**Table 1**: **All the pediatric consults, lab exams and imaging performed from January 11th2018 until present.**

| **January 11th 2018 (the initial pediatric consult) (Boy's age: ~2 years & 8 months [2y8m]) Additional dates of imaging and labs (related to this current pediatric consult): January 16th 2018** |
|---|
| **History:** hospitalized UTI (with **slight enlargement of the left kidney** on the ultrasound) **plus very high serum levels of AST, ALT and CK** (when the boy **was ~1 year old**); diagnosed with "**oligosymptomatic progressive muscular dystrophy**" (DMD with a mutation in the **52nd exon of dys-gene: a duplication of the 7547th nucleotide of dys-gene) on September 12th 2016; the maternal uncle of the boy "couldn't walk and was immobilized to bed from 7 years of age until his death at 18 years of age**" (very suggestive for DMD phenotype).<br>**Clinical exam**: Age: 2y8m; **Body mass (BM)**: 14 kg (in the normal range for age and sex: ~55th percentile); **Body height (BH):** 91 cm (under average, but in the normal range for age and sex; ~30th percentile); **Head circumference (HC)**: 47 cm (under average, but still in the normal range for age and sex; ~10th percentile); **impaired extension of the right limb when walking and running, calves pseudohypertrophy** (with symmetrical calves enlargement of ~23/23 cm maximum circumference of both calves), **slight tonus deficit of the axial/spinal muscles, extreme anxiety at the physical exam, hyperkinetic child, moderate language delay** (~20 correctly pronounced words at that age and only used pairs of words, but rarely sentences with verbs), **increased consistency stools (with defective discomfort;** probably secondary to errors in nutrition [excessive synthetic sweets frequently requested by the child and often given to him by his parents; low vegetables and fruits intake, implying low fibers intake] and also secondary to DMD, which DMD may generate lower contractility rhythm and strength of the small and large intestines);<br>**Lab exams (serum levels) (16.01.2018): GGT: 10 U/ml** (wnr); **AST: 473 U/L (~10 x nsl); ALT: 558 U/L (~17 x nsl); CK: 34 453 U/L (~201 x nsl); CK-MB: 1241 U/L (~52 x nsl;** myocardial origin); **MG (22.01.2018):2006 ng/mL (~28 x nsl); CRP (22.01.2018):** 0.61 mg/L (wnr); **ESR (22.01.2018)**: 9 mm/h (wnr)<br>**Management (including treatment): ARS** P.O. 30+30+0 ml/day (~4 ml/ body_kg/ day); **L-carnitine oral solution,** P.O. 500 mg/day ; **omega-3 fatty acids plus multivitamins oral supplement** (4.5 ml/day); **physical therapy** (rejected by parents); psychological consult (rejected by parents); prednisone P.O. temporization after the age of 4 years;<br>**Comments (including interpretations):** L-carnitine was used as an adjuvant for ARS, given that L-carnitine acts as a transporter of long-chain fatty acids into the mitochondria (where to be oxidized for energy production) and given the fact that ARS was anticipated to increase the serum levels of fatty acids, as shown by the metabolomics study conducted by prof. D. C. Nieman on ARS; the omega-3 fatty acids plus multivitamin mix was mainly prescribed for the boy's language delay: a very small dose (4.5 ml/day) was chosen, given the age and the possibility that the multivitamin (antioxidant) mix may inhibit ARS effect (by partially/totally neutralizing the free radicals from the ARS solution already absorbed in the blood). |
| **January 22nd 2018** |
| **Routine check-up** for reading the results of the lab exams (sampled in January 2018) |
| **January 28th 2018** |
| **Heart ultrasound** (28.02.2018): **normal** (with the reserve that the child was very anxious and hyperkinetic during this examination) |
| **February 15th 2018** |
| **Routine check-up** |
| **March 22nd 2018** |
| **Routine check-up. Management (including treatment):** We have recommended that the same rhabdomyolysis markers to be repeated after April 8th 2018 (after the Romanian Easter) |
| **April 10th 2018** |
| **Abdominal ultrasound** (10·04.2018): minimal hepatomegaly and otherwise normal (with the reserve that the child was very anxious and hyperkinetic during this examination); |
| **April 17th 2018 (Boy's age: ~2y11m)** |
| **Special check-up** (after ~3 months [~22.01.2018-17.04.2018] of ARS 60 ml/day [~4 ml/body_kg//day] plus L-carnitine 0.5 g/day, omega-3 fatty acids supplement ~44 mg/day and multivitamins mix) |

