KAZAKH MEDICAL UNIVERSITY OF CONTINUING EDUCATION
DEPARTMENT OF CHILDREN'S NEUROLOGY WITH A COURSE OF MEDICAL GENETICS

14.09.2019

CHILDREN NEUROLOGIST'S CONCLUSION

Akshal Ayana
Age: 1 year 2 months, born on: 29.06.2018.
Residential address: 41 Kavkazskaya, Almaty.
Contacts: mother Regina Segizekova 8 707 402 0314

Complaints: motor development delay: she rarely turns over, only turns on side, she does not sit on her own, and support is weak.

Anamnesis vitae and disease history: child is from 2nd pregnancy/1st childbirth, against the background of burdened obstetric history (1st pregnancy – pregnancy loss on 7-8 weeks), course – weak foetal movements, attacks of chronic maxillary sinusitis, dental care. Screening on 20th week – high risk of Down syndrome (according to the mother). Childbirth was on 41 week + 6 days. Childbirth stimulation. Emergency caesarean section. Birth weight is 3672 g, height is 52 cm. According to Apgar there are 8\9 points. She is latched on after 6 hours, sucking is active. She was discharged on the 5th day. In the neonatal period: on artificial feeding from 2nd week, according to the mother – weight gain is good. Initial examination by neurologist was at the age of 2 months.
From 5 months age there is noticeable decreased muscle tone, support was absent. She was observed by neurologists. She received 4 courses of massage, Cartan.
Electroneuromyography (ENMG) (02.05.2019) – data for disease of the peripheral nervous system has not been received.
At the age of 10 months (15.05-20.05.2019) there is hospital treatment in neurology department in Children's Municipal Clinical Hospital No. 2 with diagnosis of "Floppy Infant Syndrome".
At the end of May, she was examined by Myrzaliyeva B.D., neurologist. She was sent for additional examinations: magnetic resonance imaging (MRI) of the spinal cord, needle electromyography (EMG), and genetic analysis.

Examination results:
Magnetic resonance imaging (MRI) of the thoracolumbar spine and spinal cord (05.08.2019) – without pathological findings.
Sequencing the panel for "neuromuscular diseases" (12.09.2019) – homozygous deletion of chromosome 5 with approximate boundaries of 70247719-70247838 bp and 119 bps in size, capturing sections of SMN1, SMN2.

Heredity: according to parents, there are no phenotypically similar individuals among relatives; there are no cases of patients. Nationality is Kazakhs. Parents' marriage is not closely related.

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Objective findings: child's condition is serious due to hereditary neuromuscular pathology, stable. At the time of examination, there are no cerebral, focal, meningeal symptoms. Weight is approximately 10.5 kg.
Consciousness is clear. She reacts to the examination adequately. She smiles, babbles, there are simple words up to 2-3. Head is of regular shape, head circumference is 47.0. Anterior fontanel is closed. Skull brain nerves – she monitors objects, face is symmetrical, there is no nystagmus, and auditory reactions are good, there are no bulbar disorders. There is minor tongue fibrillation.
Muscle tone is diffusely reduced in hands and legs, symmetrical. Tendon reflex: from hands – depressive, from legs – knees are not triggered, Achilles – reduced. Abdominal reflexes are not triggered. Pose is of the "frog". The head is not brought with traction by the hands, it is thrown back. She holds the head upright. In the position on the abdomen – she does not raise her head, but turns to the sides. There is no support. Movement in the hands: she raises her hands, holds in front of her, brings to her mouth, and looks at them. She sits with support with a "round" back.
Contractures are formed in the ankle joints.
Nasal breathing is difficult due to rhinitis. Chest circumference is 47.5 cm.
There is hidrosis of the head after feeding, sleeping, hidrosis of the back. There is constipation. According to the parents, child has frequent vomiturition, not related to eating.

