

The Big Meeting

Summary of Breakout Meetings

Adult LCH/Erdheim-Chester/Rosai-Dorfman

This Breakout Session was moderated by:

- Dr. Kenneth McClain - Texas Children's Medical Center
- Dr. Sheila Weitzman - Hospital for Sick Children

1. Adult LCH: Questionnaires were sent out, and the answers came from a subset of 752 patients. Occurrence of adult LCH is estimated at 1-2/million. Approximately 47% of adults have family members with thyroid disease. In adult pulmonary Langerhans cell histiocytosis, approximately 20% show no symptoms, 50% have a cough, 40% have shortness of breath, and 10% have pneumothorax (lung collapse).

Most frequent abnormality is decreased DLCO (diffusion of carbon dioxide) in 70% to 90% of these patients. A CT scan is needed to define lung involvement, to see cysts and nodules. A chest x-ray will not see it. Bronchial washings are not a good method of diagnosis, only lung biopsy.

2. Erdheim-Chester: Average age at diagnosis is 53. It can affect kidney and heart, where LCH does not. Approximately 50% of EC patients have disease elsewhere than bone. ECD can be in the lung lining, but no cysts in lungs; can have diabetes insipidus, ataxia (difficulty with coordination), enhancement of brain lining, masses behind eyes (proptosis). Interferon is one of the treatments for EC, and it is usually long term.

Hemophagocytic Lymphohistiocytosis (HLH)/Bone Marrow Transplantation

This Breakout Session was moderated by:

- Dr. Thomas Gross - Columbus Children's Hospital
- Dr. Megan Burke - Cleveland Clinic Children's Hospital

HLH Causes

Improper activation of the immune system. The immune system in a patient with HLH is geared up - more active than a non HLH patient

Dr. Gross mentioned there is still limited knowledge of the specific genes that cause HLH beyond the Perforin mutation. He mentioned there was some work being done (mostly in Europe) to look at the MUNC gene for causes, but the MUNC gene was huge and has several variations which are completely normal. Therefore, it sounded like finding a specific trigger on the MUNC gene for HLH was going to take a while.

The causes currently being investigated include types of immune deficiencies and something that causes hyper reactivity in the immune system such as viruses and exposure to toxins.

There is some discussion about how vaccines impact the immune system and if the vaccines in a genetically programmed HLH person are triggering the start of the immune system ramp up. HLH may be caused or triggered by exposure to the mono virus known as Epstein Barr Virus. HLH may, in some cases, present as Lymphoma.

Two questions that were noted for follow up:

- Is a child with LCH at risk for HLH if exposed to the Epstein Barr Virus?
- Should LCH children be cautiously vaccinated due to the immune system response created by vaccinations?

Several questions related to HLH in connection with Juvenile Rheumatoid Arthritis (JRA). Dr. Burke mentioned that while some thought a bone marrow transplant (BMT) was a possible treatment for JRA and HLH related to JRA, it did not sound like doctors in the U.S. viewed BMT's as a treatment for JRA. It sounded as though using BMT's as a treatment for HLH was more prevalent in Europe. Therefore, in cases where HLH arose from JRA, if the HLH was put into remission by the HLH 2004 protocol, it did not sound like a BMT was needed.

A few questions were asked related to the possibility of continuing the HLH protocol as a treatment instead of a BMT. This was not an option due to the toxicity of VP-16. Continued use of VP-16 tends to cause the incidence of other cancers.

Systemic/Multi-Focal Langerhans Cell Histiocytosis (LCH)

This Breakout Session was moderated by:

- Dr. Barbara Degar - Children's Hospital Boston
- Dr. Jeffrey Hord - Akron Children's Medical Center

Is Langerhans cell Histiocytosis with gastrointestinal (GI) involvement considered high-risk or low? Dr. Degar said they don't really know. However, she has definitely seen cases of GI WITHOUT liver and/or spleen involvement.

The long-term effects of cladribine (2-CdA) were discussed. The panel responded that 2-CdA is still considered new. Not a lot is known about the long-term effects of treatment. At present it is not known to cause secondary cancers, unlike Etoposide (VP-16).

How long should treatment continue if a patient was NOT achieving complete remission? Should the patient get a break from chemotherapy for awhile? The panel responded that there should be no breaks. It is critical to continue treating until it is gone.

Prolonging therapy may help reduce the chance of developing central nervous system (CNS) complications for multi-focal LCH.

