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# Management of Langerhans Cell Histiocytosis (LCH)-Induced Central Diabetes Insipidus and Its Associated Endocrinological/Neurological Sequelae

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## 1. Introduction

Central diabetes insipidus (CDI) is caused by a deficiency of arginine vasopressin (AVP), also known as antidiuretic hormone. Although CDI is rare in children and young adults, it should be kept in mind that it is associated with rare histiocytic disorders in the central nervous system (CNS), namely Langerhans cell histiocytosis (LCH), xanthogranulomatosis and Erdheim-Chester disease, all of which specifically affect the hypothalamus and pituitary stalk, thereby inducing CDI (1,2). In particular, CDI is the most frequently occurring CNS event in patients with multi-focal LCH, who often have multisystem lesions, including craniofacial bone lesions (3). LCH is a rare disorder that is characterized by the proliferation of cells that bear the activated Langerhans cell phenotype (4). Early studies reported that CDI occurs in 25–50% of LCH patients but this incidence appears to have dropped to 7–20% since the introduction of systemic chemotherapy (5). CDI can develop either before, simultaneously with, or subsequent to a diagnosis of LCH based on the presence of various extracranial lesions. It can also develop during chemotherapy for systemic LCH or after therapy. Patients with LCH-induced CDI show typical clinical symptoms, such as polyuria/polydipsia, in association with abnormal radiographic findings, such as a thickened pituitary stalk or a hypothalamic mass and the loss of a hot signal (T1 weighted) for the pituitary posterior lobe on brain magnetic resonance imaging (MRI) (5–8). Once CDI develops, it becomes irreversible in most patients, who will require life-long desmopressin replacement therapy with 1-desamino-8-D-arginine vasopressin (DDAVP). In addition, 30–58% of patients with CDI exhibit anterior pituitary hormone deficiencies (APHD) during follow-up (1,7). LCH-associated APHD appears to be linked to a thickening of the pituitary stalk (6,7). In addition, patients with LCH-induced CDI can eventually develop neurodegenerative (ND) disease (9,10).

Appropriate management of LCH-induced CDI involves (a) a prompt correct diagnosis; (b) early intervention with chemo/radiotherapy to reverse the CDI, if possible; (c) appropriately treating CDI to prevent the later development of APHD or ND disease; (d) good control of CDI, once it has become permanent, with DDAVP; and ideally (e) exploring future innovative measures that could prevent the occurrence of CDI in patients with LCH.

## 2. Diagnosis of LCH-related CDI

### 2.1 Risk factors associated with the development of CDI

CDI occurs most often among pediatric patients with multi-focal LCH, particularly those with multi-system disease with proptosis (11). Moreover, LCH lesions in the craniofacial bones are seen in >75% of CDI patients (7). We also found that LCH-induced CDI is associated significantly more frequently ( $p < 0.001$ ) with multi-system multi-focal bone lesions, particularly lesions in craniofacial bones (temporal bone, ear-petrous bone, orbita, and zygomatic bone), than with single system bone lesions (12).

### 2.2 Diagnosis of CDI

CDI is generally suspected on the basis of the characteristic symptoms of polyuria/polydipsia. To correctly diagnose CDI, the water deprivation with desmopression test has long been employed (13,14). At diagnosis, to confirm that CDI has developed, it is necessary to determine plasma osmolality (reference values, 276–292 mOsm/kg H<sub>2</sub>O) together with plasma AVP levels (reference values, 0.3–4.2 pg/ml by RIA 2 antibody method). The plasma osmolality, AVP, and water deprivation test data are important for the early diagnosis of partial CDI, which is critical for preventing the progression into permanent CDI. However, sequential plasma osmolality, AVP, and water deprivation test data are not available from the pre-CDI period to partial CDI and to complete CDI phase for patients.

