early embryogenesis leads to the development of tumors in the midline, most commonly in the pineal region followed by the suprasellar region [1]. Pineal GCT typically present with signs of raised intracranial pressure (ICP) secondary to obstruction of the third ventricle. In contrast, tumors arising in the suprasellar region have a more varied presentation including endocrinopathies, visual deficits, and less commonly symptoms of raised ICP [2]. While DI is the most common endo-

crinopathy encountered with GCTs, tumors can infiltrate the anterior pituitary causing hypothyroidism, adrenal insufficiency, and growth hormone deficiency. Larger tumors in the suprasellar region can compress the optic pathway and result in compromised visual fields and acuity.

Diabetes insipidus (DI) is frequently the presenting sign of a pituitary mass or stalk thickening. The differential diagnosis for pituitary stalk thickening in children is broad and includes GCTs, Langerhans cell histiocytosis, lymphocytic hypophysitis, craniopharyngiomas, and pituitary adenomas. It is not uncommon for patients to have a long prodrome of DI symptoms prior to the appearance of a pituitary mass or stalk thickening on brain imaging [3]. Several studies have shown that continued MRI surveillance of pituitary lesions led to the discovery of germ cell tumors even several years after initial presentation with DI (see Case 2) [4–7]. There is not a clear consensus on the ideal interval for follow-up imaging of pituitary lesions/stalk thickness, but it is clearly necessary to ensure early diagnosis of neoplastic etiology and adequate treatment [4].

Germ cell tumors can be subclassified into germinomas and nongerminomatous germ cell tumors (NGGCT) as outlined in Table 6.2 [1–3]. NGGCT can be further divided based on histology into yolk sac tumors, choriocarcinoma, embryonal carcinoma, and teratomas [8]. Germinomas are histologically identical to testicular seminomas with neoplastic transformation of primordial germ cells and lymphocytic infiltration. These tumors can produce low levels of β-HCG if they contain syncytiotrophoblast ele-

Table 6.2 Subclassification of Germ Cell Tumors

Germinoma	Pure Germinoma
Non-Germinomatous Germ Cell Tumors	Yolk Sac Tumors Embryonal Carcinomas Choriocarcinomas Teratomas Mature teratomas Immature teratomas Teratoma with malignant transformation
Mixed Germ Cell Tumors	

ments [1, 3]. Yolk sac tumors are endodermal sinus tumors that are epithelial-derived and produce high levels of AFP. Embryonal carcinomas are also epithelial-derived tumors but are strongly positive for cytokeratin and much less likely to produce tumor markers. Choriocarcinomas are trophoblastic tumors with cytotrophoblastic elements and syncytiotrophoblastic giant cells producing high levels of β-HCG, often above >1000 IU/L [1, 8, 9]. Teratomas histologically differentiate into all three embryonic germ layers. Mature teratomas are fully differentiated in all three layers, whereas immature teratomas have one or two mature layers and typically have stromal elements or neuroectodermal cells. Last, mixed germ cell tumors occur and have components of more than one GCT subtype.

When a GCT is being considered, initial evaluation should include neuro-oncology consult, MRI brain with pituitary cuts, MRI of the entire spine, measurement of tumor markers in both the serum and CSF, evaluation of CSF cytology, and at times biopsy. On MRI, GCTs are typically solid masses, isointense on T1 sequences, hyperintense on T2/Flair sequences, and enhance following gadolinium contrast. Cysts can be present and are associated more often with NGGCT [1]. Though modern imaging techniques can identify a mass, it cannot definitively distinguish germinomas from NGGCTs. Thus, evaluation of serum and CSF tumor markers, AFP and β-HCG, are necessary and may aid in diagnosis (Table 6.3) [1, 9]. AFP and β-HCG are normally pro-

Table 6.3 Presence of tumors markers in subtypes of GCTs

Tumor	AFP	β-HCG
Germinomas	–	+/–
Yolk Sac Tumors	++	–
Embryonal Carcinomas	+/–	+/–
Choriocarcinomas	–	++
Teratoma	+/–	–
Mixed Germ Cell Tumors	+/–	+/–

Abbreviations: GCTs germ cell tumors, *β-HCG* β-human chorionic gonadotropin, *AFP* alpha fetoprotein

duced during embryogenesis from the yolk sac endoderm and syncytiotrophoblasts, respectively. Elevation of AFP in CSF or serum is diagnostic of a NGGCT, and obviates the need for a diagnostic biopsy. This is most common with yolk sac tumors but occasionally seen in immature teratoma and embryonal carcinoma [10]. β-HCG is classically elevated in choriocarcinomas, but also to a lesser extent in germinomas with a syncytiotrophoblast component [1, 2, 9]; thus, depending on the level of β-HCG, biopsy may be needed to differentiate between germinoma and NGGCT. It is important to measure tumor markers in both the serum and CSF, as levels may be discordant and can be higher in the serum compared to CSF [2]. After diagnosis, tumor markers should also be monitored during treatment to evaluate for response. While it is agreed that measuring tumor markers is required for work-up, the diagnostic threshold and prognostic implication of tumor markers vary between the North American, European, and Japanese oncology cooperative groups [10]. For staging, positive spine MRI or CSF cytology confirms metastatic disease.

When a definitive diagnosis cannot be reached with tumor markers alone, tumor biopsy may be indicated. One major challenge is when to pursue biopsy, particularly for patients with pituitary stalk thickening in the setting of negative tumor markers. Robison et al. noted that of children with pituitary stalk thickening, those with DI or increase in stalk thickness on serial imaging were more likely to have a neoplastic process. Additionally, among those with DI, the co-occurrence or development of anterior pituitary deficiency was a risk factor for tumor [11]. Thus, it is reasonable for patients with DI and the development of anterior pituitary deficiency or increase in stalk thickening on serial imaging to be considered for diagnostic biopsy [11, 12]. With the broad spectrum of presentation and step-wise approach to diagnosing germ cell tumors, patients require a multi-disciplinary approach with involvement of neuro-oncology, neuro-ophthalmology, neurosurgery, radiation oncology, and endocrinology for diagnosis and management.

Management

Both the prognosis and treatment approach to GCTs differ between germinomas and NGGCTs. The role of surgery has been limited in the management of GCTs; it is used primarily for biopsy or to alleviate intracranial pressure secondary to obstructive hydrocephalus. The major exception is the management of mature teratomas, which require surgical resection for cure, as these tumors are not responsive to chemotherapy or radiation therapy [1–3].

Germinomas are exquisitely sensitive to radiation therapy and chemotherapy, and thus do not require surgical resection given the risk of associated complications. Historically, localized germinomas were treated with craniospinal radiation with a boost to the tumor bed with excellent overall survival (OS) and event-free survival (EFS); however, this came at the expense of long-term consequences of radiation therapy including secondary malignancy, endocrinopathies, and neuropsychological dysfunction [13–16]. Modern treatment approaches are focused on maintaining excellent OS while minimizing the long-term debilitating consequences of radiation therapy [10]. Unfortunately, therapeutic approaches that attempted to eliminate the use of radiation or reduce the treatment field to focal radiation with chemotherapy-only treatment plans resulted in unacceptably high recurrence rates [17–20]. The current treatment approach to localized germinomas includes whole ventricular radiation therapy with a focal tumor boost, and is associated with an EFS and OS exceeding 90% [9, 14, 21]. Ongoing studies are exploring the use of neoadjuvant chemotherapy to further reduce the dose of radiation while maintaining adequate tumor control [1, 9]. Metastatic germinomas require craniospinal irradiation with focal boosts to primary and metastatic sites [18].

NGGCTs are not as radiosensitive and require more aggressive therapy for disease control. The use of radiotherapy or chemotherapy alone is associated with poor outcomes with survival rates ranging from 20% to 50% [2, 17, 22]. Current treatment uses a

combined approach with neoadjuvant chemotherapy followed by radiation therapy with OS ranging from 75% to 93% depending on the various treatment protocols and the presence of metastases [23–26]. The utilization of surgery is more often reserved for the end of induction chemotherapy given that studies reveal patients with complete remission prior to radiation have improved outcomes [9, 24, 25]. There is continued discussion and attempts to reduce the volume and dose of radiation therapy for localized NGGCTs [25, 26]; however, a recent trial from the Children's Oncology Group, using a chemotherapy response-based approach to reduce the volume and dose of radiation therapy, closed early due to an increase in spinal cord recurrences [27]. While continued attempts to minimize the radiation dose and field for NGGCT are ongoing, at present, it is clear that a multimodal treatment approach is necessary for better overall survival in patients with NGGCTs.

While outcomes for patients with GCTs are improving, the consequences of surgery, chemotherapy and radiation therapy are not benign. Patients often suffer from permanent endocrinopathies requiring lifelong hormone replacement secondary to tumor infiltration, surgical intervention, and/or radiation therapy damaging the pituitary [2, 25]. During treatment, patients with DI require close monitoring of their fluid status and sodium levels due to the hyper-hydration needed with the use of certain chemotherapeutic agents [25]. Craniospinal and even focal radiation therapy can have a significant impact on long-term neurocognitive function leading to a compromised quality of life [9, 16, 28]. Moreover, the long-term risk of secondary cancer exists for both radiation therapy and chemotherapy. There clearly remains an ongoing need to optimize treatment for the best overall survival while limiting the consequences of therapy for GCTs. Fortunately, recent studies characterizing the molecular alterations in GCTs have identified frequent alterations in the *KIT*, *CBL*, and *RAS*, particularly in germinomas, with less frequent alterations noted in the PI3K/mTOR signaling pathway, raising the future prospect of targeted treatment approaches for GCT [29–32].

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The Gist of a Rathke's Cleft Cyst

7

Madeline McKean and Craig A. Alter

Case

A 9-year-old boy presented to pediatric endocrinology with a concern of poor growth, but not short stature. He had no systemic complaints of headaches, visual changes, or abdominal pain. He had no skin rash. On further questioning, the family revealed that he had increased thirst and urination for at least 3 years; though this was not their focus for the consultation. At age 6 years, however, they had visited their pediatrician because of the high thirst and urination. At that age, he had nocturia, several times per night. A laboratory investigation ruled out diabetes mellitus with a blood glucose 80 mg/dL (5 mmol/L) and the urine had a specific gravity 1.004. After a few months, the family felt the excessive thirst and urination improved, but his thirst was much higher than that of any of his three siblings.

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C. A. Alter (ed.), *Diabetes Insipidus in Children*,
https://doi.org/10.1007/978-3-030-83248-3_7

In terms of his growth, the primary care data showed from ages 6 to 9 the height percentiles decreased from the 55th to the 22nd percentile. His BMI curve had a similar decrease (Fig. 7.1). Review of system showed he had significant fatigue for the last 2–3 years. He had parents with a mid-parental height at the 93rd percentile. His examination was notable for no skin rash (to suggest Langerhans Cell Histiocytosis). He had normal visual fields to confrontation. He was Tanner Stage I in pubertal development with normally descended 2 ml testicles.

Laboratory studies showed the following:

- Sodium 141 mEq/L
- Free T4 0.42 ng/dL (0.8–1.8)
- TSH 5.99 uIU/ml (0.6–4.8)
- IGF-1 37 ng/ml (61–252)

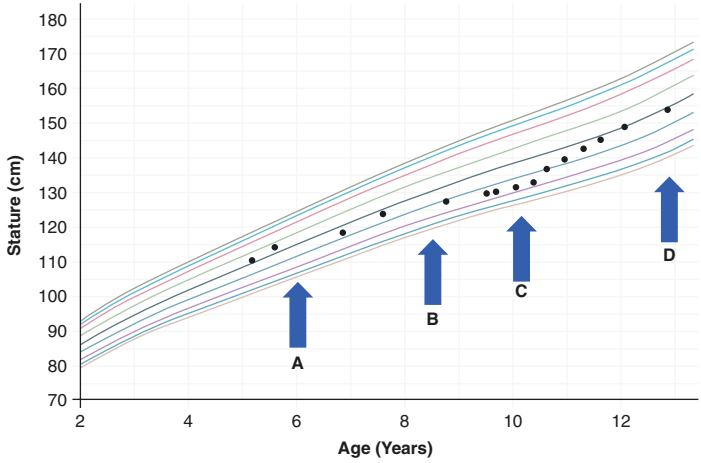

Fig. 7.1 Growth chart of our patient. Arrow (**a**) represents when he presented at age 6 years with increased thirst and urination to his pediatrician. Arrow (**b**) is 3 years later when he presented at age 9 to our pediatric endocrine practice. Arrow (**c**) shows when we started growth hormone therapy. Arrow (**d**) demonstrates the point 3 years later when he returned to his original height percentile

Laboratory studies drawn after 10 h of home fasting:

- Sodium 141 mEq/L
- T4 (total) 3.6 ug/dL (4.5–12)
- T3 Resin Uptake 17% (24–33)
- Free Thyroxine Index 0.6 (1.2–4.9)
- Free-T4 0.42 ng/dL (0.8–1.8)
- TSH 7.36 uIU/ml (0.6–4.8)
- Urine 54 mOsm/kg
- 8 am cortisol 11 ug/dL
- Prolactin 54 ng/ml (<15 ng/ml)

Clinical Impression after Initial Results and Consultation

This was a 9-year-old male with poor growth, but not short stature, although the height was discordant for the mid-parental height. He had polydipsia, polyuria, and fatigue for a three-year duration. While a water deprivation test was considered, the laboratory results suggested he had probable growth hormone deficiency (low IGF-1) and central hypothyroidism (markedly low free-T4 but only trace elevation of TSH). His cortisol level was normal. Gonadotropins and testosterone were not ordered as he was not yet of pubertal age. Based on the multiple pituitary hormone deficiencies, a clinical diagnosis of central diabetes insipidus was made and pituitary/hypothalamic imaging was ordered.

It is notable that at the initial diagnosis of hypothyroidism, his free-T4 (measured by automated immunoassay) showed markedly low levels (confirmed after three assessments) of 0.42–0.45 ng/dL (0.8–1.8). Simultaneously, his TSH, shown above, was mildly elevated to 7.36 uIU/ml (0.6–4.8). Although often in central hypothyroidism the TSH is low, one can see mild elevation in TSH as seen in this case. The authors felt that if this were primary hypothyroidism, the TSH would have been markedly elevated. That observation coupled with the symptoms of diabetes

insipidus and poor growth (and low IGF-1) led to the MRI without a water deprivation study.

The MRI showed an 8 × 8 × 11 mm, mildly heterogeneous T1 hyperintense mass above the pituitary. The mass abutted the optic chiasm with no overt compression. The posterior pituitary bright spot was not visualized. Given the appearance and location, the neuroradiologist's findings were concerning for craniopharyngioma or a Rathke's cleft cyst (RCC) with proteinaceous material. Another diagnosis considered, though less likely, was an exophytic pituitary adenoma with some hemorrhage. A non-contrast CT was requested to search for the presence of calcifications which would support a diagnosis of a craniopharyngioma. No calcifications were present.

The patient had consultations with neuro-oncology and neurosurgery, as well as endocrinology. The diagnosis was considered to be most likely a RCC, though a craniopharyngioma was not fully excluded. The imaging did not suggest a germ cell tumor, though serum alpha-feto protein (AFP) and human chorionic gonadotropin (HCG) were obtained and were normal. Neuro-ophthalmologic consultation revealed no concerns of optic nerve damage.

Case-specific questions posed at this point near the initial diagnosis of the RCC were:

1. Should a neurosurgeon biopsy and/or resect the cyst to rule out other diagnoses such as a craniopharyngioma?
2. If we followed the cyst conservatively, how often should we repeat the MRI?
3. Assuming he has a RCC, what will be the natural course of the cyst?
4. What is the presentation of RCC?
5. How can one differentiate a RCC from a pars intermedia cyst?
6. How should we address each pituitary hormone axis?

In terms of growth, his growth rate remained low at 4.5 cm/year for the first 6 months of therapy with levothyroxine and des-

mopressin. After discussion with all consultants involved, and after the MRI showed lack of progression of the mass, growth hormone was initiated about a year after the diagnosis. Serial every 3-month MRI scans were obtained to ensure there was no progression in the size of the mass on GH therapy.

Over the 4 years since diagnosis of the RCC, the size of the mass has steadily decreased until it was no longer visible (Figs. 7.2 and 7.3). Clinically, his course by hormone system is shown below:

(a) Thyroid: his dose of levothyroxine steadily increased to 100 mcg daily
(b) Growth: he continues on growth hormone with height increasing from the 13th percentile to the 50th percentile
(c) Vasopressin: he is maintained comfortably on desmopressin, 100 mcg twice daily by mouth with a rare extra 50 mcg as needed
(d) Adrenal: his morning cortisol levels continue to be robust at 18 mcg/dL on no daily nor stress dosing
(e) Puberty: At age 13 2/12, he is showing Tanner 2 pubic hair with testicular volume 5 ml bilaterally. His last testosterone

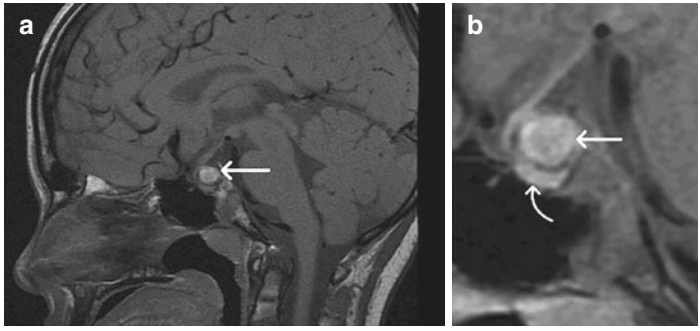

Fig. 7.2 MRI at presentation. MRI at presentation showing unenhanced T1 sagittal image (**a**) and post-contrast T1 magnified image (**b**) of the pituitary gland with bright signal cyst (straight arrow) and the enhancing pituitary gland (curved arrow). (Courtesy of Dr. Karuna Shekdar)

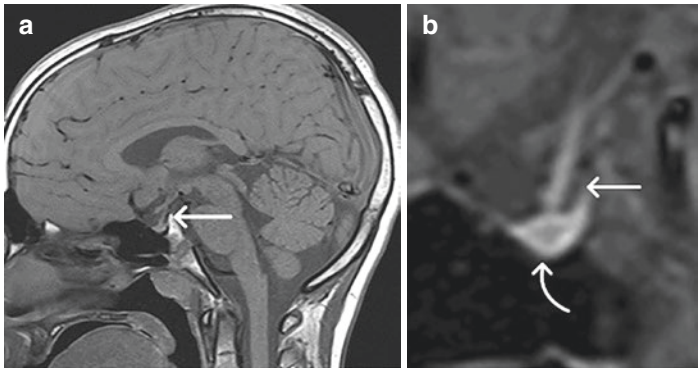

Fig. 7.3 MRI follow up after 40 months. MRI at follow up 40 months after diagnosis (**a**) unenhanced T1 sagittal image and post-contrast T1 magnified image (**b**) of the pituitary gland with complete resolution of the previously seen bright signal cyst (straight arrow) and the normal enhancing pituitary gland (curved arrow). (Courtesy of Dr. Karuna Shekdar)

was 18 ng/dL with LH 1.2 mIU/ml, FSH 0.558 mIU/ml He is on no androgen replacement therapy, but his pubertal status will be followed

(f) Prolactin: his levels have decreased from 54 ng/ml at diagnosis to 13 ng/ml, 40 months later

MRI studies were obtained and showed progressive decrease in the size of the cyst which paralleled the decrease in prolactin (Figs. 7.2 and 7.3). The posterior pituitary bright spot remained absent on all scans.

