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Neurodegenerative Central Nervous System Langerhans Cell Histiocytosis and Coincident Hydrocephalus: Treated with Vincristine/Cytosine Arabinoside

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Abstract

Background—Central nervous system (CNS) complications of Langerhans cell histiocytosis (LCH) include mass lesions and a neurodegenerative (ND) syndrome with ataxia, dysarthria, dysmetria, learning and behavior difficulties and/or characteristic changes on brain MRIs. Hydrocephalus has rarely been reported in LCH. LCH lesions of the orbit, mastoid and temporal bones ("CNS-Risk" lesions) and diabetes insipidus predispose patients to ND-CNS-LCH. Treatment options have been limited and only a case series using trans-retinoic acid (ATRA) and intravenous immunoglobulin (IVIG) have been published.

Methods—We have used cytosine arabinoside (ARA-C) with or without vincristine to treat 8 patients with ND-CNS LCH. Patients: 7 male children and one young adult male with clinical and radiologic ND- CNS-LCH were treated with a regimen of vincristine 1.5 mg/m² on day 1 and ARA-C 100 mg/m² daily for 5 days or ARA-C alone monthly for 4–19 months. Seven patients were evaluated with an ataxia rating scale (ARS) and all with serial MRIs of the brain.

Results—Five of 7 patients had decreases in their ARS scores and/or decreased T2 hyperintense lesions on MRI images. Grade 2 neutropenia was the most frequent adverse event. Vincristine-associated neuropathy occurred in two patients. Hydrocephalus caused symptoms and signs that confounded the diagnosis and management of ND-CNS-LCH in all 4 patients affected with both.

Conclusions—Subtle changes in neurologic function may be complicated by hydrocephalus. Vcr/ARA-C or ARA-C were an effective therapies for some ND-CNS LCH patients. A clinical trial using this and possibly other modalities such as IVIG or ATRA should be done.

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Keywords

CNS-Langerhans' Cell Histiocytosis; neurodegenerative disease; ataxia; treatment; cytosine arabinoside; vincristine; hydrocephalus

Background

Central nervous system- Langerhans Cell Histiocytosis (CNS-LCH) has been defined by Grois and colleagues as an important permanent consequence of LCH, especially for patients with LCH of the mastoid, temporal bone, and orbit as well as those with diabetes insipidus (DI).[1–4] These craniofacial bones are connected by the circumventricular organs to the pituitary/hypothalamic region.[5] It is possible that the anatomical pathways present in this system provide a conduit for pathologic cells from the bone lesions to migrate into the pituitary, hypothalamus, as well as the cerebellum, basal ganglia, and pons. CNS-LCH can manifest in a variety of forms, including mass lesions in the cerebrum and choroid plexus. ND-CNS-LCH is defined in two ways. Radiologic ND-CNS-LCH is characterized by MRI signal changes in the cerebellar grey or white matter, basal ganglia, and/or pons. Clinical signs of ND-CNS-LCH include ataxia, dysarthria, dysmetria, and learning or behavior difficulties. [1–4,6–8] The pathophysiology of these CNS problems may be related to CD8+ lymphocytes that have infiltrated the brain in these patients. The neurologic damage may be secondary to cytokines secreted by the lymphocytes or antibodies with a direct effect on neurons as para-neoplastic phenomena. [9] Hydrocephalus has rarely been reported in association with LCH and we could find only four case reports. [10–13]

Treatment protocols for ND-CNS-LCH have been extremely limited. The Histiocyte Society developed a protocol (LCH-CNS 2000) with a subsequent update in 2003 to study the clinical presentation; results of neurologic, radiographic, and brain stem evoked response testing; and disease progression of patients with central nervous system abnormalities. The original treatment concept was to use melatonin in a Phase II trial. Idbaih et al published a study using trans-retinoic acid for 10 patients with ND-CNS-LCH. [15] These investigators found stabilization of neurologic signs and symptoms in all 10 patients after a one year follow-up. Imashuku et al published a study using intravenous immunoglobulin (IVIG) and combination chemotherapy regimens for treatment of ND-CNS-LCH. [16] They reported 4/5 patients stabilized on the regimen over the course of 23 months of treatment and the one who progressed had received only 2 doses. One patient was taken of therapy and 6 month later developed strabismus secondary to cerebellar dysfunction. Chemotherapy and IVIG treatment were restarted and the patient has had no further neurologic deterioration.

