

# Batten's Disease (April 30, 2009)

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NCL (neuronal ceroid lipofuscinosis) is a kind of inherited neural degenerative disease affecting mainly children and only occasionally seen in adults. It is an autosomal recessive inheritance neural system disorder. In 1826, Dr. Stengel first discovered the disease and developed the concept of CL (ceroid lipofuscinosis). Dr. Zeman and his partners discovered fluorescence of brain sediments in Amaurotic Family Idiocy patients in 1963, and then six years later, they named the disease NCL (neuronal ceroid lipofuscinosis). The main symptoms of NCL are vision loss, progressive dementia, refractory epilepsy and degeneration of motor ability.

Medical history abstract & Treatment procedure:

Patient is a 6 year old girl. She had normal development from the time of her birth, up until two and a half years old. Patient had paroxysmal limbs twitch accompanied by a loss of consciousness, the main symptom was myoclonic seizures. When she was three and a half years old, she had weakness in all four extremities and slow response, from then on she had walking difficulty and gradually, she could not walk stably and she fell easily. The patient could not concentrate and had lost her ability for speech. In January, 2008, the symptoms became aggravated suddenly, the patient became bedridden, she would choke while swallowing, she had difficulty eating, and she would regurgitate her food, vision loss ensued and her breathing became difficult. She was diagnosed with Batten's disease (Late Infantile Form). Because the patient had no response to general treatment, her parents brought her to China to receive stem cell treatment done by Dr. Like Wu.

Physical examination:

Mental status is bad, and the patient is unable to speak. There was only a little bit of light sensitivity remaining. She can not complete daily things (as she had to be in bed and can not turn over any more), patient had involuntary movements of her head and tongue muscles, the neck muscles are too weak to support her head, the muscle force of her 4 limbs are 1 degree, muscle tone is lower than normal. Babinski signs of both sides are positive. She had frequent paroxysmal twitching, and she cannot cooperate with the medical examinations. Hr: 110/min, heart rhythm is regular. She had breathing difficulty, with diffused rhonchus of her lungs, other physical examinations are normal. The first treatment procedure is 7 weeks, gave the patient treatment to improve circulation, nourish neurons, anti-epilepsy and neural cells activation treatment (4 stem cells implantation), and combined with individual professional rehabilitation training. Our anticipatory goals are to improve the patient's neural system's function (movement ability, optic nerve, etc), control her epilepsy, slow down the development of the disease, improve her life quality and prolong her life. We had to change the transfusion needles everyday to ensure the full use of all medications because of her bad vascular condition. After the first treatment procedure, her symptoms of congestion, and stomach regurgitation disappeared, the involuntary movements of her head disappeared also, and there only remained some involuntary movement of her tongue muscles. The frequency of her seizure attacks has decreased greatly and once she has any seizure attacks, it only lasts several

seconds. After she returned home, she took medications regularly according to her doctors' instructions, and her parents helped her with her daily rehabilitation.

Six months later, the patient returned to our medical center for a second stem cell treatment and we found that she is noticeably much taller and heavier than before. Her seizures are much more under control, and only had seizures 5-10 times per day, and they last only 1-2 seconds. Her drooling is better than before. Patient had no involuntary movement; her breathing is quicker and shallower than normal. There are rhonchi in her lungs. Patient had difficulty coughing and expectoration. She had no obvious congestion, and she had severe body weakness and limpness.

Patient received 6 weeks of treatment which aimed at improving her muscle strength as well as controlling her seizures. During this treatment period, when the patient received daily IV, the transfusion needle remained for 3-4 days. But the patient had developed pneumonia after an upper respiratory tract infection (URI), which influenced her rehabilitation greatly. She had vomited and choked, and her seizure attacks had become more frequent than before, after active treatment, patient's infection and seizures were controlled. When the treatment was over, the patient was much more alert, mental status is better; her eyes are much brighter than before. Her pupils are much more sensitive to light, and her right eye had avoided reflex to light. Patient had a little vocal ability, when she took rehabilitation training and felt uncomfortable, she could groan. She had more facial expression, could smile and express happiness. Now her breathing is much more stable, and her sleeping is better. She still had epileptic attacks 5 times per day, which is less than before, and she had no epileptic attacks at night. Her drooling is less obvious than before. The muscle tone in her 4 limbs is basically normal, and patient is much stronger than before, she can turn over for about 45° when she is in a lateral position, when she is in a sitting posture, she can control her head and can hold her head up for 2-3 min, she has movement of her upper limbs. Muscle force is about 3 degrees; she had intentional grasping movement of her hands. She had good reaction when her therapist gave her passive training of her lower limbs, and she can coordinate part of her stretching and bending movements.