CDI may occur before, simultaneously with, or subsequent to a diagnosis of LCH that is made on the basis of biopsies of extra-cranial peripheral lesions such as those in the skin, bone, and soft tissues. The definite diagnosis of LCH is made on the basis of histopathology of granulomatous lesions that reveals the presence of CD1a-, Langerin (CD207)- and S100-positive cells (15). If the initial and only lesion in patients with CDI is a thickened stalk, it may be necessary to biopsy the stalk since it has been reported that pituitary stalk thickening precedes the typical peripheral lesions of LCH by several months (16). However, the decision to biopsy should be made carefully, but it must be done promptly. The diagnosis and treatment of such cases are often delayed because physicians tend to follow a “wait and see” policy.

### 2.3 Differential diagnosis

CDI has various etiologies. Some are idiopathic while others are mass lesions on the hypothalamic-pituitary axis caused by germinoma, histiocytic disorders (including LCH), trauma, or inflammatory or infectious diseases (1,2,17,18). According to a large study by Maghnie *et al.* (1), the etiologies in 52% of CDI cases were idiopathic, while LCH accounted for another 15%. It should be noted that LCH should be suspected first in children with CDI, and that about 70% show pituitary stalk thickening while the remaining 30% may demonstrate a hypothalamic mass. In contrast, in adults, CDI is more frequently caused by inflammatory processes such as sarcoidosis or tuberculosis and neoplastic infiltrations that do not originate from neuronal tissue (2). Another possible cause in adults is lymphocytic hypophysitis, which is also termed infundibulo-neurohypophysitis or lymphocytic infundibulo-neurohypophysitis (19). Whenever this is suspected, the diagnosis is often delayed because a “wait and see” policy is adopted; this is because the disease is thought to be essentially self-limited.

2.4 Radiographic findings

Abnormal radiographic findings that are associated with CDI are a thickened pituitary stalk or hypothalamic mass and the loss of a hot signal (on T1-weighted MRI) in the pituitary posterior lobe (**Figure 1, 2**). According to Grois *et al.* (7), by the time CDI is diagnosed in LCH patients, 71% already exhibit a thickened stalk, while MRIs performed more than 5 years after CDI onset show that the stalk is still thickened in 24% of patients. Also, in a small percentage of patients, the stalk was already thickened several months before CDI onset. In addition, in the study of Maghnie *et al.* (1), where CDI cases with various etiologies were reviewed, 37% exhibited thickening of the pituitary stalk on the first MRI scan and, in 94%, the posterior pituitary was not hyper-intense. Moreover, when the course of CDI was examined in 18 patients who had a normal or thickened pituitary stalk at presentation, changes in the thickness of the stalk were observed over time: these included normalization, a decrease in thickness, further thickening, and thickening of a previously normal stalk

Regarding the loss of the hot spot in the posterior pituitary lobe, we have often found it difficult to interpret the T1-weighted MRI findings because the hot signal in the posterior lobe is masked or overlapped by the hot signal of the dorsum sellae. This problem can be overcome if the slice on MRI is performed appropriately so that the posterior pituitary and the dorsum sellae are separated (8,20) (**Figure 1**). The high signal in the posterior lobe is due to the retention of AVP (8), while the high signal in the dorsum sellae reflects the dura membrane that covers the thin bony dorsum sellae. It has been suggested that the fat suppression technique and a horizontal direction of frequency encoding could help to differentiate the high signal of the neurohypophysis from that of the dorsum sella (20). In