Chemotherapy treatments of ND-CNS LCH have until recently been considered ineffective. Vinblastine, prednisone, methotrexate, and mercaptopurine are ineffective because patients have developed signs and symptoms of CNS LCH while on these medications (1–3,4,8). Cladribine (2-CdA) has proven effective for treating CNS mass lesions. [17] Two patients with brain MRI findings showing diffuse and localized atrophy, consistent with neurodegenerative disease, have showed no evidence of radiographic progression or regression of these changes following treatment. None of the patients with neurologic symptoms were reported to have improvements in their clinical condition. [17]. Two other cases of apparent response of infiltrative CNS-LCH lesions to 2-CdA have been reported. [18,19] In neither case did neurologic findings improve.

Cytosine arabinoside (ARA-C) is a rational choice for treatment of ND-CNS LCH because it is known to cross the blood brain barrier and accumulate in the CSF. In a study by Damon et al. patients given ARA-C at 3 g/m², 2 g/m², or 0.75 g/m² every twelve hours for 12 doses

ARA-C levels were measured in the plasma and CSF. After the first dose of ARA-C the levels of ARA-C in the CSF were 5.7% of the plasma level in the 3 g group, 14% of the plasma level in the 2 g group, and 3% of the plasma level in the 0.75 g group. The pre dose 8 levels were two fold higher in the CSF (0.22 μ M vs. 0.11 μ M), 13 fold higher (0.51 μ M vs. 0.04 μ M), and 73% of plasma (0.11 μ M vs. 0.15 μ M) in the respective groups. [20] In another study patients receiving high dose ARA-C (3g/m²) the CSF level reached 10% of the plasma level and was maintained over 4 hours, but dropped to 50% of the initial value at 6 hours. In patients given 3g/m² IV ARA-C over 3 hours the CSF level was 14% of plasma level at the end of infusion (hour 3), 400% of plasma level 3 hours later (hour 6) . and 22% of plasma level at hour 24. From hours 6–24 the ARA-C level in the CSF equaled the level in the plasma: 0.6 μ g/ml at 6 hours and 0.03 μ g/ml at 24 hours. [21] The combination of vincristine (Vcr), prednisolone, and ARA-C was described by Egler et al as an effective treatment regimen for patients at the initial diagnosis of LCH or at relapse. [22] Here we report a retrospective review of 8 patients treated with ARA-C with or without vincristine.

Materials and Methods

This retrospective review of 8 ND-CNS- LCH patients treated or evaluated at Texas Children's Cancer Center from 1999–2007 was done with an IRB-approved protocol at Baylor College of Medicine. All patients had histo-pathologically-confirmed LCH lesions of the orbit, mastoid, temporal bone, and/or diabetes insipidus with or without another site of LCH involvement. All patients had been treated with vinblastine and prednisone for their original LCH lesions and then developed signs and symptoms of CNS LCH. Two with ND-CNS-LCH were treated with a variety of therapies before the vincristine-ARA-C or ARA-C protocol with no benefit. All patients had MRIs of the brain to define evidence of radiologic ND-CNS-LCH: T2-weighted hyper intensity of the pons, basal ganglia, and cerebellum and/or mass lesions of the choroid plexus. The MRI scans done at Texas Children's Hospital utilized a 1.5 tesla MRI with multiplanar T1-W, T2-W, FLAIR, and post contrast T1-W images. MRIs were evaluated by a single neuroradiologist using the criteria described by Prayer et al for evidence of ND-CNS LCH. [2] Seven patients had serial neurologic evaluations using a standardized ataxia rating scale. [23] Objective evidence of response was based upon a 3 point or greater improvement in scores. Three patients had brainstem auditory evoked response (BAER) evaluations. Patients were evaluated for bone marrow and hepatic toxicity of the regimen by serial complete blood counts and liver function tests.

