

PW 1:
**DMD – Clinical and
genetic observations**

PW1-001	<p><u>PHENOTYPIC HETEROGENEITY OF DUCHENNE MUSCULAR DYSTROPHY (DMD) ASSESSED BY LONG TERM FOLLOW-UP AND DEFINITION OF FACTORS PREDICTING SUBCLASSIFICATION</u></p> <p>DESGUERRE I¹, CHRISTOV C², MAYER M³, ZELLER R³, BECANE H³, LETURCQ F⁴, CHELLY J⁴, GHERARDI R²</p> <p>(1) Centre de Référence Garches-Necker-Mondor-Hendaye, Paris (Necker), FRANCE. (2) INSERM U841-E10 (Institut Mondor de Recherche Biomédicale); Université Paris 12, Créteil, FRANCE. (3) Centre de Référence Pitié-Salpêtrière-Trousseau, Paris (Trousseau), FRANCE. (4) Service de Biochimie génétique, Hôpital Cochin, Paris, FRANCE.</p>
<p>To contact the author:: isabelle.desguerre@nck.aphp.fr.</p>	<p>Innovative therapies are presently being developed for DMD. Evaluating their effect will require precise knowledge of both the natural history and factors influencing the course of a disease which can be no longer considered as homogeneous in terms of severity and neurological prognosis. We investigated 75 steroid-free patients without muscle dystrophin at immunohistochemistry and immunoblotting, first detected at the St Vincent de Paul hospital and followed by the same medical team every 6 months for a mean follow-up >10yrs. We used multivariate analyses, hierarchical clustering, and logistic regression, with 3 aims: (i) detecting correlations between motor, cognitive, cardiac and respiratory variables; (ii) delineating homogenous subgroups with similar evolution; and (iii) identifying early clinical predictive factors for classification in each subgroup. Cognitive and motor variables provided a factor model with a best 4-cluster solution: group A (congenital DMD, 20%) very poor intellectual and motor outcomes; group B (classical DMD, 28%) intermediate intellectual and poor motor outcomes; group C (late onset DMD, 22%) normal intelligence and delayed motor impairment; and D (pure motor DMD, 30%) normal intelligence and poor motor outcome. Group A patients also had more severe respiratory and cardiac involvement. Mutations before exon 30 increased in proportion from group A to D, but, except for the well established link between mental retardation and the involvement of the N terminal part of the gene, particularly the DP71 transcript, no clinical-genetic correlation could be identified between motor function and type and location of mutations, suggesting some influence of, as yet unknown, epigenetic factors on motor severity. Early predictive outcome indicators were "age at initial symptoms <2yrs" combined with "psychomotor delay as initial symptom" for congenital DMD, and "lower limb manual muscle testing (MMT) score >6 at 8yrs" for late onset DMD. Then, IQ categorically segregated pure motor from classical DMD patients.</p>

PW1-002	<p><u>PITFALLS IN THE MOLECULAR DIAGNOSIS STRATEGIES OF DYSTROPHINOPATHIES</u></p> <p>THOREL D¹, MÉCHIN D¹, BÉROUD C², RIVIER F¹, COUBES C¹, JOUK PS³, LETURCQ F⁴, COSSÉE M⁵, TUFFERY-GIRAUD S⁶, CLAUSTRES M², KHAU VAN KIEN P¹</p> <p>(1) CHU, Montpellier, FRANCE. (2) CHU-Université-INSERM U827, Montpellier, FRANCE. (3) CHU, Grenoble, FRANCE. (4) APHP, Paris, FRANCE. (5) CHU, Strasbourg, FRANCE. (6) Université-INSERM U827, Montpellier, FRANCE.</p>
To contact the author:: delphine.thorel@montp.inserm.fr.	<p>In the families with a reported case of dystrophinopathy, pedigree analysis with measurement of blood creatine phosphokinase (CK) are commonly used for genetic risk assessment of relatives. Several affected cases in the same family across generations or the presence of female relatives with elevated CK levels are usually indicative of a familial case. In some instances this approach can lead to misinterpretations and we present here three situations where genetic testing has been crucial to clarify genetic status for family members.</p> <p>Case 1: deceased sporadic case of Duchenne Muscular Dystrophy (DMD) without samples available.</p> <p>In this family, the maternal aunt of the proband was found to have high CK level (three independent dosages, in the absence of known confusing factors). Thus, it was predictive of a familial transmission of a dystrophin gene mutation making the proband's mother an obligatory carrier. Haplotype analysis showed that both daughters had inherited the same X maternal chromosome. A deleterious mutation was identified in the proband's mother DNA. Unexpectedly this mutation was not detected in the DNA of the aunt. The cause of the elevated CK in this woman reminds to be elucidated.</p> <p>Case 2 : Occurrence of a merosine negative congenital muscular dystrophy (CMD1A) in a family with two first-degree cousins affected by DMD.</p> <p>Because of the familial history, DMD was the first suggested diagnosis. Genetic testing has allowed to rule out this hypothesis and to identify mutations in the <i>LAMA2</i> gene.</p> <p>Case 3 : Independent DMD mutational events in a same pedigree.</p> <p>In this apparent familial case of DMD, two second-degree cousins were found to carry distinct mutations of the dystrophin gene.</p> <p>Our data emphasize the usefulness of exhaustive familial analyses and the need to genotype all affected individuals and potential carriers in families with a dystrophinopathy.</p>