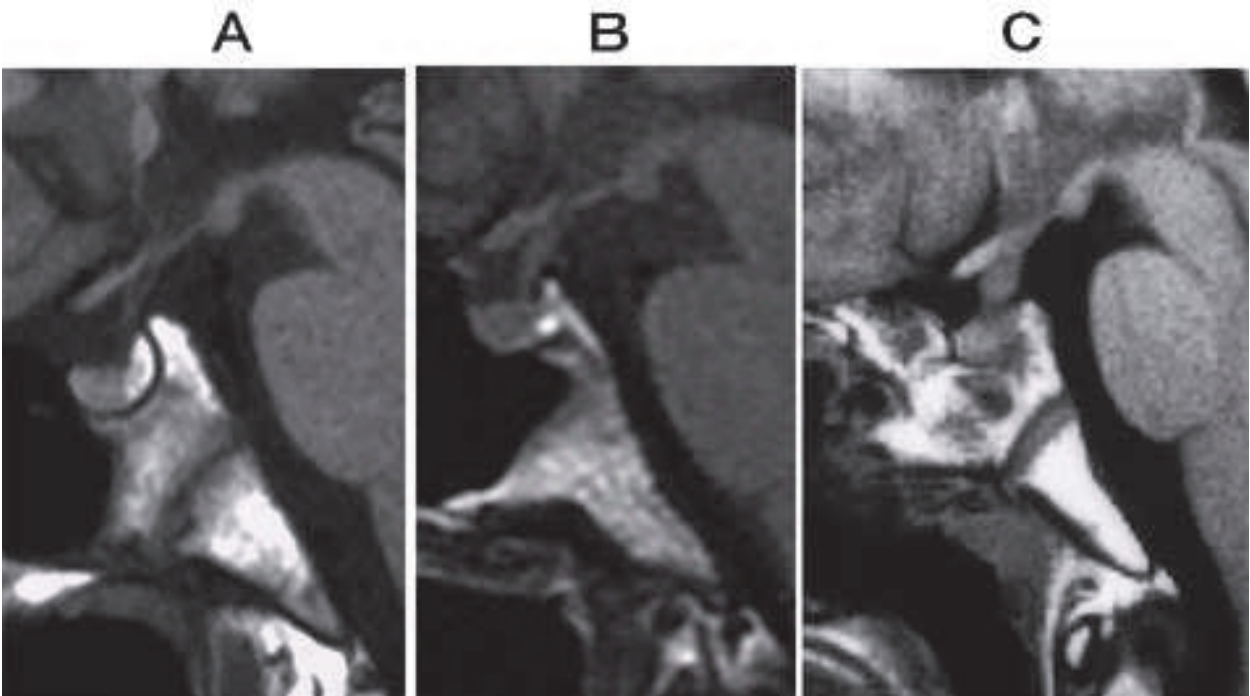


Fig. 1. MRI reveals normal and abnormal hypothalamic-pituitary regions. In two healthy controls, a hot signal in the pituitary lobe that is clearly separated from the dorsum sella can be observed (**A,B**: T1-weighted). A patient with LCH shows a thickened stalk and the loss of the hot spot in the posterior lobe (**C**: T1-weighted).