Single Site/System Langerhans Cell Histiocytosis (LCH)

This Breakout Session was moderated by:

- Dr. Megan Burke - Cleveland Clinic Children's Hospital
- Dr. Jeffrey Hord - Akron Children's Medical Center
- Dr. Sheila Weitzman - Hospital for Sick Children

SKIN INVOLVEMENT

Skin involvement can be very painful for an infant. Some skin cases can be treated for symptoms only. Children need close monitoring for the first year of life. The disease can attack other systems quickly. If the skin disease remits during the first year of life it is very likely that it will be gone for good. If it does recur later in a child's life, studies show that bone and skin are common locations.

Skin only patients start to show within 6 months of birth. Multi-organ breakout or dissemination typically starts between 6-8 months, though can occur later. Patients should be monitored frequently by their Oncologist with physical exam of liver and spleen, blood work, and skeletal survey if bone involvement is suspected.

After 8 months with no systemic progression, patients can be followed less closely (less irradiation, less invasive tests) but must continue to be followed as systemic involvement has been seen after the 8 month mark. There is no clear recommendation on how long to follow-up. Thorough exams with a knowledgeable doctor may be sufficient.

Skin-only LCH can and will “wax and wane.” There is no magic cure for itchy scalps. Doctors: when you see a persistent or severe “diaper rash” or a persistent or severe “cradle cap” think of HISTIOCYTOSIS.

Dr. Weitzman stressed that skin only involvement should ONLY be diagnosed in retrospect after years of remission with no multi-system involvement. Facial and scalp breakouts have not been directly related to the pituitary (diabetes insipidus) at this time.

Monitoring after treatment is generally every 3-6 months in the first year and related to specific bones and blood tests.

BONE INVOLVEMENT

Discussion surrounded the risk bones. The team stated that the risk bones, beginning at the eye brow level and dropping down a child's face and back to the back of the skull are the risk bones for central nervous system (CNS) involvement and diabetes insipidus (DI) in later years. Upper skull bones do not appear to increase the risk for DI and CNS as previously believed. The mastoid bones pose the greatest risk bone for these conditions. Children with mastoid involvement should be kept on chemotherapy much longer than children without. The team stated 12-24 months of treatment should be considered.

The LCH IV study will research whether or not longer treatment times are beneficial. Currently, this is not known and is subject to clinical judgment by the treatment team. Response to initial therapy is an indicator of the long term response of a child. If reactivation after the completion of chemotherapy were to occur, it is unlikely that a child will have multisystemic disease if they responded positively to chemotherapy in their past treatment. Positive response to chemotherapy in the bone presentation patient bodes well for future responses to therapy - i.e. if there is good response to the chemo treatment in treating the disease there will be good response to the same chemotherapy treatments in the future if reactivation occurs.

Dr. Burke discussed recent studies/information that indicates the remission rate in a bone patient without risk skull bone involvement is higher than has been originally thought. There are indications that when a child is treated with 2 chemotherapy agents (prednisone and vinblastine for example), the likelihood of reactivation is only 20-25%, not 50% as had been thought in the past. The team also noted that it can take years for the bones to heal and regenerate. This can be challenging when determining if a child is disease free with residual bone damage and should stop chemotherapy treatment or if the "hole" in the bone is an active lesion. Response to treatment is the best indicator as well as a doctor with good clinical judgment.

IMAGING

There was great discussion on imaging in this session. Dr. Weitzman had stated earlier in the day that skeletal surveys and bone scans complement each other and were good tests to use in the evaluation of Bone LCH. She clarified this in this session, stating that if both are done at the time of diagnosis they are beneficial and complement one another. If they are not, it is not beneficial considering the radiation risks.

The team stated that PET scans are new and in some cases they are useful. But currently, in this presentation of LCH, they are not telling more than the skeletal survey. There was some discussion about the PET scan showing active disease versus bone damage left behind in a lesion that is healing.

The risk of all this imaging on young children then became the topic of discussion and is of great concern to the doctors speaking in the panel. CT Scans, Skeletal Surveys, and Bone Scans all present risks to LCH children (or any child for that matter). They need to be used very conservatively due to the risk for secondary malignancy in a child's future. Just because they are available does not mean they need to be used or are always appropriate. This is one reason that radiation treatment has fallen by the wayside except in cases of soft tissue pressure/involvement. In most cases, the team felt that the skeletal survey is the best tool with the least risk to children at this time. It provides most of the information needed to determine if a child has active disease or is responding appropriately to treatment. There are areas that are hard to see on a skeletal survey such as the pelvis but the presenting team still said they would be hard pressed to use other imaging techniques due to the risks.