Lab exams interpretation and the additional recommendations were given online (without a new clinical pediatric consult until 17.05.2018)

**Clinical exam**: **Age**: ~2y11m;

**Lab exams (serum levels) (17.04.2018): AST: 453** U/L (~9 x nsl; of muscle origin, given the GGT wnr on 16.01.2018 [GGT was accidentally omitted to be also repeated in this new set of labs]); **ALT: 712 U/L** (~22 x nsl); **CK: 25 426 U/L** (~149 x nsl); **CK-MB: 632 U/L** (~26 x nsl); MG serum level was not repeated in this set, because of financial reasons;

**Management (including treatment):** Given the encouraging CK-MB serum level decrease of ~50% (as determined on 17.04.2018), we have recommended parents to increase the ARS dose to 50+40+0 ml/day (for a daily dose of 90 ml/day, which was equivalent to ~6.5 ml/body_kg/day) starting from 18.04.2018; we have also recommended a new set of laboratory exams for the last week of July 2018 (AST, ALT, GGT, CK, CK-MB and MG serum levels);

**Comments (including interpretations):** The ARS-based treatment from ~22.01.2018 to 17.04.2018 (~3 months) was associated with a slight AST serum level decrease of ~5%, an ALT serum level increase of ~28%, **a significant CK serum level decrease of ~26% and a very significant CK-MB serum level decrease of ~50%** (which was the main target of the ARS recommendation and may be explained by the fact that ARS has stronger NRF2 activation effect on the myocardium, where the expression of NRF2 is larger than in skeletal muscles); the significant decrease of both CK and CK-MB serum levels (by ~28% and 50% respectively) (from 16.01.2018 to 17.05.2018) may be explained by an important decrease of the oxidative stress in DMD myocytes: this effect may be produced by ARS via NRF2 pathway (an effect more pronounced in myocardium than in skeletal muscles, due to NRF2 higher concentration in the heart muscles versus skeletal muscles); because ARS was not associated with any raise in AST/ALT (implying that ARS has no detectable liver toxicity) in prof. D. C. Nieman's first metabolomics study on ARS (see pages 20 and 21 from that previously cited study), it is improbable that the increase of ALT serum level by ~28% (observed in this ~3 year-old DMD boy) to be caused by ARS through liver toxicity (the further decrease in ALT in the subsequent samples also demonstrate this fact); because the ALT serum level is the only result that goes "anti-trend" (by increasing when all the other enzymes serum levels decrease), a laboratory ALT determination error is not excluded; ALT increase by liver toxicity or hemolysis is also very improbable, because AST serum levels would have also increased; ARS was demonstrated to be an inductor of apoptosis in damaged cells in vitro, so it is possible that the observed increased ALT serum level to be produced by an increased apoptosis rate of skeletal (and possibly myocardial) myocytes: this possible increased apoptosis rate may be concomitant to an increase rate of new myocytes production (which may co-explain the decrease of CK and CK-MB, secondarily to the important decrease in the DMD myocytes plausibly produced by ARS).

**May 17th 2018 (Boy's age: ~3y)**

**Routine check-up. Clinical exam: Age**: ~3y; **BM**: 14.1 kg (in the normal range for age and sex); **BH**: 93.5 cm (in the normal range for age and sex); **Physical and mental examination**. Normal extension of the right limb (when walking), **calves pseudohypertrophy (with ~23/23 cm maximum circumference of both calves), no apparent tonus deficit of the axial/spinal muscles, no anxiety at the physical exam, no agitation, slight language delay (he uses ~30 correctly pronounced words at this age, but he builds true sentences using verbs and some simple phrases)**. The rest of the physical examination exam results were normal: cranial nerves tests in normal limits, normal breath rate and pulmonary sounds, normal heart rate (with no heart murmurs), normal abdomen (without clinically detectable hepato-/splenomegaly), **but with increased consistency stools (with painful defecations)**, normal diuresis and urination (with no kidney pain/sensibility), normal genital apparatus.