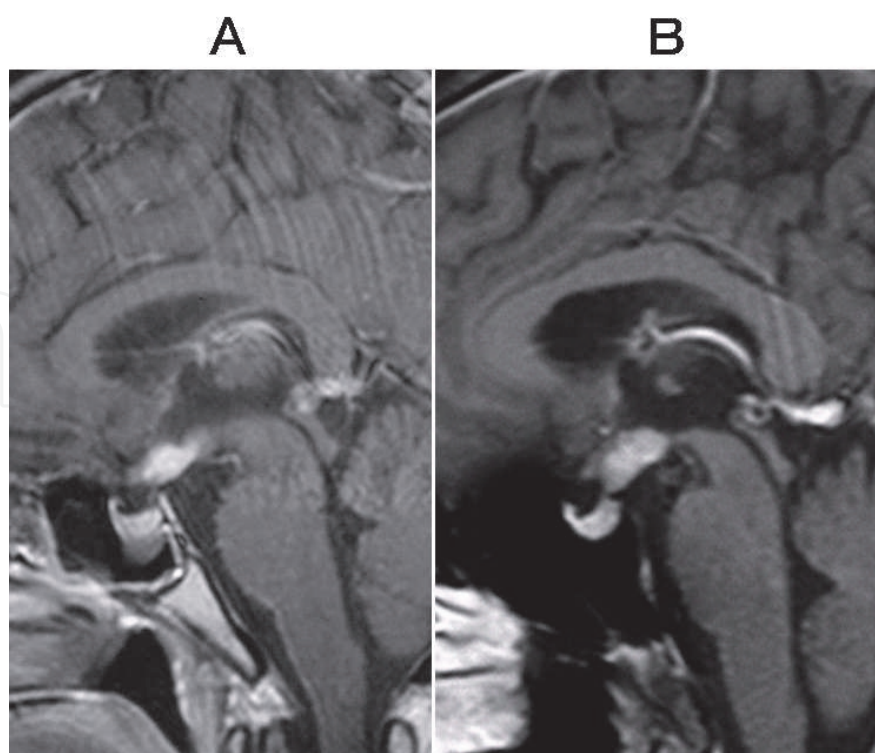


Fig. 2. Gadolinium-enhanced MRIs show a hypothalamic mass in two patients with LCH (A, B), each of which was histopathologically confirmed to be LCH by biopsy.

addition, it is recommended that to confirm the diagnosis of CDI in patients with polyuria/polydipsia, an early survey of the hypothalamic-pituitary axis by Gadolinium-enhanced MRI should be performed (Figure 2).

### 2.5 CDI-related CNS complications - Anterior Pituitary Hormone Deficiencies (APHD) and Neurodegenerative (ND) Disease

LCH-induced hypopituitarism has been described in children as well as in adults (21-24). Clinically, the symptoms start with CDI and then progress to anterior pituitary dysfunction, particularly growth hormone insufficiency. The 10-year risk of developing growth hormone deficiency is 54% in pediatric patients (25). However, sex hormone deficiency or hypogonadism has also been reported in both adult-onset cases of LCH and adults with childhood-onset LCH. Kaltsas *et al.* (23) found that at a median of 4.5 yr after the diagnosis of CDI in 12 adult cases, eight exhibited growth hormone deficiency, seven had FSH-LH deficiency, five showed TSH/ACTH deficiency, and five had panhypopituitarism. Similarly, in ten pediatric LCH cases with CDI, Amato *et al.* (24) reported growth hormone deficiency in four, obesity in three, and hypogonadism in two. Moreover, Maghnie *et al.* (1) found that the prevalence of growth hormone deficiency after the onset of CDI was 61% at a median of 0.6 year after onset (range, 0.1 to 18.0). In advanced cases, panhypopituitarism develops.

LCH-associated ND disease develops in 1-4% of LCH patients (9,10) but the correlation between CDI and ND disease is not as clear as the correlation between CDI and APHD. Grois *et al.* (7) reported that 76% of CDI patients with follow-up MRIs performed at least 5 years after diagnosis exhibited neurodegenerative brain changes, showing a correlation between CDI and ND disease. On the other hand, we have noted in Japan that 50% of patients with LCH-induced ND disease had CDI but the other half did not (10). MRI is the

most sensitive and commonly used technique for the diagnosis and monitoring of lesions in the cerebellum and basal ganglia (**Figure 3**). Symptomatic patients with this disorder show neurological dysfunction such as clumsiness, tremor, dysarthria, dysphagia, nystagmus, dysmetria and ataxia (9,10). The eventual outcome of ND disease is dismal.