Results

Table I summarizes the clinical findings of the 8 male patients. All but one presented with LCH by age 2 years. The adult male (patient 8) was originally diagnosed at age 1. Seven patients had a CNS-Risk craniofacial bone lesion and one patient (Pt.7) may have since he had chronic otitis. Patient 7 also had an extensive LCH scalp rash for many months before treatment was begun. Four patients had diabetes insipidus (DI) and 4 had growth hormone deficiency. All patients were treated with vinblastine and prednisone and often 6MP for their primary LCH lesions. The CNS symptoms began an average of 5.8 years (range 1.5–11 years) after the first evidence of LCH elsewhere in 7 patients. Patient 8 was not examined for an 8 year span, thus making it impossible to judge the true onset of his symptoms. Brain MRI scans showed T2-hyperintense signals in combinations of the cerebellar white and grey matter (8 patients), pons (7) basal ganglia (3), and medulla (1). Four patients had abnormalities of the hypothalamic/pituitary region including thickening of the pituitary stalk and loss of the posterior pituitary bright spot on sagittal T1-W images. Two patients (1,7) developed hydrocephalus as judged by increases in their ventricular dimensions on MRI scans before or near the time of onset of ND-CNS-LCH radiographic signs and the other 2 patients (3,8) 2–4 years after the CNS symptoms began. Patient 1 had mass lesions of the

choroid plexus. Seven of 8 patients had ataxia, 4 dysarthria, 3 dysmetria, 2 dysphagia, and 1 developmental delay. Neurologic assessment using the Ataxia Rating Scale (ARS) was done in 7 patients. Disability points at the time of first assessment ranged from 19 to 28. Patients 1 and 2 developed petit mal seizure disorders 2–4 years after completing their vincristine/ARA-C treatment.

Table II details the time on vincristine/ARA-C or ARA-C protocol and objective responses in ataxia rating scale and MRI images. Four of 8 patients (1,2,6,8) had improvements in their ARS scores within 2–6 months (Figure 1). Patients 1 and 2 have had stable scores over follow-up periods of 7–3 years respectively. Patients 6 and 8 had initial improvements of the ARS scores, but subsequent worsening (increases of 2 points) (Table II). Patient 1 was treated with vincristine/ARA-C for 19 months because of slow response of his choroid plexus lesions, but his ND-CNS-LCH improved by the second month. Figure 2 illustrates the improvement in his handwriting after 2 months of treatment. His ataxia rating scores improved from 19 to 8 by the end of treatment. The score is now 1 at seven years from the end of vincristine/ARA-C treatment and had no other treatments after that regimen. Patient 2 also had improvement in the clarity of his speech with treatment until the 4th month when his BAER had prolongation of latencies and his speech and ataxia worsened. It was thought that this could be evidence of vincristine toxicity so that drug was eliminated. After 4 more courses of ARA-C alone the BAER improved as well as his ataxia and dysarthria with ataxia rating scale points decreasing from 21 to 12. Patient 3 had an initial subjective response to vincristine/Ara-C, but then had marked peripheral neuropathy and weakness. In retrospect his mother remembered that he had similar problems during treatments with vinblastine. Thus, it was assumed that his deterioration was in part from vincristine neurotoxicity and this regimen was stopped. Although he seemed to have an initial good response to IVIG treatments every three weeks, he began a progressive decline in neurologic abilities. Treatment with tacrolimus seemed ineffective and made him excessively tired. At the time of stopping tacrolimus a review of serial MRI studies showed progressive hydrocephalus over the prior 3–4 years. A ventriculo-peritoneal shunt was placed followed by steady improvement in his strength, speech, and stamina. He now has further deterioration of strength and intellectual decline. Patient 4 presented with only dysarthria that improved quickly during ARA-C treatment and remains stable. Patient 5 presented with more than an 8 year history of ataxia, learning difficulty, and difficulty swallowing. He did not respond to ARA-C and is currently taking tacrolimus. Patient 6 had improvement in his ataxia, as judged by decrease in the ARS scores from 21 to 16, and behavior problems and has a stable response after 24 months. Patient 7 has previously been reported by Kereshelevich et al regarding his obstructive hydrocephalus. [9] He developed an abnormal gait and decreased cognitive skills at age 8. MRI findings of CNS LCH began appearing at age 9.75 years and hydrocephalus at age 10.5 years. The patient had two endoscopic third ventriculostomies that were unsuccessful. A ventriculoperitoneal shunt was placed at age 10.6 years. His tremors and ataxia worsened after the shunt was placed, despite proper shunt function, and he was referred to our hospital for treatment recommendations. He had some improvement in his neurologic exam by the third month of treatment with ARS score improving from 25 to 19 (Table II). However he then had progressive worsening (ARS score increased to 33) and has been given pulses of dexamethasone with the ARA-C which improved his balance. It is difficult to judge when patient 8 began having ND-CNS-LCH signs or symptoms because he had no follow-up after age 8 years when he received the second course of RT for a mastoid lesion. In the following 17 years he had learning disability, bipolar disorder, substance abuse and finally hemiballism. At age 24, he was found to have non-communicating hydrocephalus of unknown etiology and a ventriculo-peritoneal shunt was placed. After 6 months of ARA-C his hemiballism disappeared and ataxia improved.