Rathke's pouch is an upward growth of stomodeal ectoderm toward the neurohypophysis and represents the precursor to the anterior lobe. RCCs arise in the pars intermedia of the pituitary gland between the adenohypophysis and the neurohypophysis from the embryonic remnants of the Rathke's pouch [1, 2].

The walls of RCC are made up of epithelial cells and their internal fluid contains a high protein concentration [1, 2]. The Rathke's pouch is formed during the 3rd or 4th week of embryonic development and is later reduced to a cleft between the anterior and intermediate lobes of the pituitary gland that later

regresses; however, the failure to reduce the cleft and persistent enlargement leads to a symptomatic RCC [3]. A small cyst typically 3 mm or smaller is commonly found between the anterior and posterior lobes of the pituitary and is termed a pars intermedia cyst. A pars intermedia cyst is found in 13–33% on routine autopsies [4, 5]. When found incidentally, or during a workup for GH deficiency, it typically requires no repeat scans and follow-up. However, when the cyst is larger, the term Rathke's cleft cyst (RCC) is used.

RCC can exert pressure on the pituitary gland, hypothalamus, and optic nerve and chiasm [6] and become symptomatic. The clinical manifestations of a symptomatic RCC are headache, visual disturbance, anterior pituitary dysfunction, and diabetes insipidus (DI) [3, 7]. Rarely, one can present with precocious puberty, aseptic meningitis, and syndrome of inappropriate antidiuretic hormone (SIADH). Hyperprolactinemia has been repeatedly cited as the most frequent hormonal disturbance.

It is important to distinguish RCC from a cystic craniopharyngioma as well as other diagnoses including germ cell tumor, epidermoid cyst, arachnoid cyst, adenoma, glioma, and granulomatous disease. The therapy for a cystic craniopharyngioma, for example, is surgical but for a RCC there are surgical and non-surgical options which will be discussed below.

A RCC can appear as a simple cyst, with imaging features similar to that of cerebrospinal fluid (CSF). When the RCC extends suprasellar, it can appear similar to an arachnoid cyst. A RCC can also appear more complex with T1 hyperintensity but typically hypointense on T2. A craniopharyngioma also appears hyperintense on T1, but hyperintense on T2. The shape is another distinguishing feature of a RCC from a craniopharyngioma. A RCC has a typical oval shape or that of a dumbbell. A cystic craniopharyngioma has a more irregular shape and tends to have a larger maximal diameter. In one study [5], the average maximal diameter of a RCC was 19.0 mm (8–33) as compared to 34.9 mm (21–54) for a cystic craniopharyngioma [1]. One of the most distinguishing features, however, is the presence of calcifications which is rare in a RCC but seen in the majority of craniopharyngiomas. It is for that reason a CT is often obtained as a CT is

superior to an MRI for detecting calcifications. Overall, the smooth shape, size, lack of contrast enhancement, and lack of calcifications favor a RCC over a craniopharyngioma.

In a retrospective study of 45 adults (mean age 45, 17–79 years), the location was purely intrasellar in 13% and 87% showed both intrasellar and suprasellar extension. The diameter was 1–2 cm in 55%, 2–3 cm in 35%, and >3 cm in 10%. The authors found that a cyst size over 2 cm or with suprasellar extension were risk factors for visual disturbances. Pure suprasellar RCC have been described in a minority of adults with RCC [8]. In another study of 11 children with RCC, 4 were suprasellar, and 7 were intra- and suprasellar. Headache was a presenting symptom in 9 of 11 [1].

In one retrospective study of 73, mostly adults with a mean age 35 (9–78), who had transsphenoidal surgery for RCC, the effect on endocrine and visual dysfunction was described. Surgery was performed on approximately 10% of those who had an evaluation for a RCC. Surgical criteria included those with endocrine dysfunction, visual impairment, or other neurological concerns other than headaches alone. After surgery, 96% of vision issues resolved and 85% had improvement in headaches. Post-operatively each of the following five groups contained 20% of patients: normalization of hypopituitarism, improved hypopituitarism, worsened hypopituitarism, unchanged hypopituitarism, and no effect in the baseline normal pituitary function. About 16% had reaccumulation of the cyst but did not require additional surgery [7].

Our patient's endocrine presentation highlighted several interesting features. He did not have short stature, but poor growth over a several year period from ages 6 to 9 years which was the original indication for the consultation. He had, on review of systems, significant fatigue as well as polydipsia with polyuria. Interestingly, he presented with a free T4 markedly low at 0.4 ng/dL, and a mildly elevated TSH 7.36 uIU/ml (0.6–4.8). In primary hypothyroidism, with that degree of hypothyroxinemia, the TSH would have been markedly elevated. He presented with a three-year history of increased thirst and urination, for which he saw his primary care physician at age 6 who ordered laboratory studies showing normal glucose and sodium. At age 9, his growth evaluation revealed diabetes insipidus, central hypothyroidism, GH

deficiency, possible adrenal insufficiency, and hyperprolactinemia. His fatigue resolved with treatment of central hypothyroidism. Therapy with desmopressin (100 mcg twice daily) was successful in treating his DI. At age 13 years, his pubertal examination and laboratory studies (testosterone 18 ng/dL) show likely a degree of central hypogonadism.

In our case, surgery was contemplated on presentation based on the size of the lesion, the uncertainty of the diagnosis, and the co-existence of both anterior and posterior pituitary disease. Those who advocated for surgery considered that while a RCC was likely, the differential diagnosis included a craniopharyngioma without calcifications and a germ cell tumor. The decision was made to observe him with periodic MRI scans. While his endocrine function showed no evidence of recovery other than the normalization of the hyperprolactinemia, his RCC decreased in size on each subsequent scan (see Table 7.1). Interestingly, the serum prolactin concentration correlated with the size of the lesion (see Fig. 7.4).

Our case demonstrates that a RCC has different characteristics than a craniopharyngioma and can possibly regress without therapy. We therefore advocate in children with a pituitary cyst suggestive of a RCC to observe over time even when there is endocrine dysfunction. However, if there is a concern of the visual access, which was not present in our patient, or evidence of other CNS manifestations, then surgery would likely be necessary. It is unclear if worsening pituitary disease alone is indication for surgery.

Table 7.1 Cyst dimensions and prolactin levels over time

Time (months)	Mass dimensions (mm^3)	Prolactin[a] (ng/mL)
0	8 × 8 × 11	54
3	8 × 8 × 10	46
7	6 × 7 × 8	35
12	4 × 5 × 6	21
17	4 × 4 × 6	16
40	Resolved	13

[a]Nearest time in proximity to scan

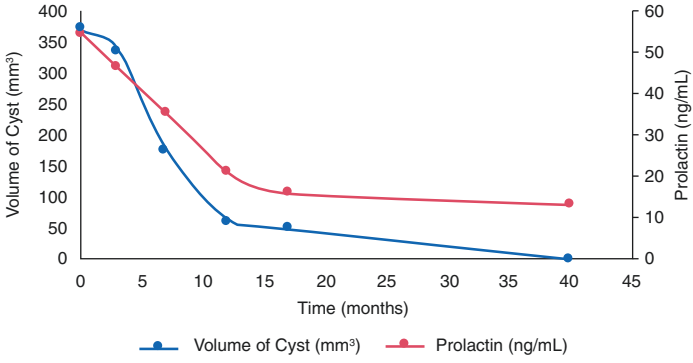

Fig. 7.4 RCC volume and prolactin serum concentration versus age

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Langerhans Cell Histiocytosis and Diabetes Insipidus

8

Chelsea Kotch and Michael D. Hogarty

Clinical Pearls and Pitfalls

- Diabetes insipidus is the most common endocrinopathy associated with LCH. Growth hormone deficiency is the second most common.
- 5-year estimated risk of pituitary involvement in LCH is ~15%.
- Serial surveillance for pituitary endocrinopathy is required for many years after completion of therapy for LCH given the risk for delayed onset of endocrinopathies despite therapy and resolution of active LCH.
- A risk factor for the development of neurodegenerative LCH is the presence of pituitary involvement.

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C. A. Alter (ed.), *Diabetes Insipidus in Children*,
https://doi.org/10.1007/978-3-030-83248-3_8

Clinical Case Presentation

Case #1

A young boy presented at 2 years of age with a limp and right leg pain noted during diaper changes. A physical exam was otherwise unremarkable. Radiographs demonstrated a lucent right proximal femur lesion. Differential diagnosis for the femur lesion included Ewing sarcoma, aneurysmal bone cyst, Langerhans cell histiocytosis (LCH), or osteomyelitis. The patient underwent a biopsy which was diagnostic for LCH, showing pleiotropic inflammatory cells with prominent histiocytes that stained positive for CD1a, CD207 (Langerin), and S-100 by immunohistochemistry. Molecular studies identified the *BRAF* V600E mutation in lesional cells. A complete skeletal radiograph series identified an additional lesion in the region of the left temporal bone. Magnetic resonance imaging (MRI) of the brain confirmed a large expansile lesion within the petrous apex of the left temporal bone with normal orbits and normal pituitary gland and stalk, including presence of the T1-bright neurohypophysis. A complete abdominal US was normal. Complete blood count (CBC), liver enzymes including GGT and synthetic functions, and serum electrolytes were all normal; C-reactive protein was elevated at 5 mg/L. There was no history of polyuria or polydipsia at the time of diagnosis and growth parameters were at the 60%ile for height and weight.

The patient was diagnosed with multi-focal (tibia and temporal) single-system (bone) LCH and was started on chemotherapy with prednisone and vinblastine. His disease was responsive to this combination and at the end of 12 months of therapy his exam, laboratory values, and skeletal imaging were normal. Two years after completion of therapy, at 5 years of age, the patient experienced nighttime enuresis and frequent urination during the day, with increased water intake. After a 14-hour at-home overnight fluid deprivation period, his mid-morning serum sodium was 144 mmol/L, serum osmolality (osm) was 297 mOsm/kg, and urine osm was 474 mOsm/kg. His symptoms of polyuria and polydipsia persisted and the patient underwent formal inpatient

water deprivation testing which again was not diagnostic of diabetes insipidus with a urine osm of 614 mOsm/kg and plasma osm of 300 mOsm/kg with serum sodium of 146 mmol/L. An MRI of the brain, however, demonstrated loss of the posterior pituitary T1-bright spot and nodular thickening of the pituitary stalk. The child was started on intranasal desmopressin with marked improvement in symptoms. At 8 years of age, the patient was noted to have slowed linear growth with height at the 10th percentile. Laboratory evaluation showed an IGF-I of 44 ng/mL (Tanner I: 59–296), IGFBP3 of 2.6 mg/L (1.6–6.5), thyroid-stimulating hormone (TSH) of 2.06 uIU/mL, and morning cortisol of 13.1 mcg/dl. The diagnosis of growth hormone deficiency was made and growth hormone replacement therapy was initiated. This case highlights the diagnosis of LCH with initially preserved pituitary function followed by delayed onset of central diabetes insipidus and then growth hormone deficiency, despite the absence of endocrinopathy at diagnosis and favorable LCH response to therapy without disease reactivation.

Case #2

A girl presented at 12 years of age with a 3-week history of worsening polyuria, polydipsia, and weight loss. While undergoing evaluation for diabetes insipidus, she was noted to have wart-like cutaneous lesions at her left wrist, which had been present over the prior 4 years. No other abnormal physical exam findings were identified. She was confirmed to have hypotonic polyuria with elevated plasma osmolality that was corrected by desmopressin, supportive of central diabetes insipidus. MRI of her brain revealed a prominent and nodular pituitary infundibular stalk, loss of the posterior pituitary T1-bright spot, and areas of T2 signal prolongation in the cerebellum. Differential diagnosis included germ cell tumor, CNS demyelinating disease, or central nervous system LCH (CNS-LCH). Serum and CSF α-fetoprotein (AFP) and β-human chorionic gonadotropin (βhCG) levels were normal. As LCH was in the differential diagnosis, a biopsy of a skin lesion was performed and demonstrated a lymphohistiocytic infiltrate at

the dermal-epidermal interface with histiocytes staining for CD1a and CD207 (Langerin) by immunohistochemistry. This confirmed the diagnosis of LCH and subsequent molecular studies identified a wild-type *BRAF* gene but an activating *MAP2K1* mutation. A complete abdominal US and skeletal survey were normal. CBC, liver enzymes including GGT and synthetic functions, serum electrolytes, and C-reactive protein were all normal. Laboratory evaluation of anterior pituitary function was unremarkable at that time. The patient was diagnosed with multisystem LCH with cutaneous and pituitary involvement (with LCH-associated DI). There was no reported change in school or athletic performance, and a detailed neurological exam was normal, including cerebellar function. Desmopressin therapy was initiated with good clinical response, return of normal weight gain, and maintained normal linear growth velocity. In addition, therapy for multisystem LCH was initiated with prednisone, vinblastine, and then clofarabine (for 12 months total) to reduce the potential for progression of pituitary disease and other LCH sequela in the CNS.

Serial MRIs of the brain showed treatment-related regression of the pituitary stalk thickening, persistence of the loss of the T1-bright spot, and increased foci of abnormal signal within white matter, basal ganglia, and internal capsules, along with progression in the cerebellar hemispheres and dorsal pons. Neurocognitive testing identified deficits in cognitive processing speed and the patient complained of headaches. Lumbar puncture showed scattered chronic inflammatory cells and proteinaceous debris with no malignant cells or oligoclonal bands identified. Monthly intravenous immunoglobulin therapy was started as an immunomodulatory therapy for CNS-LCH and imaging and clinical findings stabilized but did not improve. An inhibitor of *MAPK* signaling, trametinib, was then added to her therapy and associated with significant improvement in her headaches. These findings were consistent with neurodegenerative-LCH and this case provides an example of the potential for neurodegenerative progression in a patient with LCH and hypothalamic-pituitary system involvement as a risk factor.

Introduction

Langerhans cell histiocytosis (LCH) is caused by the aberrant function of mononuclear immune cells leading to inflammatory injury of normal tissues. It is a clinically heterogeneous disorder, and distinct disease patterns have previously been known under different names, including Hand-Schuller-Christian disease, Letterer-Siwe disease, eosinophilic granuloma, and histiocytosis X. All are now recognized as manifestations of aberrantly activated myeloid-derived dendritic cells with similarities to epidermal Langerhans cells, and are called LCH [1]. LCH has an incidence of approximately 5 cases per million children and it can present at any age, from a congenital disease to onset in childhood or adulthood, though most cases arise in children [2]. LCH presenting with bone involvement, skin involvement, or both, is most common, however, nearly any organ system can be involved. In addition, LCH has a particular tropism for the hypothalamic-pituitary axis that can manifest as a mass lesion or with inflammatory injury in the absence of a tumor. Both presentations commonly result in endocrinopathy [3].

Debate persists as to whether LCH is an inflammatory or malignant disease [1, 4–6]. LCH lesions form inflammatory granulomas, and LCH cells lack the morphological and genomic features typical of most cancer cells. However, they frequently have a somatic mutation in *BRAF* or a related mitogen-activated protein kinase (MAPK) pathway gene [7, 8]. Many cancers have such mutations, however, so do benign nevi and vascular malformations [8]. In LCH limited to one or few organ systems, the pathophysiology most reflects a dysregulated immune process and the risks to the patient are orthopedic and/or endocrine system morbidity. In multisystem LCH with risk organ involvement the pathophysiology is most similar to a myeloid cancer with the potential for lethal progression [9, 10].

Presentation, Diagnosis, Classification, and Therapy

LCH can present with a broad spectrum of symptoms reflecting involvement of diverse organ systems. The more commonly affected systems include the skeleton (80% of cases), skin (33%), and pituitary (25%). Other organs affected are the hematopoietic system (bone marrow), liver, spleen, and lungs (10–15% each), lymph nodes (5%), and the central nervous system (2–4%) [3]. In addition to a history and physical exam including close dermatologic evaluation, initial evaluations should include CBC, liver enzymes and synthetic function, electrolytes, ferritin, immunoglobulins, and coagulation studies. Imaging typically includes a skeletal survey with skull series and abdominal ultrasound. CT or MRI of the head is superior to plain radiograms to assess for craniofacial bone lesions due to the three-dimensional complexity of these structures [1–3]. Children suspected of having risk organ involvement or extensive systemic disease may benefit from whole-body PET imaging. If polyuria or polydipsia is present, morning urine specific gravity and osmolality and MRI of the brain with dedicated thin pituitary cuts should be obtained. Bone marrow biopsy with aspirate is recommended in patients with unexplained cytopenias, and endoscopy with biopsy in patients with evidence of chronic diarrhea or failure to thrive [1, 3]. The diagnosis of LCH can be suspected on the basis of clinical and radiographic features, but a histological examination of involved tissues is required for confirmation. Lesions consist of histiocytes with characteristic morphology and surface expression of CD1a and CD207 (Langerin) along with an inflammatory infiltrate with frequent eosinophils. Up to 90% of cases harbor an activating MAPK pathway mutation [8, 11].