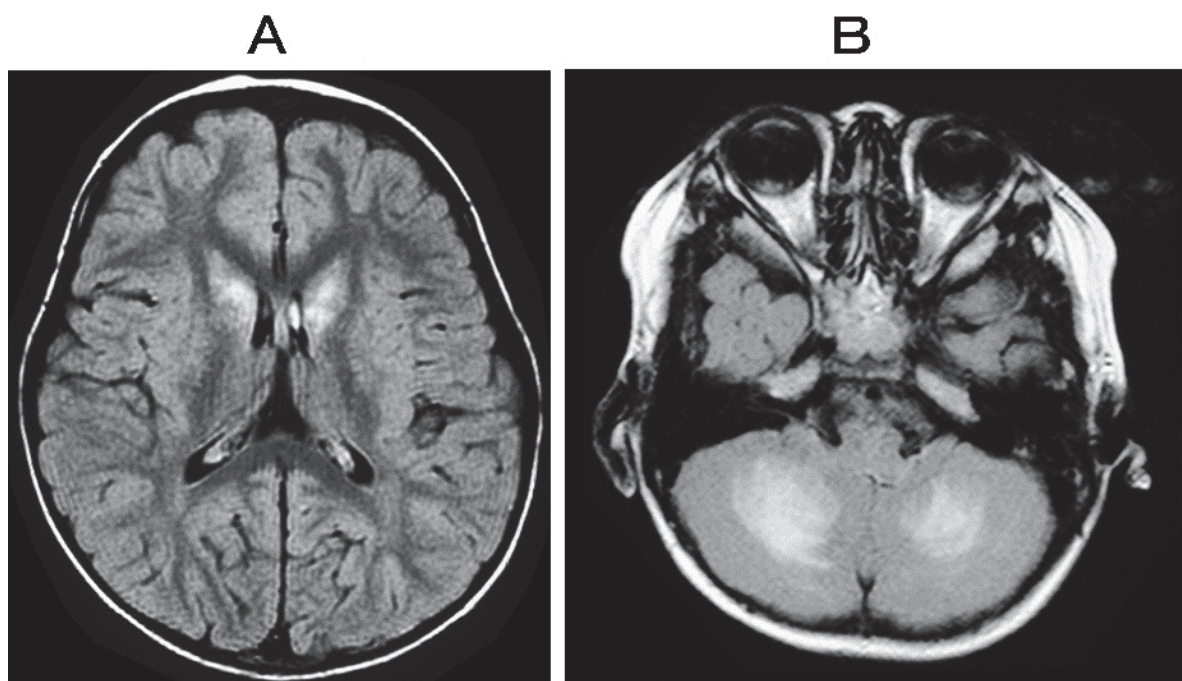


Fig. 3. MRI of patients with neurodegenerative disease after treatment for multifocal LCH show high signals at the basal ganglia (A: Flair, TR=9000) and the cerebellar dentate nuclear area (B: Flair, TR=9000).

### 3. Management of LCH-induced CDI

#### 3.1 Definition of CDI response to treatment

Complete response (CR) could be defined as no further need for DDAVP therapy, while partial response (PR) could be defined as a reduction (>50%) in the DDAVP dosage. Although Minehan *et al.* (27) included improvement in computed tomography or MRI findings in their evaluation criteria, Grois *et al.* (7) concluded that the pituitary stalk thickness changes in a highly variable manner and does not correlate clearly with the treatment outcome.

#### 3.2 Detection of partial CDI

Broadbent *et al.* (13) reported that ten of 14 children with LCH-induced CDI had "complete" CDI at onset, while the other four had "partial" CDI. This suggests that, in some cases of LCH, the early phase of CDI can be detected. Such conditions have also been described as partial, transient, or subclinical CDI. In one trial with 21 LCH patients who did not have CDI and had had LCH for less than four years (11), when the response of urinary AVP to water deprivation was measured every six months, it was found that 24% had subnormal responses during the initial test and CDI subsequently developed in two. However, it seemed difficult to predict precisely when CDI develops. Notably, Broadbent *et al.* (13) also

showed that CDI improved transiently during prednisolone therapy in one case and improved permanently after etoposide therapy in another. In addition, Ottaviano *et al.* (26) also successfully reversed partial CDI by using 2-chloro-deoxyadenosine (2-CDA). However, preventing the progression from partial CDI to complete CDI by treatment does not seem to be an easy task.