Clinical Diagnosis

Spinal muscular atrophy, type II

1. Regular medical check-up and supervision by neurologist, paediatrician, pulmonologist/ specialist in breathing support, orthopaedist and other specialists in the polyclinic at the place of residence. Examination of the child by specialists at home.
2. Additional genetic examinations: **search for deletions in the SMN1 gene, analysis of SMN2 gene copy number (for child);** analysis of a married couple for the carriage of mutations in the SMN1 gene (for parents). Family genetic counselling. Information on prenatal and preimplantation diagnostic methods.
3. Pass biochemical blood test at the level of Creatinphosphokinase (CPK), 25-ON-D3 (25-OH-Д3).
4. Direction to Medico-social Expert Board. Disability registration for the underlying disease, commission visit to home (hereditary neuromuscular disease, severe form; marked changes in the neuromuscular system function, motor development delay; complications from other organs and systems; high risk of acute respiratory failure (ARF), aspiration, consecutive infection; low rehabilitation potential). Disability registration without prior hospitalization to avoid infection and contact with infectious patients in the department!
5. Protective regimen. Keep away from acute respiratory viral infections (ARVI), injuries, and contact with infectious patients. Care. Nutrition.
6. Consultation with nutritionist/dietarian. Weight monitoring. Selection and calculation of nutrition, feeding schedule (specialized medical nutrition Nutrini, etc.) with insufficient nutrition.

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Doctor]
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7. Consultation with orthopaedist. Joint development. Manufacture and wearing of orthoses on the knee and ankle joints.
8. Measurement of blood saturation with a pulse oximeter at night (Normal – 94-99%).
9. Consultation and supervision by pulmonologist, specialist in breathing support. In case of acute respiratory viral infections (ARVI) – timely therapy according to indications, inhalations, drainage massage.
10. Consultation with gastroenterologist. Abdominal ultrasound. Coprogram.
11. Metabolic therapy:

Carnitine preparations (drinking Cartan, Elkar in drops, Levocarnitine in syrup): **Drinking Cartan 8.0 ml of Cartan in 80.0 ml of water, intake during the day, in 30 minutes before meals – 2 months.** Take in combination with preparations of group B vitamins: **Neuromultivit (or any analogue of vitamins B) 1/3 tablet 1 time per day, before meals – 2 months** (iherb.com)

Next – break and take of **Coenzyme Q** (Kudesan in solution, drops, granules) **5 drops 1 time per day, in the morning – 1 month.**

Vitamin D3 (Vigantol, Coledan) 2-3 drops 1 time per day, until 12.00 – constantly.

12. Exercise therapy – daily. Stretching, joint development. Massage courses – 10 procedures, 1 time in 2 months. Swimming. Classes on the ball. Kinesiotherapy. Breathing exercises with an Ambu-bag.
13. Control examination at the department – after 3 months.

Consultant:
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CONCLUSION
according to the results of DNA analysis by clinical sequencing

Patient: Akshal Ayana Ulankyzy
Sex: Female **Date of birth:** 29.06.2018
Referral diagnosis: "Floppy Infant Syndrome". Inherited neuromuscular disease?
Type of examination: Panel for "Neuromuscular diseases"
Date of sampling: 09.07.2019. **Date of examination:** 12.09.2019.

EXAMINATION RESULTS

Total reads	5514419	**Total revealed options**	16748
Length of reads	2x151 bp	**Options after filtration according to pathogenicity basic criteria**	1
Read nucleotides	1.52 billion		
Average coverage	89.3x		

Options, that may be the probable cause of the disease, are prioritized according to a proprietary algorithm taking into account ACMG recommendations, the presence in the databases, population frequencies, and other criteria.

Options are grouped by their pathogenicity probability degree to the patient based on the prioritization and phenotype of the patient described in the submitted documents. In groups, options are put in order of decreasing priority.

Options, that do not have pathogenicity signs, or that have some pathogenicity signs, but that do not match the phenotype described in the supporting documents, may be not included in the conclusion.

Detailed description of the examination can be found in the appendix to the conclusion.

ATTENTION! Options found as a result of the examination are not proven diagnosis, but can be used in conjunction with data from other laboratory and instrumental methods only by doctor geneticist.