PW1-003	<p><u>A TWO AMINO ACID MUTATION ENCOUNTERED IN A DMD PATIENT DRAMATICALLY DECREASES STABILITY OF THE R23 SPECTRIN-LIKE REPEAT OF DYSTROPHIN</u> LEGARDINIER S¹, LEGRAND B¹, RAGUÉNÈS-NICOL C¹, BONDON A¹, LE RUMEUR E¹, HUBERT JF¹ (1) Université de Rennes 1, UMR6026, Rennes, FRANCE.</p>
<p>To contact the author:: elisabeth.lerumeur@univ- rennes1.fr.</p>	<p>While dystrophin's native function is still largely unknown, it is well established that lack of functional dystrophin in muscle cell causes Duchenne muscular dystrophy (DMD). The native dystrophin is organised in four domains: a N-terminal actin binding domain, a potentially flexible rod domain of 24 spectrin-like repeats, a cystein rich domain and a C terminal beta-dystroglycan binding domain. In this study, we compared biophysical properties of the wild-type repeat 23 (R23) of human dystrophin rod domain and a double mutant encountered in a patient suffering from DMD, R23 E2910V-N2912D in helix C. Thermal denaturation analysis by circular dichroism showed a single transition at 67°C for the wild type repeat while a two transition behaviour with temperature of mid-denaturation of 44.5°C and 63°C was observed for the mutant repeat. This indicated that at 37 degrees, wild type repeat remains folded while the mutant repeat is one third of intensity unfolded. Urea unfolding analysed by tryptophan fluorescence showed a similar behaviour with two transitions for the mutant compared to a single transition of the wt. Refolding kinetics of urea denaturated proteins analysed by stopped flow spectrofluorimetry showed that the mutation induces a dramatic slowing down of refolding of the repeat with exponential rate constants of 50 s⁻¹ and 18 s⁻¹ for wt and mutated repeat, respectively. Molecular modelling indicated that the mutations located in helix C of the repeat, modified helix-helix interaction within the coiled coil structure. Taken together, these results show that the double mutation causing DMD changes surface properties, unfolding and refolding behaviours of R23. These data showing for the first time that a mutation in dystrophin rod domain induces unstability of the protein represent a contribution to the functional dissection of the dystrophin protein and emphasises the role of the rod domain and its putative behaviour in muscle cell.</p>