#### Case discussion:

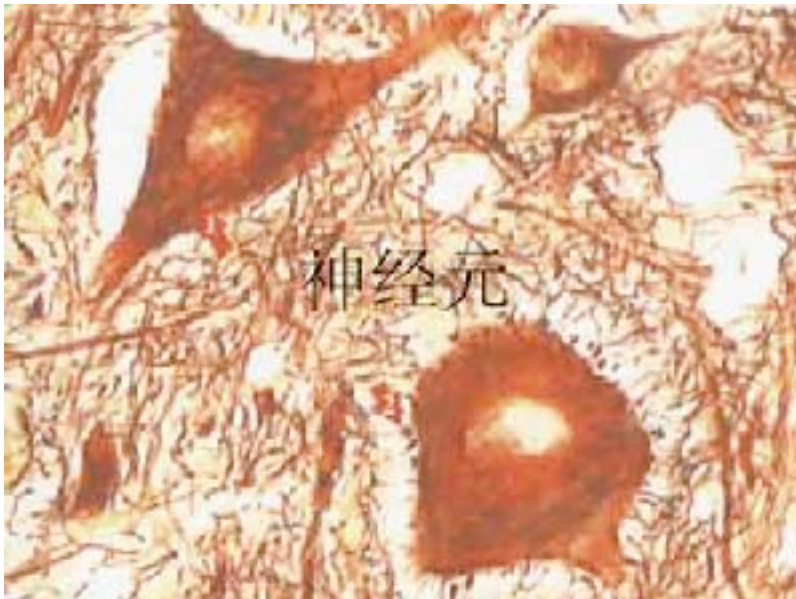
The typical Late-infantile neuronal ceroid lipofusinoses (CLN-2) can begin with children between the ages of 2-4 years old. The first signs are epilepsy, vision loss and mental retardation, followed with ataxia. There are several variants of Late-infantile neuronal ceroid lipofusinoses. For that patient, the on-set age, clinical symptoms and pathological changes are all correspondent with the diagnosis of Late-infantile neuronal ceroid lipofusinoses, and her condition is similar with the variant which Dr. Wisniewski had reported before: the onset age of this kind of variant of CLN-2 is 2-4 years old, the first sign is dyskinesia, the patient had dementia and myoclonic epilepsy, the vision disorder will happen later. This kind of variant has obvious differences from other kinds of variants: the onset age of Santavuori Type is 4-7 years old, the main symptoms are vision loss and refractory epilepsy; while in another type of variant which Dr. Edathodu had reported, the onset age is 9 years old, and the main symptom is mental disorder.

## Brain MRI:

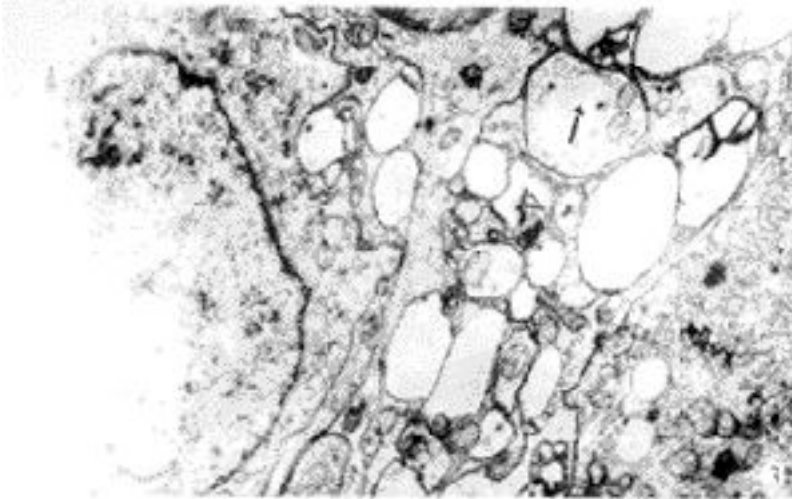
Cerebral atrophy and cerebellar atrophy, along with the development of the disease, the brain tissue atrophy is getting more severe. In the late stage, there will be a long T2 signal of white matter around the ventricle; while there will be a signal decrease in the basal ganglia and cerebral cortex. Those imaging changes can be different (including the occurrence time and the level of the change) in different subtypes of NCL, the brain MRI examination is helpful to the diagnosis and follow up of NCL disease.