Consultation with doctor geneticist is necessary to clarify the significance of the detected options, including taking into account patient's clinical presentation.

12.09.2019
Doctor Geneticist Gorgisheli K.V.
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Round seal: [* LIMITED LIABILITY COMPANY * OGRN 1077753509977 * MOSCOW Genomed]

Option (hg19)	Zygosity	Gene	Transcript	cDNA	AK replacement	Read depth
Pathogenicity signs and comments						
Syndrome						

1. Options that are the most likely cause of the disease

No relevant options were found

2. Options having one or more significant pathogenicity signs

No relevant options were found

3. Options with unknown clinical significance

No relevant options were found

4. Carriage of options in the recessive disease genes

chr6:152555026G>A	Heterozygous	*SYNE1*	NM_182961.3	c.20602C>T	p.Arg6868*	107

Signs of option pathogenicity:

Leads to termination of protein synthesis

Other information:

It is present in population databases in a heterozygous state (GNOMAD: 0.000003980; EXAC: 0.000008245)

Diseases associated with the gene:

Emery-Dreifuss muscular dystrophy 4, autosomal dominant (612998), AD
Spinocerebellar ataxia, autosomal recessive 8 (610743), AR

For a recessive disease, detected option cannot be considered as the cause of the disease without the presence of a pathogenic option in another allele.

In some cases, carriage of recessive disease options may be relevant to the patient's relatives.

5. Variations in the gene copy number

Based on the analysis of sequenced gene coverage, data were obtained in favour of a homozygous deletion of chromosome 5 segment with approximate boundaries of 70247719-70247838 bp and the size of 119 bps, capturing sections of *SMN1, SMN2* genes. Homozygous deletions of areas of the SMN1 gene are described in patients with spinal muscular atrophy (OMIM: 253300, 253550, 253400).

Comparison of the patient's phenotype with the disease phenotype is recommended. Confirmation of the presence of found imbalance by the reference method, search for deletions in the *SMN1* gene, is necessary, because sequencing is not a standard method for assessing variations in gene copies.

List of genes included in the examination

Panel for "Neuromuscular Diseases"

AARS, AARS2, ABCB7, ABCC9, ABHD12, ABHD5, ACAD8, ACAD9, ACADL, ACADM, ACADS, ACADSB, ACADVL, ACAT1, ACO2, ACTA1, ACTC1, ACTN2, ACVR1, ADAR, ADCK3, ADCK4, ADCY6, ADGRG6, ADSSL1, AFG3L2, AGK, AGL, AGRN, AIFM1, AKAP9, ALDH18A1, ALDH4A1, ALDH6A1, ALDOA, ALG13, ALG14, ALG2, ALG3, ALS2, AMACR, AMPD1, AMPD2, AMPD3, AMT, ANG, ANK2, ANO10, ANO3, ANO5, AP4B1, AP4E1, AP4M1, AP4S1, AP5Z1, APOPT1, APTX, ARHGEF10, ARL6IP1, ARSI, ASAH1, ASCC1, ATAD3A, ATL1, ATL3, ATP1A3, ATP2A1, ATP2A2, ATP2B4, ATP5A1, ATP5E, ATP7A, ATP7B, ATPAF2, ATXN2, AUH, B3GALNT2, B4GALNT1, B4GAT1, BAG3, BCAT2, BCKDHA, BCKDHB, BCS1L, BICD2, BIN1, BMPR2, BOLA3, BSCL2, BTD, BVES, C12orf65, C19orf12, C9orf72, CA5A, CACNA1B, CACNA1C, CACNA1D, CACNA1S, CACNB2, CALR3, CAPN3, CARS2, CASK, CASQ1, CASQ2, CAV3, CAVIN1, CCDC115, CCDC78, CCT5, CDKL5, CEP89, CFL2, CHAT,

CHCHD10, CHKB, CHMP2B, CHRNA1, CHRNB1, CHRND, CHRNE, CHRNG, CHST14, CISD2, CIZ1,