### 3.3 Irradiation therapy of CDI

LCH-induced CDI has been treated with irradiation with or without systemic chemotherapy (13, 27-29). In the past, hypothalamic-pituitary radiation therapy (HPRT) was the standard treatment for LCH-induced CDI in adults as well as in children (27). According to Minehan *et al.* (27), 36% of their HPRT-treated patients (10/28) responded (22% CR and 14% PR), whereas none in the untreated control group responded. It should be noted that five of the six complete responders were irradiated within 14 days of the diagnosis of CDI, and that three of the five patients (60%) who were treated with more than 15 Gy responded, as compared to seven of 23 patients (30%) who were treated with less than 15 Gy. In addition, eight of the ten responders (80%) were female, whereas 16 of the 35 non-responders (46%) were female. Greenberger (28) emphasized that the most important variable in achieving a CR or PR is the speed with which therapy is initiated after the onset of symptoms: it was suggested that therapy should be instituted within 7 days, preferably sooner. However, while these observations indicate the importance and superiority of early intervention with irradiation in CDI, a risk/benefit ratio needs to be determined. In pediatric cases, HPRT is currently not recommended (30) and chemotherapy (such as 2-CDA) is preferred to irradiation (28, 30). In addition, prolonged low dose systemic chemotherapy is indicated (30).

### 3.4 DDAVP

A synthetic analog of arginine vasopressin is the drug of choice in the treatment of CDI. Nasal or oral administration of DDAVP, a long-acting vasopressin analog, reduces the daily urinary volume (31). To maintain normal urinary volume and control the symptoms of CDI, 5–20 µg of nasal DDAVP is required per day. As little as 2.5µg may be sufficient, but the usual dose is 5–15µg/day. In oral DDAVP, the tablet contains 100µg of desmopressin acetate and the maximum plasma concentration after a single oral administration of 100µg DDAVP is obtained at 90 min (31). The average oral DDAVP dose required to obtain good control of CDI is about 20 times higher than the intranasal dose. Subcutaneous DDAVP is also available, which is useful for the treatment of infants with CDI and appears to be superior to oral or intranasal DDAVP therapy (32). Since the major complication of DDAVP therapy is water intoxication and hyponatremia, careful dose titration is required.

### 3.5 Optimal measures for APHD and ND disease

Growth hormone deficiency, thyroid dysfunction, and sex hormone (LH/FSH, testosterone) deficiency should be treated by hormonal replacement. In children, growth hormone deficiency is most common, whereas sex hormone deficiency is more frequent in adults. When the disease progresses into panhypopituitarism, cortisol replacement is also required. To date, while several reports have indicated that CDI can be reversed (as discussed above), this has not been observed for APHD (2,22,23). There is one exception: Makras *et al.* (33) reported that a 35-year-old female resumed normal menstrual cycling after steroid



administration. Since the hypothalamic-pituitary space-occupying mass lesions of LCH respond very well to 2-CDA (2, 26, 34), additional studies are needed to determine whether early administration of 2-CDA could reverse APHD as well as CDI.

Established ND disease is very difficult to treat. Although several reports have suggested that all-trans retinoic acid or a combination of vincristine/AraC and intravenous high dose gamma-globulin (IVIG) may have some efficacy (35-37), it remains unclear whether any specific type of initial systemic chemotherapy for multifocal LCH patients can limit the later occurrence of ND disease (38). There is an urgent need for research that can identify an innovative therapy for such cases.

#### 4. CDI and other CNS complications experienced in the Japanese LCH study

The cases of CDI, APHD and ND disease were analyzed in the cohort of patients treated with the JLSG-96/-02 protocols from 1996 to 2009 in Japan (39). CDI was detected in 12.4% (43/348) of pediatric multifocal LCH patients with a median follow-up of 5.0 (range, 0.2–14.0) years, with the shortest follow-up of alive patients being 0.8 years from the initiation of treatment. Of these 43 cases, CDI was detected before LCH diagnosis in 13 cases, at the LCH diagnosis in 12 cases, during the induction/maintenance treatment in five cases, and after off therapy at a median of 21 months (range, 4–116) in the remaining 12 cases. The incidence of CDI after the initiation therapy was 5.6% in our JLSG protocols, which is lower than 9.3% by Grois et al. (5). Data indicate that our treatment protocol effectively reduces the incidence of CDI by preventing the new occurrence. Of the 43 CDI patients, APHD was noted in 30.2% (13/43), with growth hormone deficiency being observed in ten of these patients. Six patients developed ND disease. In total, chemotherapy completely resolved CDI in two patients, which suggests that early intervention with chemotherapy may be able to reverse CDI (39).