## Pathological Change of NCL:

Histological: severe neuron loss, the remnant neurons continue to degenerate, combined with fibrous astroglia cells hyperplasia and monocytes infiltration. (Fig. 1)



Ultrastructural study: there are a number of curvilinear bodies with envelope, and occasional fingerprint bodies can be seen. We can also find the curvilinear bodies in spongocyte, the infiltration monocytes and cytoplasm of vascular endothelial cells. (Fig.2)



With modern day research in molecular biology, scientists have found and located the genetic locus of different forms of NCL: Infantile neuronal ceroid lipofusinoses, Juvenile neuronal ceroid lipofusinoses and Santavuori form of Late-infantile neuronal ceroid lipofusinoses. We still cannot determine for sure the genetic locus of other forms of Late-infantile neuronal ceroid lipofusinoses. Currently, the chemical composition of curvilinear bodies are not very clear, but we can determine the main part which is mitochondrial ATP synthase subunit c. It is possible that there is methylation at the lysine end of the ATP synthase subunit c, that leads to the form of stored type of mitochondrial ATP synthase subunit c, it indicates that the cause of Late-infantile neuronal ceroid lipofusinoses has some relation to mitochondrial function disturbance, while not only a kind of lysosome metabolic deficiency. Because of the shortage of the normal fat metabolizing enzyme, there are large amounts of waste/toxic substances accumulating in the patient's brain and damaging the brain neurons. In the clinic, the patient has symptoms of seizure attacks, speech ability loss, progressive degeneration of movement, blindness, and secondary lung infection that can lead to death. And because the blood brain barrier can prevent the giant molecules from entering into the intercranial circulation, so many doctors still consider Batten's disease as incurable.

Now neural stem cell treatment has developed and brings new hope for a cure for the disease: those neural stem cells/ bone mesenchymal stem cells (BMSC), after the implantation, can cross the cerebrospinal fluid and blood brain barrier, with the doctor's strict control, those stem cells can produce the protein which is lacking in the patient's own body, improve the microenvironment and help rebuild the patient's neural tissue structure.

From this particular case, we can see that the patient has the typical characteristics of Late-infantile neuronal ceroid lipofusinoses from the onset age; symptoms are consistent with the development of the disease. Patient has recurrent seizure attacks, vision loss, deficit of motor ability, and the development of the disease is fast. With the stem cell treatment, during the first treatment procedure, we slowed down the development of the disease, controlled her seizures,

improved the patient's lung functioning as well as her vascular condition; and in the second treatment cycle, we attempted to improve the patient's mobility, but the treatment results did not reach our goal, the main reasons are:

The neural system damage is diffused in Batten's disease, our stem cell treatment can clear away a part of the toxic metabolite in her brain, protect her brain functioning, and those implanted stem cells can produce normal neurotransmitters and neural growth factors to repair the damaged brain cells. But to completely improve and repair all the damage neurons, a short period of treatment is not enough.

During the treatment procedure, the patient developed an infection, which negatively influenced the medication's effect, and aggravated her seizures. Mild seizure attacks will benefit the patient by rebuilding neural functioning and will help the growth of those stem cells, but since she had so many seizure attacks, there was damage to her brain neurons and the implanted stem cells. Doctors now consider that improving the functioning of the patient's immune system will be a new approach in the treatment of the late stages of Batten's disease in children.

The rehabilitation training is a necessary part of the whole stem cell treatment procedure, even after the systemic comprehensive treatment performed during her hospitalization, in order to maintain and strengthen the stem cells treatment effect. She will still need professional rehabilitation training regularly in the future.

Generally speaking, from this case, we can see that stem cell treatment for Batten's disease is effective, although today it still cannot be cured completely, our stem cell treatment can slow down the development of the disease, and our doctors are still continuing their research in an effort to discover a cure.