Historically, as many as 40% of patients with LCH are left with permanent sequelae of their disease (hearing loss, endocrine, orthopedic) and up to 10% die from their disease, leading to a risk-adapted approach to therapy that has improved these outcomes [2, 3, 12]. Approximately half of all patients will present with a single bone lesion or isolated skin involvement and need little to no therapy as disease regression is the norm [3]. The remainder have mul-

tifocal or multisystem disease. Patients with multifocal bone involvement and/or multisystem disease (not involving risk organs) benefit from immunomodulatory chemotherapy to hasten resolution of inflammatory lesions, and lessen the risk for subsequent disease reactivation and organ injury, including the potential to lower the risk for pituitary endocrinopathy [13, 14]. Patients with involvement of specified risk organs (bone marrow, spleen, or liver) have a more aggressive clinical course with higher disease mortality than patients without this involvement. The backbone of therapy for these patients remains immunomodulatory chemotherapy; however, disease control often requires more intensive chemotherapy regimens, including the incorporation of drugs that target the *MAPK* pathway (BRAF and MEK inhibitors) [15].

Longer term follow-up is first focused on surveillance for LCH reactivation at additional body sites (often, but not always, in the same organ system as originally presenting). These are most frequently observed in the first 2 years beyond the end of therapy but can occur at any time [16]. Reactivations can be managed with similar therapies as those used at diagnosis in all but multisystem risk organ patients, for whom significant therapy intensification may be warranted.

In addition, long-term surveillance for pituitary endocrinopathy is required post-therapy since the onset of such deficits may follow the diagnosis of LCH by many years, even in the absence of ongoing disease, as will be further discussed. Finally, patients with LCH should be educated about the risks of cigarette smoking, as smoke-stimulated pulmonary histiocytes can contribute to rapidly progressive emphysematous changes leading to a risk of pneumothorax and respiratory insufficiency [17].

Pituitary Involvement, Endocrine Dysfunction, and Neurodegeneration in LCH

LCH can result in endocrinopathies due to involvement of the pituitary gland. It is speculated that mononuclear phagocytes can migrate into the CNS via circumventricular organs like the inferior hypothalamus and posterior pituitary to perform immune sur-

veillance functions. This local confluence of trafficking cells may explain the propensity for LCH damage to this gland, as trafficking hyperactivated Langerhans cells could create a focal region of inflammatory cytokines that induce pituitary injury [18]. Pituitary dysfunction in LCH patients typically starts with diabetes insipidus. While the inability to concentrate urine during a water-deprivation test is highly specific for diabetes insipidus, early in the course of disease a high index of suspicion is required as concentrating ability may be partly retained or episodic. Diabetes insipidus may be followed by growth hormone deficiency, hypothyroidism, and in some cases, panhypopituitarism [5, 16]. The onset of endocrinopathy is variable and likely reflects a chronic inflammatory injury. In the majority of patients, endocrinopathy follows the diagnosis of LCH by up to 5 years, presumably reflecting the lag-time from active inflammatory involvement to subsequent scarring with functional loss of anti-diuretic and/or additional hormone secretion [2, 16]. In a minority of patients, endocrine dysfunction is present at the time of diagnosis of LCH either as the sole manifestation (see Chap. 4) or more commonly in association with other sites of disease. In such cases, it is possible that occult LCH activity prior to diagnosis has contributed to pituitary injury over time. In any case, it is important to monitor patients for new onset of pituitary deficits, or for progression with loss of additional hormones, for years after the initial diagnosis of LCH [16, 19]. This is often done by history alone in lower risk settings, supplemented by laboratory assessments and surveillance MRI in higher risk settings.

Gadolinium-enhanced MRI is the modality of choice to evaluate the hypothalamic-pituitary axis for patients with LCH. The most common abnormalities seen are infundibular thickening (>3 mm) and absence of the normal bright spot of the neurohypophysis on T1-weighted sequences [20]. Absence of the pituitary bright spot indicates the absence of the neurosecretory granules that store antidiuretic hormone. These granules are synthesized within the hypothalamus and transported for storage in the posterior pituitary. Injury to the pituitary gland itself, or the hypothalamic stalk and associated transport machinery, leads to their

absence. It should be noted, however, that in up to 15% of normal individuals this storage occurs either diffusely or ectopically, resulting in the loss of a discernible T1 bright spot but preservation of functional antidiuretic hormone [20, 21]. Beyond stalk thickening, some patients will develop frank granulomatous mass lesions in the pituitary gland, stalk, or hypothalamus. If imaging anomalies and endocrine deficits are the presenting findings, LCH should be considered in the differential. Alternative diagnoses to consider are CNS germ cell tumor, lymphoma, or other inflammatory diseases such as sarcoid or idiopathic hypophysitis. Of note, negative germ cell tumor markers from blood and CSF, and negative cytology, cannot exclude the diagnosis of germinoma. Pituitary biopsy carries sufficient morbidity that it is recommended only in the absence of extracranial findings sufficient to make a diagnosis and with significant or progressive thickening (see Chap. 4) [22].

The 5-year estimated risk of pituitary involvement in LCH is ~15% with a lifetime prevalence of DI ranging from 15 to 50% in different series since certain risk factors strongly influence this risk [13, 19]. Factors that increase the risk of pituitary dysfunction are related to the overall disease burden of LCH (how likely are aberrant cells to be trafficking systemically) and the chronicity of LCH activity (how long have they been trafficking). Therefore, children with multisystem LCH with many sites of involvement are at higher risk, as are patients in whom LCH is active over a prolonged period, either because of poor treatment response or due to subsequent disease reactivation(s). In addition, bulky facial bone and skull base involvement by LCH is considered to be an additional risk factor, potentially through seeding of these sites and the pituitary region by aberrantly activated Langerhans cells. These include the sphenoid, ethmoid, zygomatic, maxilla, and temporal bones (including orbit and mastoid lesions) [1, 2], and LCH lesions at these sites are commonly termed CNS-risk lesions [3]. Whether skull vault bone involvement is a risk factor remains controversial. Diabetes insipidus is generally irreversible once it develops despite disease-directed therapy and children will require lifelong vasopressin therapy [13]. The extent to which

effective LCH-directed therapies can reduce the risk of pituitary dysfunction is related to the ability to minimize the number and chronicity of trafficking diseased cells through the gland.

Patients with LCH are also at increased risk for anterior pituitary hormone deficiencies. Growth hormone deficiency is the second most common LCH-associated deficiency, occurring in up to 10% of all patients with LCH, and the 5-year risk for patients with diabetes insipidus is >30% [19, 23]. Less common are deficiencies of the thyrotropes, gonadotropes, and corticotropes. For these reasons, patients with LCH should be screened serially for changes in anterior pituitary function so that appropriate hormone replacement can be initiated. This includes assessment of pubertal stratus, growth parameters (growth velocity in particular), and following for signs and symptoms of hypothyroidism. History and exam should be supplemented with laboratory studies when concern for dysfunction is present, and serial MRI of the brain and pituitary should be performed in this setting, regardless of whether prior imaging has been normal. All patients, regardless of type of LCH or history of therapy, should be followed until puberty and final growth have occurred [16, 19, 23].

CNS-LCH involves not only the hypothalamic-pituitary axis, as discussed above, but also a potentially devastating neurodegenerative process that is poorly understood and occurs in ~2% of patients [1, 24, 25]. A risk factor for neurodegenerative LCH (ND-LCH) is the presence of pituitary involvement. Aberrations identified on CNS imaging studies are more frequent than are neurologic symptoms (tremor, ataxia, dysarthria, psychiatric, and cognitive changes), and strong predictors of who will progress to clinical deficits are lacking. Imaging findings include bilateral hyperintense T2-weighted signal abnormalities in the cerebellar gray matter, basal ganglia, and brainstem with variable extension to the supratentorial white matter [21]. Progressive imaging findings are better correlated with functional deficits and these may present up to 10 years after LCH manifestations [1, 26]. ND-LCH deficits may be static or progressive but are not readily reversible, so surveillance for such changes is important to enable early intervention. Beyond ensuring an adequate LCH

therapy has been provided to reduce ongoing LCH activity, current therapies for ND-LCH include immunomodulatory intravenous immunoglobulin replacement [27], and more recently efforts to inhibit *MAPK* signaling using selective inhibitors [28]. It remains unclear whether ND-LCH is a para-neoplastic syndrome reflecting immune dysregulation in the CNS, or part of a CNS-restricted active LCH process. Evidence for the latter is emerging [26], but a better understanding of this process may enable improved interventions as current therapies for ND-LCH are suboptimal.

Thus, given the association between endocrinopathy and LCH, the diagnosis of LCH should be considered in a patient presenting with central diabetes insipidus. We recommend that all children with concern for central diabetes insipidus undergo a close dermatologic examination in addition to MRI with intravenous contrast of the brain with thin cuts of the pituitary. If the pituitary stalk is thickened, to evaluate for LCH we recommend obtaining CBC, liver enzymes and synthetic function, electrolytes, ferritin, immunoglobulins, coagulation studies, skeletal survey with skull series, abdominal ultrasound and CT or MRI of head assess for craniofacial bone lesions if insufficiently evaluated on prior imaging. Further, we recommend consultation with an oncologist and concurrent evaluation for intracranial germ cell tumor (see Chap. 4 for more details).

In summary, LCH is a rare disease with the potential for long-term adverse sequelae. The diagnosis of LCH should be considered with the onset of diabetes insipidus, and conversely, careful attention should be paid to patients with LCH for signs of pituitary endocrinopathies, especially those with CNS-risk lesions. Given the delay in development of endocrinopathy, even after disease-directed therapy and resolution of active LCH, screening for diabetes insipidus and monitoring of growth is an essential part of follow-up in all patients. Further, patients who develop LCH-associated endocrinopathy are at an increased risk of ND-LCH and require long-term follow-up. The optimal therapy to prevent LCH-related pituitary endocrinopathy has yet to be deter-

mined, and in all cases long-term surveillance for the development of endocrine dysfunction is warranted.

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9 Craniopharyngioma and Diabetes Insipidus

Clement Cheung

Case Presentation

The patient is a 7.5-year-old male who was previously healthy and presented to an outside optometrist with persistent right-sided esotropia after he was hit in the head with a baseball about 3 weeks prior to the visit. Papilledema was noted by an optometrist and a CT scan without contrast showed a suprasellar cystic mass with calcifications. He was referred to Neurosurgery in our institution. On review of systems, he had significant weight gain and occasional enuresis over the last 2–3 years. He denied polydipsia, headache, nausea, or vomiting. MRI with contrast on T1 showed a hyperintense solid and cystic suprasellar mass closely associated with the optic chiasm and hypothalamus with a large peripherally enhancing cystic component extending superiorly into the third ventricle and abutting nearby arteries. No posterior bright spot was noted. There were areas of susceptibility artifact that might reflect the presence of calcium or blood products. His baseline labs showed sodium 142 mEq/L, free T4 0.8 ng/dL, TSH 1.7 uIU/mL, cortisol 1.4 mcg/dL, ACTH 16 pg/mL, prolactin 7 ng/mL, and IGF-1 147 ng/mL (+0.1 SD). His weight was

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C. A. Alter (ed.), *Diabetes Insipidus in Children*,
https://doi.org/10.1007/978-3-030-83248-3_9

51.9 kg (+3.21 SD), height was 128.6 cm (+0.52 SD), and BMI was 31.4 kg/m2 (+2.81 SD). He was in early puberty based on the Tanner II testicular examination.

Assessment and Diagnosis

The radiology findings point to craniopharyngioma (CP) as the most likely diagnosis. Despite an absence of a posterior bright spot, he did not present with classic symptoms for central diabetes insipidus, which is not unusual.

CP is a rare neuroepithelial tumor of the sellar region that accounts for 1.2–4.6% of all intracranial tumors, with a bimodal age distribution that peaks between ages 5 and 15 and between 45 and 60 years [1]. About 30–50% of all CP occurs in children and adolescents, which accounts for 5–10% of all pediatric intracranial tumors [1]. The incidence has been reported to be 1–2 per million child population per year in some of the western countries, but at 3.6 per million child population per year in Japan [2, 3]. In the United States, there were about 1380 cases of CP presented in those less than 21 years old from 2004 to 2017 [4]. Approximately 35% occurred in children between ages 6 and 11, followed by 33% in adolescence between 12 and 18. There was no obvious difference in gender distribution, with 51.5% in males and 48.5% in females. In terms of race and ethnicity, 58% were non-Hispanic White, 16% were Hispanic, 15.5% were Non-Hispanic Black, and 4.3% were Asian/Pacific Islander [4]. Patients with CP have an overall survival of above 80% at 5 years, and 62%, on average, at 20 years [1]. Survivors of CP experience increased risk for type 2 diabetes, cerebral infarction, and total mortality compared to the general population. Risk factors for these morbidities include female sex, childhood onset, history of hydrocephalus, and recurrence [5].

CPs are classified into two subtypes: adamantinomatous craniopharyngioma (ACP) and papillary craniopharyngioma (PCP). Each subtype is closely associated with a specific age group, morphology, distinct histology, and molecular phenotype (Table 9.1) [1, 6, 7]. ACPs primarily occur in the pediatric age group and

Table 9.1 Comparisons between adamantinomatous and papillary craniopharyngioma

	Adamantinomatous	Papillary
Prevalence	85–90%	15–10%
Age group	Pediatric predominantly	Adult predominantly
Location	Often adhere to third ventricle, blood vessels, and cranial nerves, distort pituitary stalk and compress pituitary gland	Often localize within third ventricle with clear boundary and less interactions with surrounding structures
Anatomy	Solid and cystic that contains oil-like substance, with calcifications	Mostly solid, without calcifications
Histology	Palisading epithelium surrounding stellate reticulum, calcifications, wet keratin; Rosenthal fibers	Non-keratinized epithelium and fibrovascular core; rarely wet keratin and palisade epithelium
Molecular biology	Mutation commonly seen in CTNNB1	May harbor $BRAF^{V600E}$ mutations
Embryology	Remnant of Rathke's pouch	Embryonal epithelium of pituitary gland and stalk
Radiology	CT: cystic structure commonly with calcification MRI: lobulated, heterogeneous, and hyperintense structure, and enhancement on contrast	CT: solid structure and rarely have calcification MRI: mostly solid isointense or hypointense structure and rarely have enhancement on contrast

account for 85–90% of all CPs. ACPs often adhere to nearby structures, including the wall of the third ventricle, blood vessels, and cranial nerves, and may interrupt pituitary function by distorting the infundibular stalk or compressing on the pituitary gland. On gross inspection, ACPs have both cystic and solid components. The cysts contain oil-like substance, which is rich in cholesterol and keratinized debris and is highly caustic to nearby structures if it leaks out, whereas the solid components often contain calcified elements. Histologically, ACPs are distinguished by the palisading epithelium that surrounds stellate reticulum, wet keratin, and calcifications; and Rosenthal fibers are signs of astro-

cytic gliosis. Advances in the molecular biology of CPs have shown that the WNT pathway plays a role in the tumorigenesis of ACPs, with activating mutations in the β-catenin gene (CTNNB1) on chromosome 3 found in close to 95% of ACPs [1, 6, 7]. In contrast, PCPs mostly occur in the adult population but have been reported in some children [1]. PCPs tend to localize within the third ventricle, have clear boundary, and have less interactions with surrounding structures. PCPs are mostly solid with little calcifications, and the cystic components, if any, do not contain oil-like substance. PCPs rarely have wet keratin and do not have palisade epithelium. Instead, PCPs have non-keratinized squamous epithelium and fibrovascular core. Unlike ACPs, CTNNB1 mutations are not found in PCPs, which instead harbor $BRAF^{V600E}$ mutations in most of the tumor cells [1, 6, 7]. Several hypotheses have been proposed to explain the origin of the tumor. One school of thought suggests an origin from a remnant of the Rathke's pouch, the pharyngo-hypophyseal stalk, during formation of the anterior pituitary gland. This hypothesis has been used to explain the origin of ACP. Another theory suggests transformation of the embryonal epithelium of the anterior pituitary gland and stalk, which some have ascribed that to the origin of PCP [1, 6, 7].

Pediatric CP typically presents when the tumor has grown to a size that impacts nearby structures to produce neurological and ophthalmic signs and symptoms. Neurological signs and symptoms are often related to increased intracranial pressure and can be relatively non-specific and chronic, such as headache and vomiting, or severe and acute, such as seizure. Ophthalmic symptoms occur when the tumor compresses on the optic chiasm or nerves, which lead to decrease in visual acuity and/or peripheral vision, as well as nystagmus or strabismus. The proximity of CPs to the hypothalamus and the pituitary render most patients at high risk for endocrinopathies [1]. Whereas neuro-ophthalmic symptoms may often be the presenting symptoms that lead to the diagnosis of pediatric CP, most endocrine abnormalities are rarely the presenting symptoms. Endocrine problems are often diagnosed only when the tumor has been confirmed despite symptoms having been in existence for months to years [8–10]. This dissociation in presentations between neuro-ophthalmic symptoms and endo-

crine symptoms is common in many midline tumors, such as optic pathway glioma, germ cell tumor, hypothalamic-pituitary astrocytoma, and hypothalamic hamartoma [10]. Studies from the early 1980–1990s showed that close to 80% of pediatric patients with CPs presented with headache and vomiting, but less than 15% of patients presented with endocrine systems; however, work up at baseline indicated endocrine deficits in up to 50–66% of patients [8, 11]. Studies from multiple countries have since confirmed that 38–83% of patients at the time of diagnosis have endocrine deficits (Table 9.2), which range from anterior and posterior hormone deficiencies to hypothalamic dysfunction, with growth hormone deficiency and/or growth impairment being the most common anterior pituitary hormone deficiencies [8, 10–14, 16–19].

