NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

Ciara's Struggle:

Missed Milestones and Making a Diagnosis

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Part I – Unusual and Concerning Behavior

The following case study tells the story of Abby and her husband Jim who adopted a two-year-old female child, Ciara, originally born in New Mexico. Ciara was homeless prior to the adoption and had no medical records aside from newborn vaccinations.

Use the data below to formulate and revise hypotheses surrounding Ciara's condition. You will submit one per group and may use the internet for researching your hypotheses.

- Abby and Jim notice that Ciara has trouble breathing and frequently appears out of breath.
- Ciara often coughs when eating her food and spits out large pieces as opposed to chewing and swallowing.
- Abby and Jim also notice that Ciara has grown clumsier since the initial adoption interview and has trouble walking and holding objects.
- Ciara has a tendency to blink frequently when looking around and her eyelids seem to droop at the edges.
- Ciara does not sleep well and cries frequently.

Questions

1. Develop a preliminary hypothesis for what is wrong with Ciara and explain your reasoning. Be sure to note the key information that led you to form the hypothesis.

2. What additional information would be necessary to support your hypothesis?

Part II – A Trip to the Physician

Abby and Jim decided to take Ciara to a local pediatrician, Dr. Vida. Dr. Vida performed all standard vital testing in addition to employing the scale for the assessment and rating of ataxia (SARA), a tool to assess mobility. Dr. Vida also conducted a preliminary eye examination but referred Abby and Jim to both an ophthalmologist and a neurologist for a more intensive examination. In order to determine whether all of Ciara's enzymes were functioning properly and to rule out any possible infections, Dr. Vida also ordered full and in-depth blood work. The document below reflects the physician's preliminary notes.

Physician's Notes:

- Patient presents occlusion in lungs; may be early dysphagia but need to rule out infection.
- Patient has unsteady gait and presents difficulty moving limbs after periods of stagnancy.
  - SARA results suggest higher than moderate ataxia.
- Patient blinks repeatedly in response to light and was unable to follow light movement during examination.
- Patient shows delay of milestones, especially speech, and reversal of milestones associated with mobility.
- Moderate to severe ataxia as rated by the International Cooperative Ataxia Rating Scale.
  - Full bloodwork panel ordered.
  - Referred for ultrasound of liver and spleen.
  - Referred to ophthalmologist for corneal and retinal examination.
- Follow up appointment scheduled in three weeks.

Questions

1. Why did Dr. Vida refer Ciara for blood work and an ultrasound?

2. Has your hypothesis changed based on the visit to the physician? Using the physician's notes, provide further support or rationale for changing your hypothesis.

3. Is there enough evidence to make a firm diagnosis? What additional tests or experiments would be needed to provide evidence in support of your hypothesis to make a firm diagnosis? Explain.

Part III – Review of Results

Ciara continued to struggle with speech and mobility, more so following a series of seizures. She had several tantrums when it was time to eat or go to sleep, which Abby believed was due to her inability to chew solid foods and sleep through the night. Abby could not tell for certain because, in the past two weeks, Ciara had been unable to clearly communicate verbally with her parents. They visited the ophthalmologist and returned to Dr. Vida to discuss the results. Notes from the ophthalmologist, results from the blood panel, and further notes from Dr. Vida are reflected below.

Ophthalmologist's Notes

- Patient cannot read below the second line on SNELLEN chart.
- Apparent vertical supranuclear gaze palsy (VSGP).
- Saccadic eye movements (SEM); referred to vision therapy.
- Prescribed glasses prescription that accounts for eye irregularities.

Physician's Notes

Table 1. Results of Ciara's blood work (Normal (N); High (H); Low (L))

Measure	*Result*
Hemoglobin	N
Hematocrit	N
Platelets	N
Cholesterol	L
Neutrophils	H/N
Monocytes	N
Liver Enzyme	H
Glycogen	N
Glucose	N
Acid beta-glucosdase	N

- Ultrasound suggests only minor splenomegaly present.
- No noticeable infection based on panel.
  - Slight elevation of neutrophils; could be due to inflammation?
- Follow up with biopsy for filipin test, cellular morphology staining and cholesterol esterification test.
- Head circumference in lower percentile (~25th) for age.
  - Minor microcephaly
- Distributed literature on lysosomal storage disorders.
  - Niemann-Pick disease type C
  - Gaucher disease.
- Follow up in two weeks.