Parents were reminded that good clinical judgment is key to your child's treatment and if you experienced any discomfort or concern regarding your treatment team's clinical judgment, you should seek additional consultations.

Parents' Primer on Practical Issues and Patient Advocacy

This Breakout Session was moderated by:

- Karen Domanski, RN - Detroit, Michigan
- Don Johnson - Houston, Texas
- Tammi Pouget, RN - Detroit, Michigan

No one knows our child like we do. We want to be the best advocates we can be for them. Learn as much as you can about the disease and how it affects your child and family. You never want to leave the doctor's office with questions you may have forgotten to ask. It is helpful to think of all possible questions you may want to address prior to the next appointment and write them down on a piece of paper to take with you. Doctors like it, really! If you can take an older sibling, cousin or friend to the appointment to play or entertain your child, it might make it easier to spend quality time with the oncologist addressing your questions & concerns while your child is playing. Accept all the help from family and friends you can get. You'll need it!

One woman stressed to the group that if you are in a hospital or seeing a doctor that you feel isn't hearing you, isn't answering your questions and isn't meeting your expectations, **CHANGE!!** Do not accept that kind of situation. Don't convince yourself the situation will improve or that you don't have a choice. You have a choice. **LISTEN TO YOUR GUT AND MAKE A CHANGE.**

When you have a concern, don't talk to the receptionist. Get to the Oncologist's nurse or the Oncologist's voicemail. Understand that if you get to voicemail, you likely will not get an immediate response. Add it to your list of questions. Ask your Oncologist, "Under what circumstances should I contact you? Your nurse? Our pediatrician? If I have an emergency, how can I contact you? What constitutes an emergency in your mind?"

When your child needs a scan (e.g. CT, MRI), find out who actually schedules the scan. Then ask them to schedule it as early in the day as possible. The more lead time you can give your scheduler (like 1 or 2 months), the more likely you will be successful at getting an early appointment. Your child will have to go without food and water for hours prior to the scan. **Child + No Food + Long Wait = Meltdown.**

Get copies of your child's medical records for your own file. Carry them with you when you travel. Write down their medications and doses. Have your doctors' (Oncologist and Pediatrician) contact information with you at all times.

Data from children not actually registered on the protocol is **NOT** used for research. The information goes nowhere unless you are registered and being treated **ON** protocol.

A doctor in the audience pointed out that there are varying degrees of Institutional Review Boards (IRB's). Some are very strict and work well. Others are "rubber stamps." Know your institution and your doctor's reputation. Ask the HAA for recommendations.

Check to see if the hospital is on the list of institutions that register patients for the LCH III protocol.

Question your doctor about their knowledge of the disease. How many patients have they treated with a similar diagnosis? What was the outcome? Do they consult with other doctors? If so, who? Are they members of the Histiocyte Society? Will your child be treated on protocol? Why or why not?

You are a PARTNER in the decision process. If you don't understand well enough to make a decision, ASK questions so you can make wise choices for your child. No one loves them more than you.

Advocacy, Fundraising and Networking Breakout Session

This Breakout Session was moderated by:

- Dr. Joseph Cosgrove - The Big Fix
- Michael Golding - Sydney Salem Golding Fund
- Beth Anne Miller - Histiocytosis Association of America

The Histiocytosis Association of America (HAA) has published information as to how donated funds are allotted: 50-60% goes to research (75% of this is traditional research, 25% to ongoing protocols); 15% of funds used for fundraising event help, and the rest goes to administrative use, such as phone, website, administration, and paper communication.

(Mike) Tips for successful fundraising: Figure out what you love to do (golf, bike ride, party, silent auction, pub crawl), surround yourself with others who also love whatever it is, and thank all participants and donors ASAP (before the check is cashed, so to speak). Follow up later with results of your efforts and thank them again. "It would not have been possible without them!"

Many businesses want to help by donating goods or funds. They need the tax write off. Find out when their donation campaign is and hit them up then.

(Beth Anne) Americans are philanthropic by nature. Tap into that! The HAA will help you with whatever fundraising idea you have. They will provide literature for you to distribute about the association and also give out pens, magnets, notepads, etc.

Donations to HAA can also be made through United Way. Many businesses give employees a donation card that has various charities on it. Spread the word that if they mark United Way some funds will go to HAA. If UW is not on their ballot, get them to add it.