Diabetes insipidus is relatively uncommon at the time of CP diagnosis in the pediatric population (Table 9.2) [8, 11–21], in contrast to its high incidence following treatment [see next chapter; 21, 22]. The rate of occurrence reported in the literature has been quite variable, ranging from an infrequent rate of 9–15% [8], to a slightly higher 17–25% [1], to a much broader 8–35% [15]. In general, only about 9–19% of children would have polyuria and polydipsia as presenting symptoms as compared to the much higher rate of neuro-ophthalmic symptoms (Table 9.2) [14, 16, 18]. With endocrine evaluation, diabetes insipidus was found in 7–35% of children at the time of diagnosis [11–15, 17, 19–21], with one study from the UK reported that 48–50% patients had diabetes insipidus that occurred in conjunction with panhypopituitarism at baseline [19]. Given that most of these studies are retrospective, the actual frequency can be affected by incomplete data or inconsistent approaches in the assessment of diabetes insipidus, which range from self-reported symptomology, clinical observations, to actual biochemical measurements. Characteristics of the CP may impact the likelihood of diabetes insipidus at diagnosis – PCP has been reported to have a higher association with diabetes insipidus than ACP at baseline [23], and infradiaphragmatic CP is associated with a much higher incidence for diabetes insipidus than suprasellar CP [24]. The speculation is that difference in tumor mass effect, intrinsic to the CP subtype and tumor location, contributes partly to the different occurrence of diabetes

Table 9.2 Endocrine deficits in children with craniopharyngioma at the time of diagnosis and diabetes insipidus as presenting symptoms or at the time of diagnosis (% expressed of number of cases over total number of patients)

Reference	Year	Country	No.	% of children with endocrine deficits at diagnosis	% of children with diabetes insipidus:	
					As presenting symptoms[a]	At the time of diagnosis
Hoffman et al. [11]	1992	Canada	50	66% (33/50)		24% (12/50)
Hetelekidis et al. [12]	1993	USA	61	38% (13/34)		23% (8/34)
Sklar [8]	1994			80–90%[b]		9–17%[b]
Caldarelli et al. [13]	2005	Italy	52	67% (35/52)		19% (10/52)
Karavitaki et al. [14]	2005	UK	41		15% (6/41)	22% (7/32)
Ghirardello et al. [15]	2006					8–35%[b]
Puget et al. [16]	2007	France	66	80%	9% (6/66)	
Cohen et al. [17]	2013	Canada	126	46% (58/126)		14% (18/126)
Hoffmann et al. [18]	2015	Germany	325	44% (142/325)	19% (23/120)	
Tan et al. [19]	2017	UK	185			7% (6/85); 49% (71/144)[c]
Tosta-Hernandez et al. [20]	2018	Brazil	57			9% (5/57)
Guo et al. [21]	2019	China	185	83% (153/185)		26% (49/185)
Overall range				38–90%	9–19%	7–49%

[a]Patients with polyuria and polydipsia
[b]Modified by main author
[c]Panhypopituitarism including DI

insipidus [23, 24]. However, the work by Hoffmann et al. shows that whereas tumor size and location are not associated with symptoms of polyuria and polydipsia in history, a smaller tumor at diagnosis correlates with polyuria and polydipsia as the first presenting symptom [18]. These diverging results speak to the need for prospective studies to examine the relationship of tumor characteristics to endocrine deficits. In addition, diabetes insipidus at baseline can be masked by untreated secondary adrenal insufficiency. It is known that antidiuresis occurs in untreated hypocortisolism when decreased negative feedback of cortisol on the hypothalamus results in corticotropin-releasing hormone-induced ADH release. In those with partial or complete ADH deficiency, replacement with glucocorticoid can unmask diabetes insipidus via both ADH-dependent and ADH-independent mechanisms [25]. As such, patients with a high suspicion for diabetes insipidus at baseline, such as those without a posterior bright spot but without symptoms, should prompt an investigation into whether there is coexisting secondary adrenal insufficiency that masks the occurrence of diabetes insipidus.

Brain imaging is important for the diagnosis and surgical planning of CPs. Patients with acute neuro-ophthalmic symptoms are seen in the emergency room whereby a head CT is obtained to confirm a sellar or suprasellar mass with cystic structure and calcification. Cysts in ACP can be hypodense or hyperdense, solitary or in multiples, and of various sizes. Density of the cyst is in proportion to the amount of protein content and the cyst walls often enhance with contrast. Calcification is a common finding in ACP (Fig. 9.1a), occurring in up to 90% of pediatric cases, and a peripheral calcification is almost pathognomonic for ACP aside for an aneurysm [1, 26]. CT imaging can detect expansion or erosion of the sellar, which may help to differentiate ACP from pituitary adenoma. PCP, which is less common in children, appears mostly as a spherical and solid mass, with isodense signal and infrequent calcification [1, 26]. Patients who present with indolent symptoms or endocrinopathy, including diabetes insipidus, and raise suspicion for central lesion will usually receive MRI as the first line of imaging. ACP on MRI often appears as a mixed

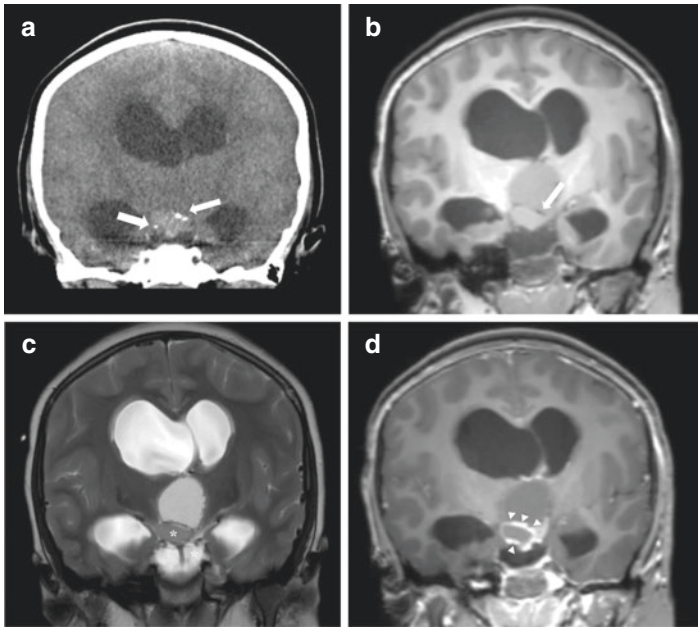

Fig. 9.1 (**a**) Coronal, non-contrast CT image demonstrates a suprasellar mass with multiple foci of calcification (arrows). (**b**) Coronal, T1-weighted MR image demonstrates a lobular, suprasellar mass with minimal and variable degree of intrinsic T1 shortening (arrow). (**c**) Coronal, T2-weighted MR image demonstrates a suprasellar mass with heterogenous T2 signal reflective of proteinaceous material (asterisk). (**d**) Coronal, post-contrast T1-weighted MR image demonstrates a component of rim enhancement (arrowheads) within the suprasellar mass, which is not necessarily something seen in Rathke's cysts

cystic-solid structure that is lobulated and heterogeneous. Cysts contents are often hyperintense on T1- and T2-weighted images (Fig. 9.1b, c). Calcification may not always appear on MRI images, but can present as hypointense signal on T2-weighted images; however, a CT should be obtained as it is superior to MRI in detecting calcification. Furthermore, cyst wall and solid portion can enhance with contrast (Fig. 9.1d). In contrast, PCP on T1-weighted images shows nodule that is typically isointense and

the cyst, which is less-proteinaceous than ACP, remains mostly hypointense. Ultimately, both PCP and ACP can have similar radiological features and require biopsy to determine the histological diagnosis [1, 26].

Management

Treatment of pediatric CP invariably involves surgical resection, but multiple factors determine the necessity of other surgical interventions that precede resection, the approach and extent of surgical resection, and whether non-surgical adjuvant therapies should precede or augment surgery. Ultimate goals are to ameliorate neuro-ophthalmic and endocrinological symptoms and to minimize surgical damages to the nearby neurovascular structures, optic pathway, pituitary gland, and the hypothalamus. Patients with hydrocephalus from tumor obstruction of the third ventricle may need ventriculostomy to relieve increased intracranial pressure. ACP with a large cystic structure can benefit from intracystic drainage and treatment, such as with interferon-α. Radiation sometimes precede surgical treatment if the tumor has invaded the hypothalamus. For surgical management, there is no clear consensus on the best approach and that factors such as age of the patient, size of the tumor, and tumor location in relation to nearby structures may determine the feasibility of a gross total resection (GTR) versus subtotal resection, and the use of endoscopic endonasal approach versus open transcranial approach [1, 7]. From the endocrinology standpoint, approaches that can minimize further exacerbation of hypothalamic obesity (HO) are preferred given a lack of efficacious treatment for HO and the high morbidity associated with it. With respect to postoperative diabetes insipidus, permanent condition is seen in 49% of patients with preservation of the pituitary stalk but 95% of patients in whom the stalk was sacrificed [27]. At times, subtotal resection is the desirable option if GTR lead to significant morbidity or increased mortality. In children with residual tumor, adjuvant therapies include radiotherapy and targeted therapy [1, 7]. Though a benign

tumor, the unique biological and anatomical features of pediatric CP make its clinical management highly challenging. It is critically important to strike a balance between curative approach with factors affecting the quality of life, and the growth and development of a child. Multidisciplinary approach and ongoing research are needed to improve clinical outcome.

Outcome

He was noted to have central precocious puberty and manifested persistent polyuria and polydipsia upon treatment with preoperative glucocorticoid. He underwent an intrahemispheric craniotomy with sub-total resection due to adherence of cyst to the third ventricle. Pathology confirmed adamantinomatous CP. He developed hypopituitarism and HO postoperatively, and was treated with levothyroxine, hydrocortisone, and desmopressin. He was also treated with pubertal blocker due to central precocious puberty. Because of the residual tumor, he received 54 Gy focal radiation to the sellar. He eventually developed a seizure disorder and was started on ketogenic diet and oxcarbazepine, which is known to increase renal tubular water reabsorption. He developed ongoing hyponatremia and was subsequently taken off desmopressin. He has been able to maintain eunatremia with set fluid goal without desmopressin.

Clinical Pearls and Pitfalls

- Craniopharyngioma is a benign tumor of neuroepithelial origin of the sellar region, with a bimodal age distribution. Pediatric cystic suprasellar mass with calcification is almost always a craniopharyngioma, specifically the adamantinomatous subtype.
- Neuro-ophthalmic abnormalities are usually the presenting symptoms, but endocrine deficiencies are often found at baseline and may precede the diagnosis by years.

- Polyuria and polydipsia occur as presenting symptoms in 9–19% of patients, and diabetes insipidus can be found in 7–49% of patients at the time of the craniopharyngioma diagnosis. The rate is less common compared to other pituitary dysfunctions such as growth hormone deficiency. Untreated central hypocortisolism may mask diabetes insipidus at baseline. Most diabetes insipidus associated with craniopharyngioma occurs post-operatively.

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10 Diabetes Insipidus After Craniopharyngioma Resection

David M. Werny

Case Presentation

An 11-year 5-month-old previously healthy boy presented to the emergency department with progressively worsening nausea, vomiting, and headaches over the preceding 3 weeks. A head CT was performed showing a cystic suprasellar lesion and moderate hydrocephalus. An MRI was obtained which showed a mixed solid and cystic suprasellar lesion with calcifications, consistent with a craniopharyngioma (Fig. 10.1).

Initial labs demonstrated intact thyroid hormone and cortisol production. IGF-1 was low, concerning for growth hormone deficiency. The patient had not noted any polyuria or polydipsia, and sodium level was normal.

Initial lab evaluation at 9:21 PM

- Sodium 136 mEq/L (135–145)
- TSH 0.51 (0.50–4.50)
- Free thyroxine 1.0 ng/dL (0.8–2.0)
- Cortisol 19.3 mcg/dL
- Prolactin 7 ng/mL (2–14)
- IGF-1 44 ng/mL (112–454)

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C. A. Alter (ed.), *Diabetes Insipidus in Children*,
https://doi.org/10.1007/978-3-030-83248-3_10

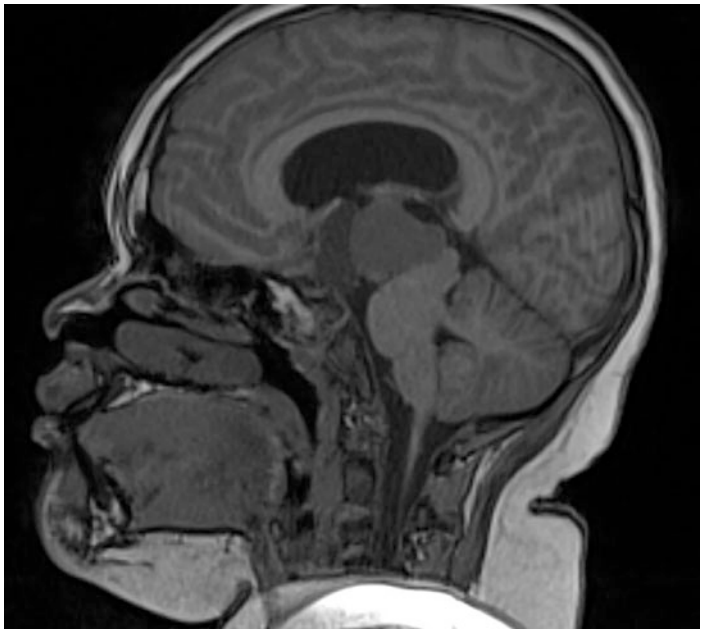

Fig. 10.1 MRI sagittal T1-weighted image demonstrating a large sellar and suprasellar mass, consistent with a craniopharyngioma

Soon after, he underwent surgical management of his hydrocephalus with cyst fenestration, 3rd ventriculostomy, and placement of an external ventricular drain (EVD). He was then observed in the PICU for several days while plans were made to attempt a complete resection of the presumed craniopharyngioma. During this time, he did not demonstrate polyuria or polydipsia.

He subsequently underwent an endoscopic transsphenoidal gross total resection of his suprasellar mass, and pathology confirmed the diagnosis of craniopharyngioma.

Post-operatively he was transferred to the PICU in the evening. Dexamethasone was started for management of cerebral swelling and normal saline fluids were initiated at a maintenance rate. The patient was allowed to drink to thirst.

Intake and output were followed closely, and he was noted to have urine output of 3.9–7.6 mL/kg/h over the first several hours in the PICU. He developed nausea and somnolence and did not drink well. His sodium rose to 148 mEq/L in the context of dilute polyuria, with urine osmolality of 155. A vasopressin infusion was started for management of diabetes insipidus, with appropriate decline in urine output to 1–3 mL/kg/h. His normal saline (NS) maintenance fluids were decreased to 1/3rd maintenance rate once the vasopressin infusion was started.

Over the next 72 hours he remained on a vasopressin infusion in the context of waxing/waning mental status. His level of alertness, confusion, agitation, and interactivity fluctuated, and he continues to express nausea as well. His ability to express thirst and seek out water independently was inconsistent. During this time, he received four ½ NS boluses to correct fluid deficits that occur. Serum sodium ranged from 135 to 142 mEq/L.

On post-operative day (POD) #4 his urine output declined such that his vasopressin infusion is decreased, and his sodium declined to 133 mEq/L. His vasopressin infusion was then discontinued.

Over the next 3 days his serum sodium ranged from 129 to 137 with urine output of 0.5–3.0 mL/kg/h. He received two 2% saline boluses for treatment of hyponatremia, as well as due to intermittent concerns from the PICU staff that he had developed cerebral salt wasting, as urine sodium measurements ranged from 101 to 400 mEq/L. Additionally, he was noted to have CSF leaking from his nose and he developed an intermittent low-grade fever. Antibiotics were started for empiric management of meningitis.

By POD #7 his mental status had improved, but his nausea was persistent. He had return of dilute polyuria about 12 hours before he was scheduled to return to the operating room for patching of his CSF leak. Due to the patient being NPO for his procedure, he is started on a vasopressin infusion and normal saline fluids are run at 1/3rd maintenance rate.

The morning after his CSF leak repair, on POD #8, he was drinking well with no complaints of nausea. He was started on oral desmopressin with an initial dose of 50 mcg.

Over the next week the patient had normal mental status and intact thirst. Desmopressin was dosed initially on an as-needed basis when he demonstrated breakthrough urination. His desmopressin dosing was gradually increased, and within 48 hours effective diuresis on twice daily dosing was established. His EVD was weaned and eventually removed by POD #14. By discharge on POD #15, his desmopressin dosing had been increased to a dose of 100 mcg in the morning and the evening with good control of polyuria and polydipsia.

Discussion

This case demonstrates the complexity and evolving course of the post-neurosurgical patient, including several examples of dysnatremia. Important elements for discussion are the initial development of post-operative DI, the triphasic response, concerns regarding cerebral salt-wasting, and establishment of a safe oral desmopressin dose for discharge. These problems were encountered in the context of a patient with sometimes altered mental status, a changing ability and desire to take fluids orally, and the development of post-operative complications. These factors complicate the management of dysnatremia.

Post-operative DI is a well-recognized complication of surgery involving the pituitary gland, stalk, and hypothalamus [1, 2]. It can develop shortly after surgery and is often transient. If the patient can drink, and their thirst sensation is intact, they may be able to self-regulate their water balance if given free access to water. This is a reasonable strategy for initial DI management, particularly if the patient is thought to have transient DI that will be improving in the next 24 hours. However, in a pediatric patient (as in this case), this strategy may be less likely to be effective due to post-operative fatigue, nausea, or altered mental status, which tends to limit young children's ability and interest in drinking water sufficiently. Additionally, some patients with particularly large suprasellar masses may have surgical resections that directly disrupt the regions of the hypothalamus necessary for normal thirst sensation, specifically the subfornical organ [3, 4]. These

patients will have permanently dysregulated thirst sensation, resulting in adipsic DI, the management of which is outside the scope of this chapter.

For this patient, a vasopressin infusion was started in the early morning hours of post-operative day 1, after the sodium level had risen to 148 mEq/L with dilute polyuria, confirming the existence of DI. It is important to note that post-operative polyuria is common and can simply be due to appropriate diuresis of intravenous fluids given in the operating room. For this reason, it is good practice to confirm the diagnosis of DI prior to starting management of vasopressin and desmopressin, as inducing an unnecessary anti-diuresis could cause symptomatic hyponatremia.

While desmopressin is commonly used in adult management for management of immediate post-operative DI, we favor the initial use of a vasopressin infusion in pediatric patients. In our experience, post-operative hypernatremia due to DI can develop quickly in children and use of a vasopressin infusion allows for more rapid control of urine output, preventing the development of severe hypernatremia. Additionally, the potentially transient nature of post-operative DI is well served by a form of management that can be quickly adjusted downward should the DI resolve in the first 12–24 hours. Desmopressin's longer half-life, and sometimes initially prolonged anti-diuretic action, might predispose children to hyponatremia if DI resolves or SIADH develops in the first 24 hours.