Before continuing further, watch the following video on lysosomal storage disorders: <**https://youtu.be/lQ3z7cAvriI**>.

Questions

1. What can you infer from the blood panel and ultrasound?

2. What test or experiment could be used to determine the irregularity that is causing the symptoms?

3. Is the blood panel enough to determine the exact pathobiology? Explain.

4. What new information would a biopsy provide? Explain.

5. Can a diagnosis be made at this stage? Why or why not?

6. Has your hypothesis changed with the addition of new information? Explain.

Part IV – The Neurologist and Pathologist

Ciara had a severe seizure after the follow-up appointment with Dr. Vida, which led Abby and Jim to expedite the appointment with the neurologist. The neurologist performed another SARA screen and explained that the progressive ataxia was likely due to the loss of specific neurons in the cerebellum but that she could not be completely certain at this stage. She completed an MRI and requested a follow-up appointment.

At the appointment with Dr. Vida, the pathologist came in to explain the procedure used to determine whether their daughter had a lysosomal storage disorder. She explained that the biopsy from Ciara was used to grow live cultures of skin cells that were incubated with low density lipoprotein (LDL) before being treated with several cellular stains to determine if the cellular recycling organelle was functioning properly. She explained that the results strongly suggested that Ciara was experiencing a lysosomal storage disorder due to a positive reaction with the chemical filipin. She recommended DNA sequencing to make a definitive diagnosis so that Ciara could go to the appropriate specialty clinic.

Neurologist's Notes

- MRI shows what appears to be frontal lobe atrophy when compared to a normal scan of a patient her age.
- Severe ataxia.
  - Scores on high end for all categories.
- Provided a wheelchair to reduce likelihood of falls.
- Follow up appointment in two weeks.

Physician's Notes

- Severe decline in mobility, communication, and cognition.
- Pathologist delivered explanation of biopsy to parents.
- Neurologist data confirm minor microcephaly.
- Data strongly suggest NPC, T2.
  - Sent for genetic screen.
- Ciara admitted for long-term residence in the children's hospital.

Questions

1. How are microcephaly and ataxia related to a lysosomal storage disorder?

2. Why did the pathologist incubate Ciara's cells with LDL and filipin? What macromolecule is being improperly processed in the lysosome? Explain your rationale.

3. What gene mutations should be screened for during DNA sequencing? Why?

    a. What do these genes encode?

    b. In a normal cell, where would the protein encoded by this gene be found? Describe their role in the cell.

4. Why did the blood test show normal to low cholesterol?

    a. What is the impact of this mutated protein on the membrane?

    b. What can you infer about intracellular transport in Ciara's cells?

5. Can this explain all of Ciara's symptoms? Explain.

6. Using all of the information make a diagnosis for Ciara. Use evidence to support your diagnosis.

Part V – Diagnosis and New Beginning

Ciara passed away shortly before her fourth birthday with a final diagnosis of NPC2 from a specialist in lysosomal storage disorders (LSDs). Abby and Jim donated Ciara's brain for research in an effort to help develop therapies for LSDs. Upon investigation, her autopsy revealed large-scale neurodegeneration in several areas of the brain. Abby and Jim decided to adopt another child and started a fundraiser for lysosomal storage disorder research.

Questions

1. Why do lysosomal storage defects lead to cell death?

2. Is it possible that other processes are affected?

3. Is there dysfunction of other cellular organelles as a consequence?

4. Would clearing the lysosome of accumulated debris be beneficial in these diseases? Is it possible that it is the accumulated substrate that is detrimental, or is it causing something else that leads to degeneration?

5. There is no current treatment for the neurodegeneration observed in Niemann-Pick type C. Suggest a new therapy focused on reducing neurodegeneration in this disease.