(Mojo) Find your passion! Get a celebrity. Find a personal connection with each small business that you approach for donations (such as, "we eat here twice a week", etc).

Silent Auctions have the best profit margin because (obviously) services/items are donated.

If there is an existing event in your area, consider approaching them to add on an HAA fundraiser.

Even your child's birthday party could be a fundraiser. You could request donations instead of gifts while enjoying a day at Chuck E. Cheese.

If you want to raise funds for several entities, consider creating a foundation. This is not a requirement for fundraising.

LCH with Central Nervous System (CNS) Involvement

This Breakout Session was moderated by:

- Dr. Barbara Degar - Children's Hospital Boston
- Dr. Joanne Hilden - Cleveland Clinic Children's Hospital

LCH children who have been in remission may still develop “late-stage” effects, even many years later. This is more likely for the patient who had central nervous system (CNS) involvement and those with mastoid or facial bone tumors. These “late effects” are believed to be scar-tissue damage in the brain, which can manifest as behavioral problems and learning disabilities. These problems cannot always be detected with an MRI.

Psychological testing should be done to determine any problems. A baseline test is recommended at the first opportunity, though the test is not very helpful when the child is younger than school age. There is definitely a difference between the basic test given by schools and one administered by a professional.

Brain involvement and late-stage effects are two different things. Brain involvement includes active lesions and can be treated with chemotherapy that crosses the blood-brain barrier. Late effects are not active disease, but most likely “scar tissue” left behind. Late effects are not known to be reversible. The only known “treatment” for these late effects is therapy to help train the patient to “bypass” these “scarred” areas of the brain.

Those patients with diabetes insipidus (DI) are at a much greater risk for learning disabilities later in life.

Treatment Protocols/Clinical Trials/Research

This Breakout Session was moderated by:

- Dr. Kenneth McClain - Texas Children's Medical Center

Approximately 80% of pediatric leukemia patients are on some sort of clinical trial.

Why don't we see new wonder drugs used for LCH? New drugs must first be tested on animals and then adults before they can ever be used for children. Until very recently there has never been an animal model for LCH. However, a group in Switzerland may now have an animal model. Also, LCH cells cannot be cultured.

There is a movement in private health care institutions to eliminate clinical trials and Institutional Review Boards (IRBs) because of concern over liability issues by hospital management. Dr. McClain asked participants to write to their government representatives about this and urge clinical trials to continue.

Many physicians will treat LCH patients "according to the LCH III protocol." However, this does not mean that the patients are actually registered on the protocol. Every patient signs a "consent to treatment" form, but that is not the same as registering on the protocol. There is separate paperwork to actually be registered on the protocol. One must not assume that because they are being treated "according to the LCH III protocol" that they are registered on the protocol and that their data is being used for research. Data from patients not actually registered on the protocol are NOT used for research. The information goes nowhere unless you are registered and being treated ON protocol.

A clinical trial requires randomization. A clinical trial usually compares standard therapy to "new" therapy, which is theorized to be better or more improved. Randomization is required to eliminate possible bias. Randomization means that the patient is assigned to an arm of therapy randomly and the patient and his physician cannot select the arm to which he is assigned. In the case of the LCH III protocol, patients are randomized with respect to the use of methotrexate.

A lot of paperwork must be completed by a doctor to get a protocol through a hospital IRB. Once a protocol is approved, the sponsoring doctor must "renew" the protocol with the IRB annually even if the protocol has not changed. The continuing effort required by doctors to "push" a protocol through hospital boards contributes to doctors' reluctance to do so, especially if they only see one or two LCH patients per year. Doctors are offered monetary reimbursement for their time to "push" protocols through IRBs by the Histiocyte Society.

Even after sponsoring a protocol through IRBs, some doctors fail to provide follow up data on patients. However, most of those doctors will provide follow up data when reminded to do so. Dr. McClain said he was fortunate in that he has a data analyst whose job is to provide information about patients on protocols. However, his situation is not typical of other doctors who usually do not have support personnel.

Doctor McClain and other histiocyte research physicians have tried to present poster presentations at large, national meetings of other specialists (e.g., Otolaryngologists (ENT) or Pulmonologists) to raise awareness of histiocytosis and encourage registration on protocols. But, their efforts have not been very successful to date. Dr. McClain has met ENTs who are very resistant to treating LCH with chemotherapy.