Vasopressin and IV fluid protocols for the management of diabetes insipidus vary across institutions. We start with an initial rate of 0.5 milliunits/kg/hour and favor an approach that attempts to achieve a lower urine output (< 2 mL/kg/h), while similarly minimizing IV fluid administration, with 1/3–½ maintenance rate fluids [5]. We feel this strategy of minimizing input and output helps prevent rapid changes in the serum sodium. Similarly, we generally recommend against giving boluses of IV fluids for urine output replacement, unless there is acute concern for intravascular depletion and impaired perfusion.

The patient experienced frequent agitation and decreased alertness for the first few post-operative days. Because his thirst sensation was not reliable at that time, it was felt that continuing a

vasopressin infusion with a low urine output target would better control his diabetes insipidus. This was considered in opposition to transitioning to oral desmopressin, which may be more likely to result in rapid sodium increases when breakthrough urination develops in a patient without a reliable thirst sensation. On the other hand, if a patient recovering well from surgery with minimal nausea, we will consider transitioning them to oral desmopressin on POD #2 if they have persistent DI. However, it is important that such patients not be placed on scheduled desmopressin, and instead be dosed only on an as needed basis after they demonstrate breakthrough urination. This is to avoid severe hyponatremia that can develop should they progress through a classic triphasic response, with development of the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

The triphasic response is a triad of initial diabetes insipidus, followed by SIADH, and completed with the establishment of permanent DI. It is thought to arise from initial injury to vasopressin producing neurons in the supraoptic and paraventricular nuclei of the hypothalamus (initial DI), followed by cell death of these same neurons and subsequent release of antidiuretic hormone (SIADH), and completed by the eventual exhaustion of all stored ADH and the presence of permanent DI. While the timing of these phases can certainly vary, phase 1 is felt to last for 1–3 days, with SIADH present on average from post-operative days 4–7, and permanent DI reoccurring afterward [6]. The triphasic response does not occur in all post-operative patients, and in one series of pediatric patients undergoing transcranial resection of craniopharyngioma was seen in 6 out of 21 patients [6].

Vigilance for and appropriate management of post-operative SIADH is important as symptomatic hyponatremia and/or seizure is a potential complication during this phase. Management of SIADH is classically done with water and fluid restriction, with the goal of inducing a negative fluid balance [7]. Vasopressin infusions, or desmopressin dosing, should be stopped when SIADH is suspected to have started.

A frequent diagnostic dilemma in the postoperative neurosurgical patient is the determination of whether hyponatremia is due to SIADH or cerebral salt-wasting (CSW). The distinction is

important because the two conditions require opposite management: fluids restriction for SIADH, and IV fluid replacement of a sodium deficit for CSW. The diagnosis is best made by an assessment of the patient's intravascular volume status, with SIADH patients being euvolemic (or hypervolemic), and patients with CSW having intravascular depletion [8]. However, volume status can be difficult to assess in the post-operative patient, as tachycardia can be due to pain and nausea. Careful review of intake and output records and weight changes from the period just prior to the development of hyponatremia may help in differentiating whether the decline in serum sodium was associated with volume loss or gain.

A further point of confusion is that urine sodium is often assessed by providers to differentiate these conditions. However, an elevated urine sodium is expected for both conditions. During SIADH the euvolemic state causes relative inactivation of the renin-angiotensin-aldosterone system. This results in appropriate excretion of sodium by the kidney. The amount of sodium excreted will depend on the patients' sodium intake, but it can be quite high in patients eating solid foods or receiving IV fluids. This sodium excretion, in combination with the relatively high urine concentration seen with SIADH, can result in seemingly elevated urine sodium measurements. CSW results in similarly high urine sodium measurements; however, it is considered inappropriate in the context of intravascular depletion. Therefore, intravascular volume status assessment remains the best way to differentiate these two conditions. Regardless of the cause, severe, symptomatic hyponatremia is best treated quickly with a bolus of hypertonic saline.

It should also be noted that CSW has been primarily described in association with subarachnoid hemorrhage [9], and therefore in the patient recovering from pituitary surgery SIADH is much more likely. Therefore, in the absence of strong evidence for intravascular depletion, patients that develop hyponatremia while recovering from pituitary surgery can be first managed as if they have SIADH. This would include cessation of vasopressin infusion and desmopressin dosing, fluid restriction, and close sodium monitoring.

In our case, the patient's hyponatremic SIADH phase resolved by POD #7. At this time, he was noted to have return of DI. After returning to the OR for repair of a CSF leak, he had improvement in his nausea and resumed a normal diet. He was then switched to oral desmopressin to prepare for management of permanent DI after discharge at home.

Initial dosing of desmopressin in pediatric patients is complicated by the wide variability in responses to desmopressin. Generally, we start with relatively small dosing of 50–100 mcg for the initial dose in most children, and 25 mcg for smaller children such as toddlers. Based on the length of time antidiuresis is achieved from the initial doses, subsequent doses are increased or decreased to try and achieve a twice-daily dosing schedule. For patients with an intact thirst sensation (such as the patient in the vignette above), the goal is to provide antidiuresis overnight that allows for minimal interruptions in sleep. Daytime dosing is titrated to allow the child to participate in school and other activities without excessive thirst or urination interfering. Because individual dose effectiveness can vary day to day, perhaps due to variable GI absorption of the medication, a smaller as-needed dose of desmopressin in the afternoon is sometimes helpful to bridge patients to the evening dose.

While working up to his final dose, our patient was initially on prn, or "as needed" dosing of desmopressin. While criteria for such dosing vary by provider and institution, we have attempted to standardize these dosing requirements to facilitate communication among care team members and to minimize delays in medication administration (Fig. 10.2). While these criteria were initially used for our patient after the completion of the SIADH phase, they can often be used for patients tolerating oral intake in the first few days after their surgery, when the permanence of their DI phase is uncertain, and the SIADH phase may be developing. Using such criteria instead of scheduling desmopressin administration can minimize the chances of giving a dose of desmopressin to a patient who is entering the SIADH phase, which can worsen their severity of hyponatremia.

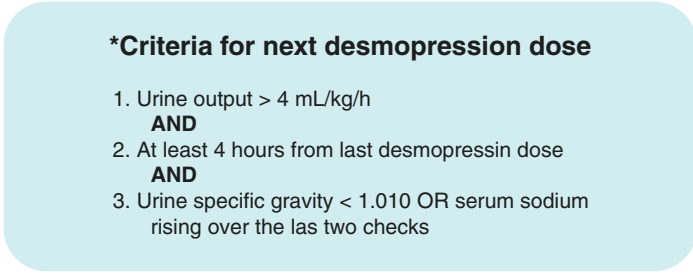

Fig. 10.2 Criteria used for dosing of desmopressin on an as-needed basis for patients at risk for developing post-operative SIADH. Serum sodium levels are checked initially every 4 hours, but this frequency can often quickly be decreased in patients that have a reliably intact thirst sensation

Clinical Pearls and Pitfalls

- Diabetes insipidus is common following surgery involving the pituitary or hypothalamus, and it may be transient or permanent.
- The management of diabetes insipidus with vasopressin or desmopressin should consider the patient's ability to regulate their water balance with spontaneous water intake. This can be affected by disruption of the thirst centers of the hypothalamus, or by post-operative complications such as nausea, pain, and altered mental status.
- Patients with post-operative DI may have a triphasic response, in which SIADH follows the initial DI and places the patient at risk for dangerous hyponatremia. Scheduled desmopressin dosing should be avoided during this time, and intake and output should be tracked closely.
- Patients with permanent DI and an intact thirst sensation should have their desmopressin dosing titrated to allow for comfortable sleep at night and participation in school and other activities during the day.

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11 Partial Central Diabetes Insipidus Following Endonasal Biopsy

Meghan E. Craven and Shana McCormack

Case Presentation

A 31-month-old female presented with 6 weeks of headaches and associated photophobia. Her parents reported no polyuria, polydipsia, or nocturia. She was found to have a suprasellar lesion on MRI. Pituitary hormonal evaluation was reassuring, including sodium of 139 mmol/L, serum osmolality of 292 mOsm/kg, and urine osmolality of 329 mOsm/kg. She was taken to the OR the following day for biopsy and resection via endonasal endoscopic skull base surgery. Post-procedure, she developed increased output of dilute urine with elevated sodium levels to 153 mmol/L, consistent with post-operative DI; she was started on a vasopressin infusion to which she responded with an expected decrease in urine output and serum sodium.

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C. A. Alter (ed.), *Diabetes Insipidus in Children*,
https://doi.org/10.1007/978-3-030-83248-3_11

Assessment and Diagnosis

Given the elevated sodium level, the patient described in the vignette has most likely developed postoperative DI due to surgical pituitary stalk manipulation. Although many patients experience post-operative diuresis, the increase in serum sodium in the context of pituitary surgery is most consistent with DI. In some cases, the surgical interruption of the pituitary stalk can lead to destruction and retrograde degeneration of hypothalamic vasopressin-producing neurons. As expected given this mechanism, lesions closer to the hypothalamus are more likely to cause permanent damage. In retrospective studies of adults undergoing endoscopic transsphenoidal surgery, the overall rate of postoperative DI was approximately 15%, with only about 5% of patients developing permanent DI [1]. A systematic review by Lee et al. (2020) however found a much higher rate in the pediatric population of 27% of all patients postoperatively developing new permanent DI following endonasal endoscopic skull base surgery [2]. Moreover, the later pediatric studies did have a significantly lower rate of permanent postoperative DI when compared with studies prior to 2001 (21% vs 33%) [2].

For this case, since transient DI is relatively frequent and permanent DI is less common, the care team decided to wean off vasopressin. Given steroids can increase free water clearance, the team waited until approximately 48 hours following the discontinuation of steroids to initiate the trial off vasopressin. The patient's sodium initially rose to 149 mmol/L with a substantial increase in urine output. Serum and urine osmolality, 308 mOsm/kg and 118 mOsm/kg respectively, confirmed the continued presence of DI. The patient was then transitioned to desmopressin dosing as needed for breakthrough, and her last dose of desmopressin was administered on postoperative day #4. She was discharged on postoperative day #10 with a sodium of 138 mmol/L, stable urine output, and a presumed diagnosis of transient postoperative DI due to pituitary stalk manipulation.

However, 1 day following discharge the patient re-presented for acute onset of polyuria and polydipsia. She drank greater than 150 ounces of mostly water and had 15 full wet diapers in the span of 24 hours. During this re-admission, the patient completed a water deprivation test and at about 18 hours her urine concentrated to 675 mOsm/kg. Due to the technical difficulties in administering this cumbersome test, the most recent sodium value available at the conclusion of the test, 142 mmol/L, had been obtained 3 hours prior. This sodium result was discordant with the serum osmolality obtained earlier in the day of 309 mOsm/kg; the presence of an apparent osmolality gap in this patient added complexity to her diagnostic evaluation. Of note, at 12 hours of water deprivation testing, her serum sodium was 139 mmol/L and urine osmolality was 474 mOsm/kg. Given her apparent urine concentrating capacity, she was presumed to have a low likelihood of DI, and the possibility of disordered thirst and/or habitual drinking behavior was discussed with the family with a plan to limit fluids to 30 ounces per day. The family was given the important anticipatory guidance that if she developed further increased urine output without increased drinking, she may require additional management at that time.

On follow-up she continued to wake up overnight every 1–2 hours to drink and urinate. When the family tried to cut down her drinking, she would start screaming; she was drinking 150–160 ounces daily (~8 L/m^2/day) and as a result she continued to have difficulty with weight gain despite starting nasogastric feeds. Given her current fluid intake was not sustainable and disruptive to her daily activities, before further attempting to reduce her fluid intake substantially, the care team proposed an inpatient trial of desmopressin to test empirically for the possibility of partial DI.

Although the indirect water-deprivation test is the current reference standard for the diagnosis of DI, the results can be challenging to interpret, especially in differentiating between patients with primary polydipsia and central partial DI. The indirect water-deprivation test measures the maximal urine concentration during prolonged withholding of oral liquids which can lead to difficul-

ties in interpretation since (1) chronic water diuresis may compromise the renal medullary concentration gradient by promoting a downregulation of kidney aquaporin-2 water channels and (2) urine concentration can be higher than expected in patients with impaired glomerular function or chronic central diabetes insipidus (i.e., AVP deficiency), as a result of a compensatory increase in AVPR2 gene expression [3]. Previous attempts to improve the diagnostic performance of this assessment, especially for cases of partial central DI, using direct measurement of circulating arginine vasopressin were unsuccessful due to technical difficulties of measuring arginine vasopressin. However, more recently it became possible to measure copeptin, the C-terminal segment of the arginine vasopressin prohormone and a vasopressin surrogate [4]. Use of stimulated copeptin measurement is currently being investigated as a diagnostic tool for the differential diagnosis of hypotonic polyuria in adults. Fenske et al. (2018) assessed the diagnostic performance of measuring copeptin that was osmotically stimulated by hypertonic saline infusion as compared with the indirect water-deprivation test [5]. Overall, the direct measurement of hypertonic saline stimulated plasma copeptin had greater diagnostic accuracy than the water-deprivation test in patients with hypotonic polyuria; hypertonic saline infusion test distinguished primary polydipsia from partial central DI in 95.2% of cases compared to the 73.3% diagnostic accuracy of the indirect water-deprivation test [5]. The "gold standard" diagnosis in this series included detailed clinical case review with the benefit of several months of follow-up. However, hypertonic saline–stimulated produced side effects including headache, nausea, vomiting, and hyperkalemia, and may therefore be less likely to be applied in pediatrics in the future [6, 7]. In contrast, arginine-stimulated copeptin measurements, using an established pediatric provocative growth hormone testing procedure, have been shown to improve diagnostic accuracy with a favorable safety profile [8]. Future studies are needed to determine the most appropriate indication and diagnostic accuracy of this test for complex DI in the pediatric population.

Management

Examining this patient's course, it seems likely that she has partial central DI, which can occur with brain tumors and/or after neurosurgery. She had clear DI after her biopsy which responded as expected to desmopressin, and when she was re-admitted, despite having a lower blood sodium concentration than expected, she had high osmolality with inappropriately dilute urine. Although she was able to concentrate her urine up to 675 mOsm/kg during an indirect water deprivation test, it seems that the osmolality threshold she required to secrete vasopressin was higher than typical, corresponding to incomplete or partial central DI [9]. She was started on a trial of desmopressin with slow titration up on doses and substantial improvement was seen in her polyuria, polydipsia, and inadequate weight gain. In addition, given her preceding history of malnutrition, and long-standing chronic DI, we suspect she may have also had total body sodium depletion. Although excess solute usually worsens diabetes insipidus, the care team decided to start gentle supplementation with sodium chloride to slowly replace her stores.

Outcome

As summarized above, the patient was started on a very low dose of desmopressin of 0.025 mg as needed which was titrated upwards to 0.025 mg in the morning and 0.05 mg in the evening while inpatient. Her sodium supplementation was weaned slowly as sodium levels improved and was discontinued at 2 months. A year following, with much improved nutritional status and increased solute intake, she was requiring much higher doses of desmopressin, 0.15 mg in the morning and 0.2 mg in the evening. With this regimen and while drinking to thirst, she continued to maintain normal sodium concentrations, improved appetite and weight gain, and no longer required supplemental nasogastric tube feedings.

Clinical Pearls and Pitfalls

- Water deprivation test results need to be taken in context of the clinical scenario. Continue to revisit the diagnosis of DI and be aware of testing limitations.
- Be mindful of variations in physiology.
  - Sodium does not always entirely reflect serum osmolality.
  - Urine concentration can be higher than expected in central DI as a result of a compensatory increase in AVPR2 gene expression. This may be especially true with long-standing DI.
- In cases where the diagnosis is unclear, consider initiating therapy empirically with close monitoring to assess response.

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12 Septo-optic Dysplasia Spectrum

Elizabeth Rosenfeld

Abbreviations

ACTH	Adrenocorticotrophic hormone
DI	Diabetes insipidus
GH	Growth hormone
IGF-1	Insulin-like growth factor 1
IGF-BP3	Insulin-like growth factor-binding protein 3
MRI	Magnetic resonance imaging
SOD	Septo-optic dysplasia
TSH	Thyroid stimulating hormone

Case Description

A 6-month-old male was referred for endocrine evaluation from ophthalmology clinic where he presented with parental concern that he was not tracking objects and his eyes "wandered." He was born at term with birth weight 3.1 kg. He developed hypoglycemia requiring intravenous dextrose at 12 hours of life and

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https://doi.org/10.1007/978-3-030-83248-3_12

hyperbilirubinemia within the first 72 hours of life. Hypoglycemia was attributed to neonatal sepsis and was reported to have resolved prior to discharge at 1 week of age. Following hospital discharge, there was no reported history of polyuria, polydipsia, or hypoglycemia symptoms. He had normal growth pattern and phallus size. Ophthalmologic examination revealed roving nystagmoid eye movements, and small, pale optic discs bilaterally. Magnetic resonance imaging was subsequently performed with findings of absent septum pellucidum, mild hypoplasia of the optic nerves and chiasm, absent posterior pituitary bright spot, and thin pituitary stalk with normal appearing anterior pituitary confirming a diagnosis of septo-optic dysplasia. Initial laboratory evaluation was significant for sodium 147 mmol/L, urine osmolality 186 mOsm/kg, glucose 90 mg/dL, TSH 9.79 uIU/mL (0.5–3.8 uIU/mL), free thyroxine 0.8 ng/dL (1.0–1.8 ng/dL), ACTH 45.1 pg/mL (5.0–46.0 pg/mL), cortisol 7.2 mcg/dL (9.0–22.0 mcg/dL), IGF-1 14 ng/mL (7–93 ng/mL) IGF-BP3 1.83 mg/L (1.11–3.18 mg/L), and prolactin 20.7 ng/mL (2.0–25.0 ng/mL). Arginine-glucagon stimulation testing was subsequently performed with peak GH 1.55 ng/mL and peak cortisol 14.6 mcg/dL.