**July 31st 2018 (Boy's age: ~3y2m)**

**Routine check-up and lab results reading** (after ~3 months [~22.01.2018-17.04.2018] of ARS 60 ml/day [~4 ml/body_kg//day] plus L-carnitine 0.5 g/day, omega-3 fatty acids supplement ~44 mg/day and multivitamins mix; PLUS another ~3.5 months [18.04.2018-31.07.2018] of ARS 90 ml/day (~6-6.5 ml/body_kg/day) plus L-carnitine 0.5/day, omega-3 fatty acids supplement ~44 mg/day and multivitamins mix)

**Clinical exam**: **Age**: ~3y2m; **BM**: ~14.2 kg (in the normal range for age and sex: ~50th percentile); **BH**: 96.5 cm (in the normal range for age and sex: ~50th percentile); **Physical and mental examination**. Normal extension of the right limb (when walking), **calves pseudohypertrophy (with ~23[right]/23 cm[left] maximum**

**circumference of both calves), no apparent tonus deficit of the axial/spinal muscles, no anxiety at the physical exam, no agitation, slight language delay (he uses ~30-40 correctly pronounced words at this age, but he can imitate over 100 words and builds true sentences using verbs and some simple phrases)**. The rest of the physical examination exam results were normal: cranial nerves tests in normal limits, normal breath rate and pulmonary sounds, normal heart rate (with no heart murmurs), normal abdomen (without clinically detectable hepato/splenomegaly), **normal stools without any defecation discomfort (after dietary measures),** normal diuresis and urination (with no kidney pain/sensibility), normal genital apparatus.
**Lab exams (serum levels) (24.07.2018): GGT**: **10 U/L** (wnr); **AST: 205 U/L; ALT: 492U/L; CK: 13 900U/L** (~148 x nsl); **CK-MB**: **365 U/L** (~26 x nsl); **MG: 886 ng/ml** (~28 x nsl);
**Comments (including interpretations)**. The GGT serum level wnr (after ~6.5 months of ARS P.O.) indicates that ARS has no liver toxicity up to 6.5 ml/body_kg/day). In the first ~6.5 months of ARS P.O. treatment: the AST serum level decreased by ~56%; the ALT serum level decreased by ~12%; the CK serum level decreased by ~60%; the CK-MB serum level decreased by ~70%; the MG serum level decreased by ~55%;

**December 17th 2018(Boy's age: ~3y7m)**

**Routine check-up and lab results reading**. (after ~3 months [~22.01.2018-17.04.2018] of ARS 60 ml/day [~4 ml/body_kg//day] plus L-carnitine 0.5 g /day, omega-3 fatty acids supplement ~44 mg/day and multivitamins mix; PLUS another ~8 months [18.04.2018-17.12.2018] of ARS 90 ml/day (~ 6-6.5 ml/body_kg/day) plus L-carnitine 0.5/day, omega-3 fatty acids supplement ~44 mg/day and multivitamins mix)
**Recent history**. Two episodes of UTI were reported in the last 4 months (manifested by fever and dysuria [associated with occasional constipation, thus the UTI episodes were probably favored by these occasional episodes of constipation, additionally to DMD, which DMD may also favor urinary stasis and incomplete elimination by ureteral and urinary bladder probably lower contractility rhythm and strength]; diagnosed only clinically and treated by his family doctor [general practitioner] with 7 days of oral antibiotic per each episode, at home, without any prior urine culture, without any blood count, without any prior/subsequent renal/abdominal ultrasound)
**Clinical exam**. **Age**: 3 years and 7 months; **BM**: ~14.2 kg (in the normal range for age and sex: ~30th percentile); **BH**: 98 cm (in the normal range for age and sex: ~40th percentile); **Physical and mental examination: normal extension of the right limb (when walking), calves pseudohypertrophy (with ~23.5[right]/23.5 cm[left] maximum circumference of both calves), no apparent tonus deficit of the axial/spinal muscles, he doesn't become tired more than usually (comparative to the anterior consult when aged 3y2m), but "he climbs stairs slightly more difficult" (and "asks for help after climbing a couple of stairs" [as parents have said]) than in the anterior consult (when aged 3y2m), no anxiety at the physical exam, no agitation, slight language delay (he uses about 50-100 correctly pronounced words at this age, but he can imitate over 100-150 words and builds true sentences using verbs and some simple phrases)**. The rest of the physical examination exam results were normal: cranial nerves tests in normal limits, normal breath rate and pulmonary sounds, normal heart rate (with no heart murmurs), normal abdomen (without clinically detectable hepato/splenomegaly), normal stools without any defecation discomfort at the moment of this examination (after dietary measures; however, occasional constipation episodes still occur, mainly secondary to persistent nutritional education errors committed by the parents towards their boy, parents who tend to spoil the child, given its serious diagnosis of DMD), normal diuresis and micturition (with no kidney pain/sensibility), normal genital apparatus.
**North Star Ambulatory Assessment (NSAA)[1] (17.12.2018): 34 (maximum score);**
**Lab exams (serum levels) (11.12.2018): GGT: 11 U/L** (wnr)**; AST: 262 U/L; ALT: 461U/L; CK: 16 271U/L; CK-MB: 437 U/L; MG: 885 ng/ml;**