#### 5. Recommendations and future trials

In practice, when LCH patients, particularly those with craniofacial bone lesions, are diagnosed, treated and followed up, they must be examined carefully for any signs suggesting that CDI is developing. In particular, inquiring about the symptoms of polydipsia/polyuria and occasional tests for plasma osmolality with plasma AVP may help to diagnose CDI early after onset. Moreover, in young females, the presence of amenorrhea and/or morbid obesity could be a first sign of pituitary dysfunction together with CDI. Repeated brain MRI examinations are also useful for detecting the early signs of CDI and/or ND disease. Once the precise diagnosis of CDI has been made, nasal or oral DDAVP is a safe therapeutic option that effectively controls CDI. Patients with anterior pituitary dysfunction require other hormonal replacement therapies.

Effective measures that can reverse CDI or other CDI-related neurological complications, or prevent them from newly occurring, remain elusive. Studies have shown that in LCH-induced CDI cases, the CDI is already present at the start of chemotherapy in half of the cases, while the remaining half develop CDI during chemotherapy or after off therapy. Ideally, the early introduction of chemotherapy should be able to reverse pre-existing CDI and prevent the new occurrence of CDI. Unfortunately, however, therapeutic regimens for patients with LCH that consistently achieve these goals have not yet been identified. However, we recently found that IVIG may be able to prevent the progression of ND



disease in patients with LCH (10, 35). Given this observation and the fact that IVIG is also effective for other CNS inflammatory diseases, we have hypothesized that pre-emptive measures that include high dose IVIG may reduce the incidence of LCH-related CNS diseases, namely CDI and its related neurological complications, if they are given early and are combined with chemotherapy. To that end, we have proposed that the initial treatment of patients with “CNS-risk”-LCH should contain a high dose (2g/kg/dose) of IVIG combined with conventional induction chemotherapy (40). However, precise efficacy of immunomodulatory agents such as IVIG for treating LCH, particularly for preventing the development of LCH-related CNS diseases, needs to be explored by future studies.

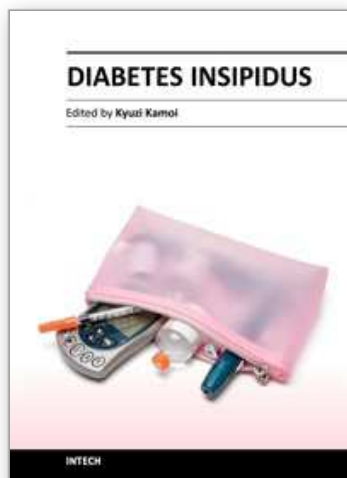
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## **Diabetes Insipidus**

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The first chapter of the book reports on the management of Langerhans cell histiocytosis (LCH)-induced central diabetes insipidus and its associated endocrinological/neurological sequelae in the national survey. The next chapter addresses DI and head injuries. Next, the management of neuroendocrine instability during maintenance of potential organ donors is described. Organ transplants have gradually increased worldwide. To have maintenance of appropriate potential organs, AVP is needed. Furthermore, nephrogenic DI-the potential therapeutic drugs and analysis of membrane protein stability is the topic of the next two chapters, followed by new insights into the diagnosis and management of pregnancy-related DI. The seventh chapter reports on the problems with differential diagnosis in a case of central DI in a female patient with bipolar disorder. The lithium treatment usually resulted in nephrogenic DI. Finally, over the last years, the development of MRI imaging on the pituitary gland with the stalk and hypothalamus has advanced. The final chapter interprets imaging techniques in DI in detail.

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