Assessment and Diagnosis

Septo-optic dysplasia (SOD) is a clinically heterogenous disorder defined by the presence of two or more of the following features: optic nerve hypoplasia, hypothalamic-pituitary dysfunction, and midline developmental abnormalities of the brain, including absent septum pellucidum and thinning or agenesis of the corpus callosum. Cortical brain malformations, such as schizencephaly, polymicrogyria, and gray matter heterotopias, may also be associated; the term SOD-plus has been proposed to describe these cases [1]. It is estimated that ~30% of SOD cases have all features of the classical triad [2]. Given significant heterogeneity in clinical phenotype, there has been ongoing debate regarding both the exact diagnostic criteria and correct nomenclature. The etiology and pathogenesis of SOD is not fully understood. Mutations in genes regulating early brain development, including *HESX1*,

OTX2, *SOX2*, *SOX3*, *PAX6*, and *PROKR2*, have been implicated; however, a genetic diagnosis is established in <1% of cases, suggesting a role for environmental and/or epigenetic factors [3].

SOD may present in the neonatal period with signs and symptoms of hypopituitarism (hypoglycemia, jaundice, microphallus), in infancy with visual abnormalities (nystagmus, strabismus, blindness), or much later in childhood with growth failure and mild, undetected visual abnormalities. Increasingly, diagnosis is prompted by identification of associated neuroanatomic features on prenatal imaging.

Diagnosis is established clinically when two or more features of the classical triad (optic nerve hypoplasia, hypothalamic-pituitary dysfunction, and midline developmental abnormalities of the brain) are present. Diagnosis is thus based upon findings on ophthalmological examination, neuroimaging, and clinical and biochemical assessment of pituitary hormone function. Optic nerve hypoplasia is most commonly diagnosed based upon findings of a small optic disc on ophthalmoscopic examination. Additional findings may include a ring of hypo- or hyperpigmentation surrounding the disc ("double ring sign"), tortuous retinal vessels, or alternatively, abnormally straight vessels with decreased branching. MRI brain, including dedicated assessment of the intracranial optic nerves and pituitary, is the optimal imaging modality, and permits both confirmation of optic nerve hypoplasia and identification of associated brain abnormalities. Neuroradiographic abnormalities of the pituitary gland may include a small or absent adenohypophysis, ectopic or absent posterior pituitary, and thin, interrupted, or absent pituitary stalk.

The reported prevalence of hypopituitarism ranges widely from 30% to 80%, reflecting pervasive limitations in the published literature on SOD, including varied populations studied (due to referral bias, differences in diagnostic classification, etc.) and limited longitudinal follow-up. The degree of pituitary dysfunction ranges from isolated hormone deficiency, most commonly growth hormone deficiency (~20%), to panhypopituitarism, as was present in this vignette. Growth hormone deficiency is observed most frequently followed by central hypothyroidism and adrenal insufficiency [4]. Both central precocious puberty,

secondary to hypothalamic dysfunction, and delayed pubertal onset or progression, due to hypogonadotropic hypogonadism, may be observed. Prevalence estimates for gonadotropin deficiency are limited due to insufficient follow-up time in most published studies. Central diabetes insipidus (DI), with or without abnormal thirst, occurs in 5–20%. DI near universally presents among those with anterior pituitary hormone deficits [4–6].

Hormone deficiencies in SOD often develop asynchronously. The majority, ~85%, of those who develop hypopituitarism will manifest an initial hormone deficiency by 5 years of age, and 90% present by 10 years of age [4, 7, 8]. However, onset of the first hormone deficit has been reported as late as 14 years, with diabetes insipidus onset reported as late as 16 years [4].

Several studies have endeavored to identify patients at greatest risk of developing endocrinopathy based upon clinical features at presentation. Ectopic posterior pituitary and abnormal pituitary stalk have been associated with both increased risk, and earlier onset, of anterior pituitary hormone deficiencies [4, 7, 9]. As in other causes of DI, an absent posterior pituitary bright spot is the most common finding, but a normal posterior pituitary is observed in up to 25% of cases [4]. Importantly, normal pituitary anatomy on neuroimaging does not preclude hypopituitarism. While septum pellucidum and corpus callosum abnormalities are common among those with optic nerve hypoplasia, these midline malformations do not appear to confer increased risk of hypopituitarism [4, 5, 8]. Thus, individuals with optic nerve hypoplasia should be considered at risk of hypopituitarism regardless of the presence or absence of these findings on MRI. Developmental abnormalities of the corpus callosum, but not septum pellucidum, have been associated with cognitive and neurodevelopmental delays [4, 5, 8]. Accordingly, many have proposed renaming and redefining diagnostic criteria for SOD to better reflect the observed clinical, versus neuroanatomic, phenotypic spectrum.

From a biochemical perspective, hyperprolactinemia has been associated with development of hypopituitarism by age 5 years, specifically growth hormone deficiency. Akin to the neuroanatomical features, hyperprolactinemia is not a reliable predictor as hypopituitarism may evolve in a large portion of those with

normal prolactin levels [10]. More recently, blindness, as a marker of severe visual phenotype, has emerged as a risk factor [7]. In contrast, neither the presence of bilateral versus unilateral optic nerve hypoplasia, nor the size of the optic nerve has been shown to reliably distinguish between those with and without endocrine dysfunction [4, 6, 7]. In one small study, retinal vein tortuosity distinguished those with pituitary hormone deficiency from those with normal function, although these findings have not been replicated [11]. Ultimately, while some clinical risk factors have been identified, neuroimaging and phenotypic findings within SOD incompletely predict the evolution of endocrinopathy.

Management

If not already performed, children with features of SOD should be referred for ophthalmologic examination, endocrinologic evaluation, and MRI brain, including dedicated pituitary sequences. Referral to neurology and/or neurodevelopmental therapists is indicated for those with additional central nervous system malformations, seizures, or developmental delays. Endocrine assessment includes clinical and biochemical evaluation of growth, thyroid and adrenal function, pubertal status, and water balance. In infants, evaluation should also include assessment for hypoglycemia, as well as for micropenis in males. Notably, hypothyroidism may be missed by newborn screen employing primary TSH measurement. Identified hormonal insufficiencies should be treated. Importantly, thyroid and/or glucocorticoid replacement may unmask previously subclinical diabetes insipidus. Longitudinal assessment of pituitary function is required as deficiencies not present initially may develop over time.

Outcome

This patient was started on hydrocortisone, followed by levothyroxine and growth hormone replacement, after completion of his initial evaluation. Hormone replacement doses have since been

titrated to hydrocortisone 9 mg/m2/day (when well, with instructions for moderate stress dosing of 50 mg/m2/day and injectable 100 mg hydrocortisone sodium succinate for emergencies), levothyroxine 62.5 mcg daily (3 mcg/kg/day), and GH 0.15 mg/kg/week administered nightly. Diabetes insipidus was initially managed without medication as serum sodium was maintained between 145 and 149 mmol/L on ad lib feeds with standard infant formula. Around 15 months of age, he began to wake every 2 hours overnight to drink. Oral desmopressin (DDAVP®) was started at a dose of 0.05 mg nightly, and he is currently well-controlled on doses of 0.05 mg in the morning and 0.075 mg at bedtime. Now 4 years of age, he is growing along the 55%ile, with sodium 140–146 mmol/L, and thyroxine 9 mcg/dL (4.5–12 mcg/dL). Gross motor and social development are mildly delayed. He has severe visual impairment but does respond to visual stimuli. He is followed every 3–4 months in endocrinology clinic and annually by neurology and ophthalmology. He receives speech therapy, occupational therapy, and full visual support services through school and has been making developmental progress.

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13 Familial DI and Genetic Workup

Rachana Shah

Case Presentation

The patient is a 14-month old male, initially evaluated for poor weight gain. He was born full term with birthweight 7 pounds 2 ounces and had no issues with neonatal hypoglycemia. He nursed well as an infant, had no illnesses during this time, and was growing appropriately until around 1 year of age. Per the parents, he began drinking excessively (greater than 40 ounces per day), including drinking bath water, flower pots, puddles, and pet water bowls. He is requiring diapers changes every 1–1.5 hours, leaking with urine. He sometimes wakes at night and cries for water, and will quickly drink 8–10 ounces if offered. He prefers to drink water over milk or juice, and has a poor appetite for solid foods.

Of note, mother was diagnosed with central diabetes insipidus at age four and has been on desmopressin. She recalls that on imaging, her pituitary was "missing something". She had no issues with growth as a child, and no fertility concerns. Father has no pertinent medical history. 3-year-old sister does not have similar symptoms, and has normal growth and development.

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C. A. Alter (ed.), *Diabetes Insipidus in Children*,
https://doi.org/10.1007/978-3-030-83248-3_13

Physical exam is unremarkable. Normal genitalia and descended testes bilaterally. Random and first morning labs have shown normal glucose of 75–96 mg/dl and sodium 138–142 mg/dl. Creatinine was normal, and urinalysis showed no blood, protein, leukocytes, glucose, or ketones.

The patient was admitted for a water deprivation test, and had a sodium of 146 mmol/L after 18 hours without food or liquid intake. Urine output was calculated at 2.5 mL/kg/hour. Plasma osmolality was 298 mOsms/kg and urine osmolality was 300 mOsms/kg with urine specific gravity of 1.005. A pituitary MRI showed an absent posterior pituitary bright spot. Remainder of pituitary screening tests (thyroid hormone, cortisol, growth factors) were normal.

Assessment and Diagnosis

There are familial forms of both neurohypophyseal and nephrogenic diabetes insipidus (Table 13.1). Familial neurohypophyseal DI is most often due to autosomal dominant *arginine vasopressin* (*AVP*) mutations. 72 mutations have been identified, the majority in the NPII moiety or the signal peptide, though a few mutations in the AVP moiety have been described (Fig. 13.1). Most are missense or nonsense mutations, though a few deletions, indels, and splice site mutations have been found. Mutations lead to disor-

Table 13.1 Overview of familial DI

	Affected gene	Inheritance (# of mutations)	Age of onset
Neurohypophyseal DI	AVP	AD (73) AR (3)	1–6 years Early infancy
	WSF1	AR (>170)	2nd-3rd decade
Nephrogenic DI	AVPR2	X-linked (>200)	Early infancy
	AQP2	AR (52) AD (11)	Early infancy Early childhood

Fig. 13.1 The structure of the AVP gene related to components of the AVP peptide (prepro-AVP), including the N-terminal signal peptide (SP), the AVP moiety, the NPII moiety, and the C-terminal copeptin

dered processing or folding of AVP precursors; in most cases, the mutant is expressed, but retained in the endoplasmic reticulum, leading to cell death [1–3]. This is supported by autopsy studies showing absence of vasopressinergic neurons in affected subjects [4, 5]. There is also evidence to suggest that the mutant prohormones heterodimerize with wild-type AVP, preventing processing in a dominant negative manner [6]. The only evidence of genotype-phenotype correlation is with the c.55G > A (p.Ala19Thr) mutation, which causes abnormal cleavage of the signal peptide and is associated with later onset [7].

Onset is gradual due to progressive destruction of vasopressinergic neurons; thus, in early phases of the disease, AVP may be released during water deprivation, falsely confirming a normal response [8, 9]. Patients can present from a few months to a few years of age with polyuria, polydipsia, and failure to thrive. Presentation can be variable, even within the same family. There have been 3 autosomal recessive mutations in the *AVP* gene identified. All have presented with onset of DI in infancy, and good response to desmopressin.

Autosomal recessive mutations in the *WSF1* gene are associated with Wolfram's syndrome which presents with central diabetes insipidus, diabetes mellitus, optic atrophy, and deafness, (DIDMOAD) [10, 11]. Central DI is seen in 70% of patients; there is one reported case of isolated familial DI with WSF1 mutation. DI usually presents later in Wolfram's, in the 2nd to 3rd decade of life; the mechanism of neuronal destruction has not been identified but mutant wolframin is known to cause ER aggregates and ER stress in other cell types, suggesting this may also be causal in hypophyseal cells [12]. Case reports have also described central DI due to mutations in *PCSK1* and *FGF8*. There is also a report of X-linked transmission with no mutation yet identified [13–15].

Familial nephrogenic diabetes insipidus is caused by inactivating mutations of *AVPR2* (AVP receptor) in 90% and *AQP2* (aquaporin 2) in 10% of cases. Both lead to insensitivity of the distal nephron to AVP. Mutations in *AVPR2* are associated with X-linked inheritance, and thus the majority of cases are in males with onset of complete diabetes insipidus in early infancy [16, 17]. Some female patients have been reported, with milder phenotype, thought to be related to skewed X-inactivation [18]. Over 200 mutations have been reported, mostly missense mutations causing misfolded protein and ER retention.

AQP2 mutations are autosomal recessive homozygous or compound heterozygous in the majority of cases, though some heterozygous autosomal dominant mutations are described [19]. 52 mutations have been identified. Missense mutations throughout the *AQP2* gene result in misfolding and ER retention which ultimately causes cell death and complete diabetes insipidus. A few mutations do result in some cell surface AQP2 expression, and partial DI phenotype that may respond to desmopressin [20].

11 mutations in *AQP2* are associated with autosomal dominant inheritance. These tend to be in the c-terminal, and impede cell trafficking and localization [21]. These mutations exert a dominant negative influence when mutant protein forms heterotetramers with wild-type protein, leading to misrouting, and reduced expression at cell surface. Depending on the mutation, there may still be functional wild-type homotetramers; thus onset of AD disease is later in onset and milder than other forms [22].

Management

Patients with genetic forms of diabetes insipidus should be treated similarly to those with non-familial forms, using 1-desamino-8-D-arginine vasopressin (desmopressin) for neurohypophyseal disease and thiazide diuretics or indomethacin for nephrogenic cases. There are novel therapeutics in development for X-linked nephrogenic DI, including cell-permeable AVPR2 agonists that act as molecular chaperones and prevent misfolding of protein, leading to cell surface expression [23]. Secretin receptor agonists and

phosphodiesterase inhibitors are also being targeted to activate alternate pathways (bypassing AVPR2 activity) to AQP2 surface expression [24, 25].

Outcome

After the water deprivation test, desmopressin was given and led to decreased urine output. He continued treatment with desmopressin and showed improved appetite and weight gain, decreased polyuria and polydipsia. Genetic testing revealed mutation in AVP gene in patient and mother, and no mutation in father or older sister.

Clinical Pearls and Pitfalls

- Familial forms of DI include AR, AD, or X-linked inheritance and are primary caused by mutations in *AVP* in central DI and *AVPR2* and *AQP2* in nephrogenic DI.
- Mutations in *WSF1* cause Wolfram (DIDMOAD) syndrome which is associated with DI in 70% of cases, in addition to diabetes mellitus and optic atrophy.
- Phenotypes can vary, even within a family with the same mutation.
- Diagnostic testing early in disease process may be misleading, so if family history is suggestive, the diagnosis should not be excluded.
- Treatment of familial DI is similar to non-familial forms.

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14

Treatment with Thiazides in Infants with Central Diabetes Insipidus

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Case Presentation

Endocrine was consulted by the neonatology team on a 31-day-old female for glucocorticoid recommendations when she was noted to have hypotension and clinical deterioration after brief discontinuation of glucocorticoids. She was born at 32 weeks of gestation with a birth weight of 1080 grams via elective C-section due to uteroplacental insufficiency, oligohydramnios, and severe intrauterine growth retardation (IUGR). She was diagnosed with lobar holoprosencephaly by head ultrasound which was later confirmed by MRI, shortly after birth. She was transferred at day of life 19 to our tertiary care NICU for deteriorating respiratory status. Screening of pituitary function revealed a low TSH of 0.58 mIU/L (0.59–5.78 mIU/L) and a low free T4 of 0.29 ng/dL (0.59–1.17 ng/dL); a low cortisol of 0.2 mcg/dL (2–20 mcg/dL); an undetectable IGF-1 of less than 16 ng/mL and a low growth hor-

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C. A. Alter (ed.), *Diabetes Insipidus in Children*,
https://doi.org/10.1007/978-3-030-83248-3_14

mone of less than 0.1 ng/mL. She was started on thyroid hormone replacement for central hypothyroidism and growth hormone therapy for growth hormone deficiency in addition to glucocorticoid replacement for cortico-adrenal insufficiency. Hypoglycemia resolved soon after growth hormone and hydrocortisone initiation. On day of life 32, she was found to have hypernatremia with a sodium of 154 meq/L (135–145 meq/L) and increased urine output of 6.9 mL/kg/hr over the previous 24 hours. Her calculated serum osmolality, based on a sodium of 154 meq/L (135–145 meq/L), BUN of 40 mg/dL (5–25 mg/dL), and glucose of 105 mg/dL (70–120 mg/dL), was elevated at 324 mOsm/kg (280–300 mOsm/kg), urine osmolality was 226 mOsm/kg (241–1328 mOsm/kg), and urine sodium was 49 mmol/L.

Assessment and Diagnosis

Given the infant's condition of holoprosencephaly and multiple other pituitary deficiencies, her excessive urinary output in the setting of hypernatremia, elevated serum osmolality, and low urine osmolality leads to the diagnosis of central diabetes insipidus (DI). She was started on vasopressin drip on day of life 32 which was titrated in increments of 0.5 mU/kg (max 10 mU/kg/h) to maintain urinary output at a starting goal of 2–4 cc/kg/h. Despite the use of the vasopressin drip and frequent titrations, she had wide fluctuations in her sodium levels. When she was noted to have relatively more stable sodium levels, she was given 0.01 mcg of subcutaneous desmopressin twice daily on day of life 60 to wean her off the vasopressin drip. The dose was reduced to 0.01 mcg once daily when her sodium dropped down to 132 meq/L (133–145 meq/L). Subsequently, she had hypernatremia to 165 meq/L (133–145 meq/L) as she was on stress doses of hydrocortisone at that time for critical illness, worsening her diabetes insipidus. Her hypernatremia resolved after her hydrocortisone was weaned down to a physiologic dose. Though she remained stable initially on the daily 0.01 mcg dose of desmopressin administered subcutaneously, 8 days later, she became hyponatremic with a sodium of 125 meq/L (133–145 meq/L). The desmopressin was thus held and she required fluid restriction until sodium levels

normalized. Once the sodium levels started to rise again with an increase in urinary output, subcutaneous desmopressin was attempted again. This was unsuccessful since she continued to have lability of her sodium levels and urine output. The decision was made on day of life 125 to start chlorothiazide 5 mg/kg/dose twice a day and a low solute formula (Similac PM 60/40).