[1] For a detailed description of NSAA and its reliability in DMD, see URLs:
(**1**) www.musculardystrophyuk.org/assets/0002/5040/North_Star_Ambulatory_assessment.pdf
(**2**) www.musculardystrophyuk.org/assets/0000/6388/NorthStar.pdf
(**3**) www.sciencedirect.com/science/article/pii/S0960896610002683
(**4**) www.academia.edu/8687388

**Abdominal ultrasound (17.01.2019; by dr. Camelia Kouris): moderate hepatomegaly (with abnormally inhomogeneous and hyperechogenic liver parenchyma structure on ultrasound, but with normal caliber bile ducts)** and otherwise normal (with the reserve that the child had a large volume of gases in the intestines, decreasing the ultrasound precision and reliability);

**Management (including treatment).** Given the increased child's weight and (especially) height (thus his progressively increasing muscular mass) plus the slight increase of AST, CK, CK-MB serum levels (when compared to the values from 24.07.2018) we have recommended parents to increase the ARS dose to 50+50+0 ml/day (for a daily dose of 100 ml/day, which was equivalent to ~7 ml/body_kg/day) starting from 18.12.2018. We have also recommended: a routine urinalysis and urine culture (plus urinalysis and urine culture prior to a potential future UTI episode, before starting any antibiotic); a temporized voidingcystourethrography; a temporized radioisotope renography. Given the child's unsatisfactory weight gain (partially secondary to a capricious food appetite), we have also recommended a hypercaloric dietary supplement solution (Nutridrink® by Nutricia®, 200 ml bottles, 1/3 bottle x 3/day, after each main meal, each 3rd/4th day [1 bottle, 2 times a week]); given the moderate hepatomegaly (with abnormally inhomogeneous and hyperechogenic liver parenchyma structure on ultrasound), we have decided to temporarily stop L-carnitine and omega-3 fatty acids (and multivitamins) for the next ~4.5 months until the next scheduled pediatric control and the next set of labs (in the 1st week of May 2019). We have also recommended that the child have regular physical activity and to be filmed when he runs and/or climbs stairs (and that these movies to be sent to us by email): however, the parents didn't send us any movies until present. We have also temporized the 6-minute walk test (6MWT)[2] and the hand-held dynamometry / myometry **(HHD)**[3] for the future (because not having yet the technical conditions and the equipment needed to perform these tests/measurements)

**May29th 2019(Boy's age: ~4y)**

**Routine check-up and lab results reading. (AFTER ~3 months [**~22.01.2018-17.04.2018] of ARS 60 ml/day [~4 ml/body_kg//day] plus L-carnitine 0.5 g /day, omega-3 fatty acids supplement ~44 mg/day and multivitamins mix; **PLUS another ~8 months** [18.04.2018-17.12.2018] of ARS 90 ml/day (~ 6-6.5 ml/body_kg/day) plus L-carnitine 0.5/day, omega-3 fatty acids supplement ~44 mg/day and multivitamins mix)**PLUS another ~5 months** [18.12.2018-29.05.2019] of ARS 100 ml/day (~ 6-6.5 ml/body_kg/day), but**without** L-carnitine and omega-3 fatty acids supplement (from 18.12.2018 until present)

**Recent history**. NoUTI episodes in the last ~5 months.

**Clinical exam**. Age: ~4 years; **BM**: ~15.5 kg (in the normal range for age and sex: ~75th percentile, above average); **BH**: 101 cm (in the normal range for age and sex: ~50th percentile); **Physical and mental examination: normal extension of the right limb (when walking), stable/non-progressivecalves pseudohypertrophy (with ~23.5[right]/23.5 cm[left] maximum circumference of both calves), no apparent tonus deficit of the axial/spinal muscles, he doesn't become tired more than usually (comparative to the anterior consult when aged 3y7m), no anxiety at the physical exam, no agitation, slight language delay (he uses about 100-200**

[2] For a detailed description of 6MWT and its prediction/prognostic value in DMD, see URLs:

**(1)** www.ncbi.nlm.nih.gov/pubmed/23681930
**(2)** www.ncbi.nlm.nih.gov/pubmed/19941337
**(3)** www.academia.edu/8687388

[3] For a detailed description of HHD its reliability in DMD, see URLs:

**(4)** https://www.researchgate.net/publication/282267205
**(5)** www.researchgate.net/publication/19781656
**(6)** www.medicaljournals.se/jrm/content_files/download.php?doi=10.1080/16501970510044043