MRI scans of 5 patients (1,2,3,5,8) showed improvements at some time during their treatment.(Figures 3–7). Patients 3 and 5 had transient improvements in their clinical status that coincided with the improved MRI findings. However, both patients subsequently had clinical and radiologic deterioration. Patients 6 and 7 had no or minimal MRI changes. The MRI improvements consisted of relative decreases in the signal intensity in the cerebellum, pons, basal ganglia, or medulla. In no case did the abnormalities completely resolve.

BAER examinations were done on three patients (2,4,6). Patient 2 had a normal BAER in April 2003 just two months after radiologic evidence of ND-CNS-LCH (hyperintensity in the cerebellum, pons, midbrain and medulla), but no clinical signs were found. At age 6 6/12 there was increased latency of waves I and III which was worse 5 months later (age 6 11/12). The wave latency was stable when examined at age 7 3/12. After three months of vcr/ARA-C the latencies were worse and we decided to stop using vincristine. By age 7 10/12 (2 months after stopping ARA-C) the latencies had improved. Patient 4 had a single BAER examination one month before starting ARA-C that showed mild prolongation of wave form latencies. Patient 6 had severely abnormal brainstem central conduction of wave forms that was at the mid point of treatment, but worsened by the end of treatment. His ARS score improved from 21 to 16. The only toxicities besides neuropathy in patients receiving vincristine were grade 1–2 neutropenia and mild elevation of liver enzymes.

Discussion

This retrospective case series of patients with ND-CNS-LCH treated with vincristine/ARA-C or ARA-C alone shows improvement in the clinical condition of some affected by this usually devastating complication of LCH. Five of 8 patients had objective signs of improvement as judged by improvement in their ataxia rating scale scores (patients 1,2,6,8) and one (patient 4) had marked improvement in his speech. Dysmetria was improved in 3 patients, dysarthria in 2, and hemiballism in 1. Patients 1 and 2 had nearly complete resolution of their ataxia, but still mild tremors. This occurred in 3 months for patient 1 and 12 months for patient 2. Patients 6 and 8 were improved over the 6 months of treatment but still had abnormal exams, with patient 8 showing an increase in his ARS scores. All of the patients who improved had 1 year or less of abnormal neurologic symptoms before treatment was started. Patient 1 was treated the longest (19 months) and had the best overall response with Ataxia Rating Scale scores changing from 19 at onset of clinical ND-CNS-LCH to 1 now 7 years from the end of vcr/ARA-C treatment. As compared to other treatment regimens for ND-CNS-LCH this regimen was associated with partial resolution of cerebellar signs or symptoms occurred in some instances. Four patients (1,2,4,6) have stable neurologic signs and one (8) has slight worsening scores on the Ataxia Rating Scale. We speculate that either the doses of vincristine/ ARA-C used were too low for efficacy in patient 8 or that neurons damaged by the effects of LCH may not be repairable whereas younger patients have this possibility. MRI images of three of the 5 the responding patients showed modest decreases in the T2 hyperintense signals in the cerebellum or pons.