Management

Management of central diabetes insipidus in infancy is challenging. Treatment options for central diabetes insipidus include replacement with free water deficit and desmopressin. Desmopressin works by acting on the V2 vasopressin receptor on the distal tubule and collecting duct of the kidney to increase water reabsorption [1]. However, the nature of fixed diuresis along with a diet that is primarily composed of high fluid intake puts DI infants treated with desmopressin at a high risk of hyponatremia and water intoxication [2].

Thiazides have traditionally been used in the management of nephrogenic diabetes insipidus. They have also been found to be efficacious in the treatment of infants with central diabetes insipidus [3]. The exact mechanism of thiazide in DI is unknown, but the most commonly accepted theory is that the effect is paradoxical. Thiazide diuretics work by inhibiting the Na-Cl co-transporter at the distal convoluted tubule which initially results in renal sodium loss. This leads to extracellular volume contraction causing a decrease in the glomerular filtration rate (GFR). As such, there is increased proximal tubular sodium and water reabsorption which leads to decreased water and solutes at the distal tubule and collecting duct. Therefore, there is decreased solute and urinary output loss (Fig. 14.1) [4]. Studies done in animals illustrate that they enhance water reabsorption at the level of the medullary collecting ducts through increased osmosis thus playing a role in reducing urinary output [1].

The use of thiazides in the treatment of infants with central DI was first described in a case series of three infants published in 2000 by Pogacar et al [1, 3]. Since then, there have been numerous case series replicating the success of this treatment. The recom-

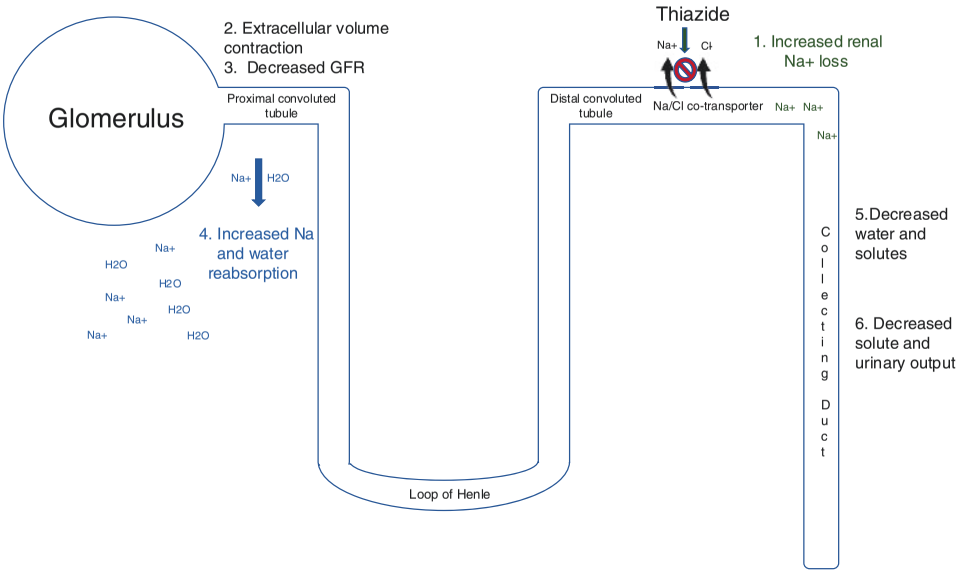

Fig. 14.1 This depicts the proposed mechanism of action of thiazides in treating central diabetes insipidus. Negative inhibition of the Na-Cl co-transporter at the distal convoluted tubule leads initially to renal sodium loss (1), which results in extracellular volume contraction (2) and decreased GFR (3). As result, there is increased sodium and water re-absorption at the proximal tubule (4). This then leads to decreased solute and sodium at the distal tubule and collecting duct (5) and eventually decreased urinary solute and output loss (6) [4]

mended starting dose when using chlorothiazide is 5–10 mg/kg/day which can be divided into two doses per day [5]. This dose can be titrated up to 30 mg/kg/day divided into three doses per day [6]. The dose for hydrochlorothiazide is 1–2 mg/kg/day, though, chlorothiazide is used at our institution and is reported to be more widely used in the literature [5]. Use of thiazides can cause hypercalcemia and hypokalemia. The former is due to indirect decreased renal secretion of calcium at both the proximal and distal tubules while the latter to an indirect increased in secretion of potassium [7]. Another side-effect of thiazides includes hyperglycemia as a result of hypokalemia-induced hyperpolarization at the islet cell membrane resulting in the inability of the cell to release insulin [8]. Therefore, it is recommended to screen for these electrolyte abnormalities periodically while on a thiazide and to monitor particularly for hypokalemia during times of illness [5].

In addition to thiazides, a low solute formula can also be used in the treatment of DI in infants. Urinary output is determined by the renal solute load which consists of the total amount of solute that needs to be excreted by the kidney. An increased renal solute load would increase urinary output. Therefore, a low-solute formula has a lower renal solute load which would result in decreased urinary output. Breastmilk is also found to have a low renal solute load and can be used as an alternative to traditional formula [4]. Previous studies show that thiazides are most effective when the patient is on a primarily liquid, diet, and generally a lower solute containing diet. As such, transition to demopressin was recommended when solid foods were introducted to the patient's diet [4]. However, more recent literature suggests that this may not be necessary and that thiazides may be continued until their effectiveness has worn off, which would be illustrated by an increase in polyuria, polydipsia, and hypernatremia while on a thiazide [5].

Outcome

Our patient initially required chlorothiazide dose adjustment given elevated sodium levels. The dose was increased to 20 mg/kg/day divided into two doses. She remained stable and on day of life 188 she was discharged home on this dose and did not

require any additional doses of desmopressin. She is currently a 7-year-old female who continues to follow in the endocrine clinic for management and routine follow-up for panhypopituitarism. Her diabetes insipidus is well controlled on 16 mg/kg/day divided into two doses of chlorothiazide with normal serum sodium levels in the 140–149 meq/L range (133–145 meq/L) and urine output of 2.6 mL/kg/day, without any indications for desmopressin. She is still primarily fed via G-tube with minimal oral intake. Her total fluids including feeds and free water equate 105 mL/kg/day; about 45% of the total is water, and about 55% of the total is a standard commercial formula. Overall, due to minimal oral intake, her solute load on this feeding regimen can be described as low. She developed mild hypokalemia as one of the side effects of chronic thiazide use for which she now takes daily potassium chloride supplementation.

Clinical Pitfalls and Pearls

- Desmopressin in infants should be used with caution as it can increase the risk of symptomatic hyponatremia and water intoxication.
- Thiazides are a good alternative treatment in infants with central DI as they do not result in wide fluctuations in sodium levels and the risk of hyponatremia is decreased.
- The starting dose when using chlorothiazide is 5–10 mg/kg/day divided into two doses, which can be titrated up to 30 mg/kg/day divided into three doses. When using hydrochlorothiazide, dose is usually 1–2 mg/kg/day.
- Infants on a thiazide need to be monitored for hypercalcemia periodically and for hypokalemia, especially during times of illness.
- Monitoring hyperglycemia can be based on the patient's signs and symptoms.
- Thiazide diuretics can be used for management of central diabetes insipidus beyond the age of infancy, especially if solute loads remain relatively low. This requires close and frequent monitoring with prompt recognition of indications to add or switch to desmopressin.

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15 Absent Thirst and Diabetes Insipidus

Karla F. Leavens and Amy Wood

Case Presentation

A 4-year-old male with no prior medical history presented to the emergency department due to acute onset ataxia and left esotropia over the prior 24 hours. He and his parents denied any recent headaches, dizziness, nausea, vomiting, polyuria, or polydipsia. On physical exam, he had a wide-based ataxic gait, left 6th cranial nerve palsy and bilateral papilledema on fundoscopic examination. Rapid neuroimaging revealed a 3.8 cm partially solid/partially cystic suprasellar mass, consistent with a craniopharyngioma. Endocrine labs, including thyroid-stimulating hormone, free thyroxine, and cortisol were normal. Serum sodium at presentation was 140 mEq/L (normal range 135–145 mEq/L).

He was admitted to the pediatric intensive care unit and underwent an uncomplicated right frontal craniotomy with tumor resection the following morning. Two hours following surgery, his urine output abruptly increased to 7.5 mL/kg/hour and his

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C. A. Alter (ed.), *Diabetes Insipidus in Children*,
https://doi.org/10.1007/978-3-030-83248-3_15

serum sodium increased to 167 mEq/L with an inappropriately dilute urine (urine specific gravity 1.0002 and urine sodium <20 mEq/L), consistent with diabetes insipidus. He was started on a vasopressin drip, which was titrated along with fluids to achieve urine output of approximately 3 mL/kg/hour. He remained in the PICU for 3 weeks following surgery before being transferred to the rehabilitation unit for 2 months for sodium management and titration of intermittent desmopressin dosing. He was determined to have panhypopituitarism following his surgical recovery, and was started on levothyroxine and physiologic hydrocortisone. Daily sodium monitoring while in the rehab unit showed wide-ranging sodium levels, from 130 to 162 mEq/L. His parents and his medical care team noticed that his voluntary fluid intake did not seem to change even when his sodium levels were in the 150–160 mEq/L range.

Assessment and Diagnosis

This case is taken from the experience of one of the co-authors, whose 4-year-old son was diagnosed with a craniopharyngioma in May 2015. The day started as any typical day and ended with our family in the emergency department facing this startling discovery. Sodium management became a struggle in the coming weeks and months after tumor removal, as it was discovered that our son had no desire to drink water despite significantly high serum sodium levels. This led us to the realization that his thirst would not be a reliable indicator of his fluid and sodium status. During the first year of recovery, managing his adipsic diabetes insipidus was the biggest challenge for us and for his medical team. Sodium fluctuations triggered two seizures and multiple hospitalizations in the first 9 months after his surgical resection.

This case presents a particularly challenging aspect of DI management: maintaining appropriate fluid status, and therefore electrolyte levels, when the patient does not have an intact sense of thirst, termed adipsia or hypodipsia. Individuals with an intact sense of thirst and free access to water are able to maintain euvolemia by drinking liters of water a day to counteract persistent diuresis even in the complete absence of anti-diuretic hormone secretion. While most patients with DI are managed pharmacologically with intermittent desmopressin dosing, having an intact sense of thirst helps minimize sodium fluctuations during diuresis/anti-diuresis cycles. When patients are not able to sense when their serum osmolality rises and drink appropriately, this can result in hypovolemic hypernatremia, leading to shock, seizures, brain damage, and even death. Alternatively, patients may continue to drink in the setting of low serum osmolality, which can exacerbate over-diuresis while on desmopressin, leading to fluid overload and hyponatremia. Patients with DI who have adipsia have increased risk of morbidity and mortality compared with those with intact thirst [1–3].

Changes in blood osmolality are the main driving force of thirst, as well as ADH release, though the neurobiology of these processes is likely distinct. These changes are detected by two structures in the lamina terminalis, the subfornical organ (SFO) and the organum vasculosum of the lamina terminalis (OVLT), though the underlying mechanism of osmolality detection is unknown [4, 5]. The SFO and OVLT lie outside the blood-brain barrier adjacent to the third ventricle and can therefore quickly sense changes in blood osmolality. There is likely additional input on thirst of angiotensin II through action in the SFO, and possible influence of baroreceptor activation by hypotension through the brainstem [4, 5]. A third region of the lamina terminalis, the median preoptic nucleus (MnPO), acts with the SFO and OVLT to integrate fluid status sensing and response. Neurons from the lamina terminalis directly synapse with neurons in the paraventricular hypothalamus and supraoptic nucleus and activate release of ADH from the posterior pituitary [4, 5]. While thought to be distinct from this neuroendocrine pathway, the neural pathway which results in the complex perception of thirst is not well-defined, and

many interactions of the lamina terminalis with the cortex, midbrain, hindbrain, thalamus, and hypothalamus have been proposed to play a role [4, 5]. Regardless of the precise downstream pathways, thirst is typically activated, as is ADH release, in response to a 1% elevation of plasma osmolality above normal, typically 295–298 mOsm/kg [4, 5]. Conversely, thirst will be inhibited to prevent overhydration in response to a 2% decrease in plasma osmolality, typically 277–280 mOsm/kg, though this can vary among individuals [4, 5]. While thirst is not directly activated by sodium levels, in the absence of hyperglycemia, fluctuations in serum sodium levels are the biggest influence on osmolality and therefore largely drive the thirst response.

Individuals with disruptions in the structures of the lamina terminalis, its neuronal projections, or the hypothalamus can have an altered sense of thirst [4, 5]. Though most commonly seen in patients with DI, there have been rare case reports of patients with isolated adipsia without DI [6–9]. Craniopharyngioma resection is the most common cause of adipsic DI, as seen in our patient. While there is increased risk of adipsic DI following any pituitary surgery, either suprasellar or intrasellar, the risk is highest following craniopharyngioma resection [2, 10, 11]. In 2 retrospective reviews, 7–13% of individuals with craniopharyngioma resection had adipsic DI, accounting for approximately 9–17% of those with DI [12, 13]. Other reported causes of adipsic DI include clipping of anterior communicating aneurysms [14–17], midbrain anomalies, such as agenesis of the corpus callosum [3, 18], neurosarcoidosis [15], toluene exposure [19], and CNS infections [3, 20, 21]. Interestingly, there have been reports of individuals recovering their sense of thirst after years of adipsia, though this is likely uncommon [15, 22, 23].

Individuals without intact thirst can have a range of thirst impairment. Some patients will report a completely absent thirst drive even with very elevated serum sodium levels, while others will become thirsty at a higher plasma osmolality than typical. Some patients will continue to drink inappropriately at a low serum sodium level when thirst should be suppressed. Finally,

some may have inconsistent thirst, feeling thirst and drinking appropriately only some of the time. While not strictly adipsic due to neuronal dysfunction, certain populations may be considered to have "functionally-absent" thirst. Individuals who are unable to communicate with caretakers due to intellectual or communicative disability may be unable to express their need for hydration though their neuronal thirst circuit is intact. In addition, individuals who are physically disabled may not be able to access hydration without assistance when they are thirsty. This can be an issue for individuals with congenital panhypopituitarism who have associated brain anomalies, such as holoprosencephaly, which result in significant cognitive and physical disabilities.

Appropriate recognition of an absent thirst mechanism in an individual with DI is essential for management. Diagnostic tests, such as water deprivation tests and hypertonic saline infusions, can be performed and subjective thirst can be monitored in response to rising blood osmolality [6, 24, 25]. However, these tests are rarely necessary outside of research settings as a careful history and discussion with the patient or family is often sufficient to determine that someone's thirst response is not intact. Certainly, a documented plasma osmolality of >298 mOsm/kg or a sodium level above the normal range (typically >145 mEq/L) without a reported increase in thirst by the patient or family is highly suggestive that thirst is not intact [4]. This may be during an episode of hypernatremia requiring medical intervention or on routine lab monitoring. In some patients with decreased or inconsistent thirst response, rather than total adipsia, it may be challenging to determine if their thirst mechanism is reliable. One question for patients and families is whether the patient starts increasing fluid intake during times of breakthrough between desmopressin dosing as thirst should be activated when serum sodium levels and osmolality rise during diuresis. In addition, patients with an intact thirst mechanism should crave and seek out water, especially cold water, when becoming hypernatremic. Some patients will happily drink sugar-sweetened beverages when not actually thirsty, as these are often an appealing drive for children or those with hypo-

thalamic-driven hyperphagia. In our patient's case, he clearly did not have an intact sense of thirst from the beginning due to a lack of thirst during documented hypernatremic episodes. However, he was not fluid-averse, and would often try to drink juice even when his serum sodium was low while refusing water when his sodium was elevated.

Management

When it became clear early during the first year following our son's diagnosis that his sense of thirst was not going to be an indication of his need for fluids, we turned to other indicators to guide us. We struggled to optimize his desmopressin dosage because of his somewhat random fluid intake exacerbated by his inconsistent response to desmopressin. We attempted to track his fluid status by measuring ins-and-outs (I&Os) and replacing fluids with daily reporting to our endocrinologist. We monitored his weights on an accurate scale at home daily. We averaged three urgent lab visits a week and often found ourselves in the emergency department on weekends to measure his serum sodium level when things seemed "off." Certainly, sodium monitoring is important for safety, but for many younger patients with DI, these frequent lab draws become very traumatic with multiple sticks in a sitting due to dehydration.

We learned of the handheld blood analyzers that are typically used in hospital emergency departments and intensive care units, urgent care clinics, and veterinary offices. These self-contained devices can perform a basic metabolic panel on a small sample of blood with results in minutes. Given the frequency with which we were having to get laboratory sodium checks to guide our son's management, being able to measure his sodium levels at home via a finger stick

seemed ideal. However, handheld blood analyzers are not currently FDA-approved and are unfortunately very difficult and expensive for individual purchase outside of a hospital setting. We were able to obtain it with the help of community fundraising and my son's pediatrician who purchased the device and agreed to oversee its usage in this off-label situation. Using the handheld blood analyzer at home, we could test his sodium level frequently (typically 1–2 times per day) and combine this knowledge with his I&Os and body weights to eventually land on his daily fluid needs. Use of this device mitigated constant lab visits and hospitalizations, and helped us develop a stable care management plan, including fluid goals with scheduled and break-through desmopressin dosing. It can be invaluable to patients and families struggling to managing DI with absent thirst; however, it is worth noting that testing cartridges is expensive (approximately $10/per test) and requires up to 20 drops of blood when using home lancets (100–200 uL). This makes frequent testing challenging so patients and families still have to rely on other mechanisms to judge fluid balance between tests.

While the handheld blood analyzer can be a valuable tool in managing adipsic DI, careful I&O and weight monitoring is essential. Judicious monitoring of fluid intake and urine output can often give a very good indication of a patient's fluid status. We recommend combining this with precise body weight monitoring using a scale with accuracy of 0.1 kg. Once data from a typical home routine is collected, a goal daily fluid intake can be determined, with daily adjustments based on body weight fluctuations, either holding fluids for weight gain or adding fluids for weight loss. Sodium monitoring typically has to be performed more frequently than in individuals with intact thirst, at least until a routine is established. Even adipsic patients who have fairly stable sodium levels when well unfortunately will require increased

monitoring when sick to ensure they do not become hypo- or hypernatremic.