**correctly pronounced words at this age and he builds true sentences using verbs and some simple phrases).An upper respiratory tract infection(most probably of viral etiology: nasal and pharyngeal mucosal secretions with secondary wet cough, with minimal tonsillar and pharyngeal inflammation and no fever at the moment of examination nor the days before) was also diagnosed at the moment of consult and treated with symptomatic medication only (including natural cough syrup [with secretolytic and anti-inflammatory effects], sterile sea water for cleaning nasal secretions)**. The rest of the physical examination exam results were normal: cranial nerves tests in normal limits, normal breath rate and pulmonary sounds, normal heart rate (with no heart murmurs), normal abdomen (without clinically detectable hepato/splenomegaly), normal stools without any defecation discomfort at the moment of this examination (after dietary measures), normal diuresis and micturition (with no kidney pain/sensibility), normal genital apparatus.**The next consult was scheduled after 4 months (the last week of September 2019 ora the 1st week of October 2019).**

**North Star Ambulatory Assessment (NSAA) [4] (29.05.2018): 34 (maximum score) vs 34 (17.12.2019; maximum score)**

**Lab exams (serum levels) (21.05.2019): GGT:** 10 U/L (wnr); **AST: 370** (vs 262*) U/L; **ALT**: 683 (vs 461*) U/L; CK: 18 537 (vs 16 271*) U/L; **CK-MB**: 486 (vs 437*) U/L; **MG:** 275 (vs 885*) ng/ml; (*all these serum levels were determined on 11.12.2018 and were mentioned for comparison)

**Abdominal ultrasound (27.06.2019; by dr. Camelia Kouris; after ~1 month after the clinical consult): discretely hyperechogenic liver parenchyma structure on ultrasound (with normal caliber bile ducts)** and otherwise normal;Conclusion: normal abdominal ultrasound for sex and age;

**Management (including treatment).** Given the increased child's weight and (especially) height (thus his progressively increasing muscular mass) plus the slight increase of AST, ALT, CK, CK-MB serum levels (when compared to the values from 11.12.2018) we have recommended parents to increase the ARS dose to 55+55+0 ml/day (for a daily dose of 110 ml/day, which was equivalent to ~7.1 ml/body_kg/day) starting from 30.05.2019.. We have also recommended that the child have regular physical activity and to be filmed when he runs and/or climbs stairs (and that these movies to be sent to us by email): the parents did send us some movies in May 2019 with their boy climbing stairs, walking and running; short selected sequences from these movies were uploaded on author's personal site (www.dragoii.com) and are available at the following URLs:

**i.** www.dragoii.com/ARSinDMD_HighStairStepsClimb_6sec.mp4 (the boy climbing stairs with high steps – 6 seconds movie selection)

**ii.** www.dragoii.com/ARSinDMD_LowStairStepsClimb_9sec.mp4 (the boy climbing stairs with low steps – 9 seconds movie selection)

**iii.** www.dragoii.com/ARSinDMD_HorizontalWalk_4sec.mp4 (the boy walking on a horizontal plane - 4 seconds movie selection)

**iv.** www.dragoii.com/ARSinDMD_HorizontalRunning_4sec.mp4 (the boy running on a horizontal plane - 4 seconds movie selection)

[4] For a detailed description of NSAA and its reliability in DMD, see URLs:

(**1**) www.musculardystrophyuk.org/assets/0002/5040/North_Star_Ambulatory_assessment.pdf

(**2**) www.musculardystrophyuk.org/assets/0000/6388/NorthStar.pdf

(**3**) www.sciencedirect.com/science/article/pii/S0960896610002683

(**4**) www.academia.edu/8687388

We have once again temporized the 6-minute walk test **(6MWT)**[5] and the hand-held dynamometry / myometry **(HHD)**[6] for the future (becausenot having the technical conditions and the equipment needed to perform these tests/measurements yet)

[5] For a detailed description of 6MWT and its prediction/prognostic value in DMD, see URLs:

**(7)** www.ncbi.nlm.nih.gov/pubmed/23681930
**(8)** www.ncbi.nlm.nih.gov/pubmed/19941337
**(9)** www.academia.edu/8687388

[6] For a detailed description of HHD its reliability in DMD, see URLs:

**(10)** https://www.researchgate.net/publication/282267205
**(11)** www.researchgate.net/publication/19781656
**(12)** www.medicaljournals.se/jrm/content_files/download.php?doi=10.1080/16501970510044043