Two patients had neuropathy that seemed closely associated with vincristine infusion so we recommend eliminating this from the regimen. Vincristine has been shown to have a direct toxic effect on cerebellar neurons.[24] Patient 3 illustrates a difficulty in evaluating the neurologic status of patients on any treatment regimen. After slight improvements on IVIG and tacrolimus he clearly deteriorated. It was initially thought that these regimens were ineffective. However, we discovered he had developed increasing ventricular size over the course of many months which was so subtle that it was not recognized until MRIs over a four year span were compared. After receiving a ventriculo-peritoneal shunt his strength and ataxia improved although this lasted only 4 months. The hydrocephalus was responsible for a major part of his neurologic decline. Clinicians caring for patients with ND-LCH should

be alert to subtle signs of deterioration that may be from hydrocephalus, not the ND-LCH. One may incorrectly conclude that therapy for the ND-LCH is not effective

It may be necessary to treat longer than 6 months for patients with ND-LCH or re-institute ARA-C infusions at higher doses when response is slow or deterioration occurs. We believe that it is better to treat these patients early in the course of their ND-CNS-LCH as patients who have neurologic symptoms for over 1 year usually did not to respond to this regimen. The ARA-C dose (100 mg/m²) originally chosen for this pilot study was based on that used by Egeler et al for their patients with recurrent LCH.[22] We have currently increased the dose to 170 mg/m² as we speculate that some patients may not achieve therapeutic levels in the CSF at the lower dose.

Previous reports on the use of ATRA and IVIgG for treatment of ND-CNS-LCH have shown these therapies may stabilize the neurologic deficits of ND-CNS-LCH patients. Our treatment regimen of Vcr/ARA- or ARA-C alone shows improvement in neurologic signs and MRI findings in our patients. These treatment proposals should be studied prospectively.

Only 4 cases of hydrocephalus in LCH patients have been published to date. [10–14] Our patient 7 has previously been reported with description of endoscopic third ventriculostomy (ETV). [10] A second and third ETV was required because of ventriculostomy occlusion, and finally a ventriculoperitoneal shunt was placed. A 16 year old male with generalized LCH during in infancy, who died after acute intracranial hypertension. [11] A 19 year old female diagnosed with LCH at 4 years developed a posterior fossa tumor at 14 years of age and obstructive hydrocephalus at 18 years of age. [12] A 37 year old male was reported with a history of CNS LCH and symptoms of increased intracranial pressure due to obstructive hydrocephalus, secondary to a huge xanthogranuloma involving falx cerebri and tentorium cerebelli. [13]

Two extensive reviews of magnetic resonance images (MRI) in LCH patients have been published including a retrospective review of 474 MR images in 163 patients and a review of 83 patients with LCH and at least two MRI of the brain. [2,8] Smaller series have also been published including a review of MRI features in 13 patients registered as isolated ND-LCH, a review of 12 cases where neuropathology findings were correlated with the MRI morphology and clinical presentation, and a prospective review for CNS-related permanent consequences. [4,6,7] None of these series have documented any cases of CNS or ND-LCH complicated by hydrocephalus. We found hydrocephalus in 50% of our cases of CNS-ND-LCH. It is possible that the symptoms and signs of cerebellar and brain stem infiltration by LCH preceded hydrocephalus, but when the patients presented the prominent ventricles were the finding focused on by the treating physicians. The symptoms and signs of these two CNS abnormalities may overlap.

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Fig. 1.

A.

B

Fig. 2.

Handwriting samples of Patient 1. A. Before treatment with vincristine/cytosine arabinoside.

B: After 2 months of treatment.

Fig. 3.

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 7.

Table I**Patient Characteristics and Therapy for Primary LCH Lesions Prior to ARA-C Regimen**