As described above, some patients, families, and medical professionals advocate for the use of home sodium monitoring through the use of clinical handheld blood analyzers. This becomes especially appealing if patients are requiring multiple laboratory sodium checks per week to ensure safety. It allows for correlation of sodium levels in response to I&O and body weight monitoring and further adjustment of patient care plans. It also allows for sodium checks in cases of illness or concerning symptoms to know if additional intervention or medical attention is required. While there is minimal literature on this topic, several case reports have suggested this approach can be efficacious and safe with appropriate patient and family education [26–28].

Currently, there are no home monitoring devices for sodium levels or osmolality which are FDA-approved, so all usage is off-label. Furthermore, handheld blood analyzers are expensive and not typically available for purchase by consumers. If a motivated patient or family obtains one for home sodium monitoring, there are several considerations for management. These devices are designed for use in a hospital or clinical setting using venous blood rather than capillary blood, and most devices have a slightly different range than laboratory serum or plasma sodium levels. However, in one of the few case series on this topic, there was good correlation between the sodium measurement on handheld monitoring device and in the laboratory so that the clinical decision-making outcome was similar [26]. Patients and clinicians must be prepared to know how to incorporate this information into the treatment plan: we recommend partnering between patients and families and their medical teams to establish timing and frequency of testing and actions to take in response to the results. It remains to be seen if home sodium monitoring through the use of handheld devices becomes more widely used or if even more frequent monitoring devices are developed in the future, akin to the movement from glucometers to continuous glucose monitors in the management of diabetes mellitus.

Outcome

The patient in the case presentation, also known as my son, is doing very well with no recent hospitalizations for hypo- or hypernatremia. Our daily management protocol includes a body weight measurement first thing in the morning, at noon, and in the evening to assess any sudden increases or decreases in weight which can help indicate whether fluids need to be replaced or held. His goal fluid intake is 1–1.5 L of sugar-free fluids daily. We test his sodium level using the handheld blood analyzer several times a week or if he has any concerning symptoms. If we get a sodium level outside of his goal range, we repeat testing through the day until he is back in the normal range. We will adjust his PRN desmopressin dose based on all of these parameters in collaboration with his medical team. While managing my son's DI is still sometimes like hitting a moving target, we consistently rely on the handheld blood analyzer to monitor sodium and make fluid adjustments with successful results over the past 6 years.

In 2017, the Raymond A. Wood Foundation (RAWF) was founded with the mission of empowering hypothalamic-pituitary brain tumor survivors for improved quality of life by providing access to education, technology, and evolving treatments. As part of that mission, RAWF provides handheld blood analyzers to pediatric brain tumor patients with adipsic diabetes insipidus with the treating physician's consent to use it in the patient's care plan. Currently, RAWF is working to develop an at-home sodium measurement solution that would be FDA-approved, available with a provider's prescription, easy to use and affordable.

Clinical Pearls and Pitfalls

- Individuals with adipsic DI can be particularly challenging to manage clinically.
- Recognition of an absent thirst response is important for DI management, and can typically be done through careful history-taking with the patient and family.
- Management of adipsic DI requires vigilant I&O and daily body weight monitoring.
- Handheld blood analyzers are not currently FDA-approved for home sodium monitoring but may be beneficial in the management of some patients with adipsic DI who closely partner with their medical care team.

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16 Nephrogenic Diabetes Insipidus

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Case

A 4-year-old male presented with a medical history of diabetes insipidus (DI) for which he was taking intranasal desmopressin DI was initially diagnosed at an outside facility at 2 years of age when he was being evaluated for developmental delay. Initial magnetic resonance imaging (MRI) of the brain did not visualize the pituitary, however, a repeat MRI reported an absent posterior pituitary bright spot (suggestive of central DI). Endocrine evaluation on the patient revealed undetectable IGF-1 suggestive of growth hormone deficiency and central hypothyroidism. Adrenocorticotropic hormone (ACTH) stimulation test was normal. With a history of polyuria and polydipsia consistent with central diabetes insipidus, he was started on intranasal desmopressin.

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C. A. Alter (ed.), *Diabetes Insipidus in Children*,
https://doi.org/10.1007/978-3-030-83248-3_16

At our center, he received intranasal desmopressin, oral desmopressin, and then subcutaneous desmopressin with very minimal response as polyuria and polydipsia persisted. He developed hypernatremia (153–157 mEq/L), with a urine output of 5 L per day. Urine osmolarity 2 hours after oral desmopressin administration was 60 mOsm/L. To differentiate between central and nephrogenic DI, the patient was administered vasopressin 5 units subcutaneously but showed no response, with urine osmolarity remaining between 60 and 80 mOsm/l and serum osmolarity over 300 mOsm/l. This seemed to be consistent with a diagnosis of nephrogenic DI (NDI) rather than central DI. A renal bladder ultrasound (RBUS) evaluating for renal dysplasia or obstructive uropathy as secondary causes for NDI was noted to be normal.

Genetic tests for an AVPR2 gene (X-linked) and AQP2 gene (autosomal) revealed that the patient had normal Aquaporin 2 (AQ-2) genes, however a hemizygous gross deletion or genomic rearrangement of an AVPR2 gene (X-linked) was noted.

Desmopressin was stopped and our patient was started on Amiloride 2.5 mg twice daily with little effect on reduction of his fluid intake. He was therefore started on indomethacin, hydrochlorothiazide, and omeprazole. This resulted in an over 50 percent reduction in his fluid intake, improved solid food intake, and he began to thrive.

Discussion

Nephrogenic diabetes insipidus (NDI) is a disorder that involves the late distal tubules and collecting ducts, which are unresponsive to endogenous vasopressin resulting in an inability to concentrate urine. NDI may be congenital or acquired and is characterized by polydipsia and polyuria [1].

Collecting duct cells express aquaporin-2 (AQP2) channels on their luminal surface that are key in regulating body water balance [2]. The peptide hormone arginine vasopressin (AVP), released by the posterior pituitary, operates these channels through activation of the type 2 vasopressin receptor (AVPR2) on the basal cell surface [3]. Dysfunction or dysregulation of either the AQP2 channel or AVPR2 results in NDI [4].

Congenital NDI is a result of a mutation in either the AVPR2 or AQP2 genes [4]. Secondary causes of NDI are associated with systemic disorders, renal dysplasia, partial obstructive uropathy, antimicrobial agents and other drugs such as lithium, electrolyte abnormalities, Fabry's disease, and Fanconi syndrome [4] (see Table 16.1).

Management of NDI can be challenging. Currently treatment is symptomatic and involves use of a low-solute diet, thiazide and potassium sparing diuretics, and prostaglandin inhibitors (non-steroidal anti-inflammatory agents) [5]. However, ongoing research into AVPR2 and AQP2 has opened the possibilities for development of targeted gene therapy to treat congenital NDI [6].

Table 16.1 Etiologies of nephrogenic DI

Congenital causes of nephrogenic DI	
X-linked	AVPR2 (arginine vasopressin receptor 2)
Autosomal recessive or dominant	Ch12q13 mutation encoding AQP2
Acquired causes of nephrogenic DI	
Kidney	Renal dysplasia Partial obstructive uropathy
Systemic disorders	Amyloidosis Langerhans cell histiocytosis Sarcoidosis Sjogren syndrome Sickle cell disease
Antimicrobials	Foscarnet Methicillin Rifampicin Bactrim
Other drugs	Lithium Ifosfamide Colchicine
Other associations with NDI	Hypokalemia Fabry disease Fanconi syndrome

Congenital Nephrogenic DI

Epidemiological evidence indicates that approximately 90% of congenital NDI cases are attributable to X-linked mutations in the vasopressin receptor and about 10% to autosomal dominant or recessive mutations of AQP2 [6].

AVPR2 Gene Mutations

AVPR2 gene mutations have been differentiated into five classes [7, 8]:

- *Class I*: Defects in transcription, mRNA processing, or translation (such as promoter alterations, dysfunctional splicing, anomalous exon skipping, frameshift, and nonsense mutation) [7].
- *Class II*: Known to be the most common form of AVPR2 defect [7]. This class exhibits misfolding of AVPR2 due to underlying mutations including missense, insertion, or deletions. This results in retention of fully translated AVPR 2 proteins in the endoplasmic reticulum itself, preventing transport to the plasma membrane [7].
- *Class III*: Despite appropriate transport to the plasma membrane, this class involves defective functions (such as impaired G protein binding and intracellular signaling) due to misfolding of the AVPR2 [7].
- *Class IV*: Shows decreased binding affinity to AVP but has no apparent defects in protein trafficking to the plasma membrane [7].
- *Class V*: These mutants are directed inappropriately to various other subcellular organelles like arrestins-positive endocytic vesicles [9, 10].

AQP2 Gene Mutations

The AQP2 gene is situated on human chromosome 12q13 and codes for the 271 amino acid polypeptides forming the AQP2 protein [11]. Defects in AQP2 gene compromise proper synthesis,

processing, or plasma membrane localization of the gene product, thereby hindering the antidiuretic action of AVP in the collecting duct principal cells [6, 12].

As of 2017, 65 mutations of the AQP2 gene had been identified to be associated with autosomal NDI, predominantly of recessive inheritance [6]. Most commonly identified defects have been missense mutations that affect amino acids in the AQP2 transmembrane domains, resulting in protein misfolding [6]. Accumulation of mutant AQP2 protein may occur in the endoplasmic reticulum (ER), some mutants retain intrinsic functionality as water channels and show partial activity [13]. Cellular evidence suggests that in some instances there may be abnormal subcellular localization of AQP2 rather than a complete loss of function. This is of therapeutic significance as in these instances, focus should be on restoring appropriate trafficking of these mutants [6, 14].

Genetic testing for NDI is recommended in all patients with a family history of the disease [15]. In neonates and infants who develop clinical manifestations of DI, mutations in either the AVPR2 or AQP2 genes should be suspected [15]. A timely diagnosis is important as delayed diagnosis may result in repeat episodes of hypernatremia and dehydration with a concomitant risk of cerebral venous thrombosis [15]. Genetic characterization enables early diagnosis, enables prenatal diagnosis in subsequent pregnancies, and facilitates genetic counseling of family members [15].

Current Management Approaches for NDI

Nutrition

Dietary management is helpful in decreasing solute load to the kidneys in children with NDI [16]. It is recommended that a diet that is low in sodium with recommended daily allowance (RDA) protein with high calories content is given (high calorie: solute ratio). Sodium intake should be restricted to 1–2 mEq/kg/day and protein intake to about 2 g/kg/day. It is more prudent to restrict salt than protein to minimize the effect on growth [17]. Nutritional supplementation may be required via nasogastric tube or in some

instances via gastrostomy tube [18]. Children with NDI need to have free access to water in order to maintain normal tonicity [17].

Diuretics

The use of thiazide diuretics is a long-established treatment for NDI [19]. They act at the distal convoluted tubule and inhibit cotransport of sodium and chloride [19], in doing so they decrease extracellular fluid volume, facilitating water and sodium reabsorption at the level of the proximal tubules thereby, leading to a reduction in urine output [19]. An animal model of lithium-induced NDI demonstrated that chronic hydrochlorothiazide (HCTZ) treatment up-regulates aquaporin-2, sodium chloride co-transporter, and epithelial sodium channel, which enhances sodium reabsorption along the distal segments of the nephron [20]. A combination regimen of HCTZ with Amiloride is superior to HCTZ as it prevents urinary potassium losses, hypokalemia, and alkalosis [21]. Amiloride has an additive effect to HCTZ in that it further increases urinary sodium loss, thereby stimulating proximal water retention with further reduction in urine volume [21].

Non-steroidal Anti-inflammatory Drugs (NSAID)

NSAID such as indomethacin and ibuprofen can be used to aid in reduction of water loss. Their use may be limited by gastrointestinal (GI) and renal side effects. Combination treatment of HCTZ with indomethacin has been shown to be more efficacious than HCTZ use alone [5].

Possible Future Precision Medicine Through Targeted Gene Therapy Strategies

As AVPR2 gene mutations are the most common cause of congenital NDI, multiple approaches have been proposed to restore receptor functionality [15].

1. Utilization of chemical chaperones such as glycerol and dimethyl sulfoxide to restore plasma membrane expression of AVPR2 [22]: This is to tackle Class II mutations where AVPR2 is functional but accumulated in the endoplasmic reticulum(ER)/Golgi. Several cell-permeable AVPR2 antagonists including conivaptan have demonstrated efficacy in transportation of the functional yet ER confined AVPR2 mutants to the plasma membrane thereby restoring functionality [23].
2. A separate strategy targets trafficking of AVP-independent AQP2 to the plasma membrane therefore bypassing AVPR2 signaling: These approaches have two categories: (1) intracellular cAMP elevation by activating other G-protein-coupled receptors such as E-prostanoid receptors, calcitonin receptors, secretin receptors, beta3-adrenoreceptor or by inhibiting phosphodiesterases (PDEs); and (2) cAMP-independent pathways [15, 24].
3. Another approach is to inhibit internalization of AQP2: Treatment with statins has demonstrated prevention of AQP2 internalization with AQP2 accumulation at the plasma membrane in laboratory settings [25]. Future clinical trials may further the understanding of the efficacy of this approach in patients with congenital NDI [25].

In addition to statins, numerous substances are in various stages of testing for use in NDI including phosphodiesterase inhibitors, guanylate cyclase stimulators, secretin, protein kinase A agonists, fluconazole, prostaglandin agonists, metformin, and soluble prorenin receptor agonists.

Acquired NDI

Several systemic disorders and drugs can cause NDI (see Table 16.1).

Amyloidosis

Amyloidosis is known to compromise the concentrating ability of collecting ducts due to deposition of amyloid in the interstitium of the kidney [26]. Interestingly one of the drugs used to treat amyloidosis, Bendamustine, may induce NDI which resolves with discontinuation of the medication [27]. The NDI that occurs with use of Bendamustine can be managed with sodium restriction, hydrochlorothiazide, and desmopressin; this knowledge helps physicians allow patients to continue on Bendamustine cycles till they complete treatment if required [27].

Granuloma-Associated Conditions (Sarcoidosis and Histiocytosis)

There are rare case reports of NDI associated with sarcoidosis and, of note, sarcoidosis may also cause central DI [28–30]. Langerhans' cell histiocytosis (LCH) of bone, a disorder of histiocytic proliferation seen in both adults and children, may induce DI, although this is usually central DI [31, 32].

Sjogren Syndrome

Sjogren syndrome may present with various tubular disorders that includes NDI [33–35]. In addition to polyuria/polydipsia, patients present with symptoms of dryness (xerophthalmia and xerostomia) [36].

Sickle Cell Disease (SCD)

SCD patients have increased levels of endothelin-1 (ET-10) [37]. ET-1 is known to antagonize the tubular effects of vasopressin and to promote renal scarring [37]. Increased renal production of ET-1 can result in NDI in SCD patients through a combination of fibro-

sis and ET-1-induced functional resistance to vasopressin [37]. This important observation provides a rationale for trials with endothelin receptor antagonists in SCD nephropathy [37].

Drugs

A number of drugs have been implicated in the induction of NDI, these include but are not restricted to lithium, Ifosfamide, Foscarnet, and certain antibiotics.

Lithium

Lithium is a widely used drug in the treatment of bipolar disorder. NDI occurs with chronic lithium administration and may persist even after discontinuation of the drug [38]. Lithium enters the collecting duct's principal cells via apical epithelial sodium channels (ENaC) disrupting AVP response. ENaC shows high selectivity for both sodium and lithium, is upregulated by aldosterone, and inhibited by triamterene [39–41].

Ifosfamide

Ifosfamide toxicity may result in damage to the proximal and distal tubules, whereas proximal damage presents with features of Fanconi syndrome distal tubular damage results in NDI. The resulting NDI may be partially responsive to desmopressin. The extent of tubular damage may be dose-related [42, 43].

Foscarnet

Animal and human studies have shown that the antiviral agent, Foscarnet, causes nephrotoxicity affecting both the proximal tubule as well as the collecting duct. Foscarnet disrupts aquaporin-2 AVP-induced intracellular transport resulting in reduced ability to concentrate the urine [44, 45].

Antibiotics

There are case reports describing Methicillin and Rifampicin-induced NDI [46, 47] making it vital to keep NDI as a possible side effect in mind while prescribing these drugs.

Other Disorders Associated with NDI

Hypokalemia

Hypokalemia is a common electrolyte disorder. The presence of chronic hypokalemia can cause a defect in urinary concentrating ability that includes the collecting ducts, that is NDI [48]. Hypokalemia increases autophagic degradation of AQP2 thereby reducing AQP2 expression and the cellular composition of the kidney collecting duct [48]. This, in turn, contributes to the development secondary NDI and to hypokalemic nephropathy in general [48, 49]. Bartter syndrome may mimic the presentation of NDI in the first year of life [48]. Of note, hypokalemia may not be present initially. A distinguishing feature on history is that primary NDI is never associated with polyhydramnios while Bartter syndrome may be associated with polyhydramnios [50, 51].

Fabry Disease

Fabry disease is a lysosomal storage disorder that may present in adolescence and young adulthood with impaired urinary concentrating ability. Administration of a formal water-deprivation test followed by vasopressin challenge will confirm NDI and kidney biopsy will show findings typical of Fabry disease [52].

Clinical Pearls and Pitfalls

Etiology:

- NDI may be due to congenital or acquired causes that ultimately alter the function of either the AQP2 channel or AVPR2 receptor.
- Ninety percent of congenital NDI cases are attributable to X-linked mutations in the vasopressin receptor and about 10% to autosomal dominant or recessive mutations of AQP2.

Clinical clues and Diagnosis:

- A family history of NDI should alert pediatricians to do genetic testing as a timely diagnosis of primary NDI may

prevent repeat episodes of hypernatremia and dehydration with concomitant risk of cerebral venous thrombosis.
- Secondary causes of NDI are attributed to several systemic disorders and drugs.
- Chronic hypokalemia is a risk factor for NDI.
- Primary NDI is never associated with polyhydramnios.

Management:

- Current management strategies in NDI are through a combination of free access to water, solute reduction, and use of diuretics and NSAIDs.
- Future precision medicine in congenital NDI to restore receptor functionality of AVRP2 and AQP2 genes are of key research interest.

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C. A. Alter (ed.), *Diabetes Insipidus in Children*,
https://doi.org/10.1007/978-3-030-83248-3