	1	2	3	4	5	6	7	8
Age (yr) LCH Dx	1.5	<1	1	9	1.5	2	1	1
Extracerebral LCH	Orbit, Mastoid, Skin DI/GHD	Mastoid DI	L/Sp/fe Occip DI/GHD	Skin Temporal	Mastoid Skin GHD	Temporal DI/GHD	Skin Mastoid? Lungs	Mastoid Femur
Prior Therapy	V/P/6MP/RT Ch,VP-16/HDMP ItMtx/Hc CSA RT 2-CdA	Topical steroid RT-Pred V/P 6MP-pntxf	V/P/M/ 6MP V/P Trmt/6MP	V/P V/P/M/ 6MP	V/P×2 V/P/6MP	V/P	V/P	RT Shunt (not for primary LCH)
Time Dx LCH to Dx ND-CNS LCH (years)	1.5	2	7	4	2.5	11	7	23
CNS lesions on MRI	Choroid plexus mass, HPR,CGM CWM, pons, BG, HC	HPR, CGM,CWN, pons, medulla?	HPR,CGM CWM,pons, BG,Hppc	CGM, CWM pons	HPR, MD CGM CWM Pons Hppc	CGM CWM pons	CGM,CWM BG	HC CGM CWM Pons Temporal
Hydrocephalus	With ND Symptoms	No	4 yr after ND-CNS	No	No	No	2 years after	With ND-CNS?
CNS Symptoms at DX ND-CNS-LCH	Ataxia Dysmetria	Ataxia Dysarthria	Ataxia Dysarthria Dysmetria Sw. Prob	Dysarthria	Ataxia Dysarthria Dv Del Sw. Prob.	Ataxia Dysmetria NPsy	Ataxia, Tremors	Ataxia NPsy Hemibl
ARS points At DX ND- CNS- LCH	19	21	28	Not Done	28	21	25	19

Abbreviations: Dx: diagnosis, CNS: central nervous system, S: skin, I: intestine, fe: femur, DI: diabetes insipidus, GHD: growth hormone deficiency, L: liver, Sp: spleen, Occip: occipital bone, Temp: temporal bone, Mandib: mandible V: velban, P: prednisone, 6MP: mercaptopurine, Ch: chlorambucil, VP-16: etoposide, HDMP: high dose methyl prednisolone, ITMtx/Hc: intrathecal methotrexate and hydrocortisone, 2-CdA: cladribine, pntxf: pentoxifyline, Trmt: Trental, RT: radiotherapy, ARS: Ataxia Rating Scale, Dysmet: dysmetria, Dysar: dysarthria, NPsy: neuropsychological problems, Dv Del: developmental delay, Hemibl: hemibalismus, Sw. Prob. Swallowing problems, CGM: cerebellar grey matter, CWM: cerebellar white matter, BG: basal ganglia, HPR: hypothalamic pituitary region, Hppc: hippocampus, MD: medulla, HC: hydrocephalus

Table II**Response to ARA-C**

Patient	1	2	3	4	5	6	7	8
Age Dx ND-CNS-LCH(yr) (Radiographic/Clinical) Time to start ARA-C (yr)	6/7 1	4/6 <1	?/8 >2	14/15 1	?/4 8	?/12 <1	?/8 2.9	?/24 1
Age at ARA-C start (yr)	7 8/12	7 2/12	5 6/12	5 9/12	12 6/12	12 9/12	10 11/12	24 9/12
Duration of ARA-C (mo) Vcr (Y/N)	19 Y	6 Y(3 mo.)	4 Y	6 N	6 N	6 N	6 Y	6 N
Vcr toxicity	N	Y	Y	NA	NA	NA	N	NA
Subjective. Response	Y	Y	Y	Y	Y	Y	Y	Y
Objective Response ARS score Start/End/Last Current condition	Y 19/8/1 Stable Petit mal Sz	Y 21/12/8 Stable Petit mal Sz	N 28/37/32 Worse	Y spch.impr ND Stable	N 28/ND/28 Worse	Y 21/18/16 Stable	Y 25/19/33 Worse	Y 19/12/17 Slightly worse
MRI Improved (Yes/No) Areas	Y BG, CGM CWM	Y CGM, CWM, P	N	Y CGM, CWM, P	Y CGM, CWM, Hp	N	N	Y CGM, CWM, P
Time off ARA-C (yr)	7	2	2	2	3	3	.1	3

Abbreviations: ND-CNS-LCH: neurodegenerative central nervous system Langerhans cell histiocytosis. Vcr: vincristine, ARA-C cytosine arabinoside, Y:yes,N:no, NA: not applicable, ND, Ataxia rating scale not done, spch. Imprv: speech improvement, Hb: hemiballismus, a: ataxia, ARS: ataxia rating scale , MRI:magnetic resonance imaging, , CWM: cerebellar white matter, BG: basal ganglia, P: pons, Hp: hippocampus , Sz: seizures