PW1-004	<p><u>FEMALE WITH DUCHENNE MUSCULAR DYSTROPHY POSSIBLY DUE TO UNIPARENTAL DISOMY – A CASE REPORT</u></p> <p>SAKTHIVEL M¹, LAKSHMI R¹, THILOTHAMMAL N², VISWANATHAN V¹ (1) Sundaram Medical Foundation, Chennai, INDIA. (2) The Institute of Child Health and Hospital for Children, Chennai, INDIA.</p>
To contact the author:: sakthivelmsm@gmail.com.	<p>A 10-year-old female child presented with 2-year history of progressive difficulty in walking and getting up from supine posture. Clinical evaluation, serum creatine phosphokinase levels (2222 IU/L) and muscle biopsy was consistent with muscular dystrophy and LGMD was suspected. DMD gene deletion analysis by multiplex PCR was performed at our facility to rule out DMD. Surprisingly, multiplex PCR showed a homozygous deletion of exon 45 of the DMD gene. The gene deletion was confirmed by Multiplex Ligation-Dependent Probe Amplification (MLPA) and dystrophin gene microsatellite marker STR45. This rules out the possibility of skewed X-inactivation to be the cause of her clinical symptoms. Karyotype analysis was normal, ruling out Turner's syndrome and translocations involving the X-Chromosome. Dystrophin gene microsatellite analysis using STR44 and STR 45 revealed deletion of STR45 and homozygosity for STR44. This homozygosity for STR 44 shows the possibility of the homozygous deletion to be a consequence of Uniparental isodisomy. However, blood samples of the parents of the affected girl are not available at present with us to confirm this phenomenon. Marker studies are in progress to look for disomy of the entire X-chromosome.</p> <p>Duchenne muscular dystrophy (DMD) is X-linked recessive disorder usually affecting males. DMD in females has been described earlier, commonly caused due to skewed X chromosome inactivation or translocations involving the X chromosome at the DMD locus. Females with Turner syndrome (45,X) are affected with DMD if they carry a dystrophin mutation on the remaining X chromosome. Usually girls presenting with a DMD-like dystrophy are diagnosed as having limb girdle dystrophy rather than DMD. Our study shows that these girls need to be evaluated for DMD gene mutations to confirm this diagnosis. There is only one published report of uniparental disomy causing DMD in 1997. Ours would be a second such report, if confirmed for UPD.</p>

PW1-005	<p><u>IMPLICATIONS AND APPLICATIONS OF BAYESIANS' ANALYSIS IN GENETIC RISK ASSESSMENT OF CARRIERS OF DUCHENNE MUSCULAR DYSTROPHY (DMD) AND BECKER MUSCULAR DYSTROPHY (BMD)</u></p> <p>MAXIM D¹, OTELEA D¹</p> <p>(1) 'Matei Bals' Institute for Infectious Diseases, Bucharest, ROMANIA.</p>
<p>To contact the author:: dana_maxim@yahoo.com.</p>	<p>DMD and BMD are transmitted as an X-linked recessive traits. Risks include a family history of DMD and BMD. Bayesians' analysis may be used antenatally when DNA testing is uninformative or inconclusive .We report the family cases where the affected DMD patients were available for study and Bayesians' analysis was used for genetic risk assesment for female relatives of affected boys. We used the μ values (female germ-line mutation rate) for our prior probability for females, when possibility of new mutation is important. Average carrier risk in population is 4μ, where $f=0$ (f = reproductive fitness). Value of $f = 0$ for DMD, where affected males never survive to reproduce and $f = 0.7$ for BMD, where affected males reproduce as well as unaffected sibs." μ " values permits to calculate the population frequency of female carriers-N. Where $f=0$ then $N=4$ and where $f = 0.7$ then $N=18$. In the first pedigree, the boy III-1 is only one affected in this family. Mother (II-3) has two healthy brothers (II-1 and II-2). For one isolated case in the family we use the population carrier risk as prior carrier risk in a Bayes' analysis. The fact that II-3 has had an affected son is a conditional information. Thus, posterior probability for the first hypothesis, that II-3 is carrier , is $2/3$, and $1/3$ for the hypothesis that II-3 is non-carrier. In the second pedigree, in which two brothers are affected with BMD, the fact that the consultand has had two affected sons is a subsequent information. The conditional probability in this case is $1/4$, if we assume that I-1 is carrier and μ^2 if she is non-carrier. Thus, the joint probability is $\mu^2=0$ for the hypothesis that I-1 is non-carrier and μ for the the hypothesis that I-1 is μ carrier. Thus, the final probability is $1/2$ risk of being carrier and 0 risk of being non-carrier. Bayesian theory proposed one method to establish general probability of having or lacking a disease-causing mutation, taking in calculus all the initial possibility, and then, is indicated which probability is the only relevant to the consultand's risk.</p>

PW1-006	<p><u>CARRIER ANALYSIS IN DUCHENNE MUSCULAR DYSTROPHY BY MULTIPLEX LIGATION-DEPENDANT PROBE AMPLIFICATION.</u></p> <p>SAKTHIVEL M¹, LAKSHMI R², VISWANATHAN V³, ARTHI C⁴ (1) Sundaram Medical foundation, Chennai, INDIA. (2) Sundaram Medical foundation, Chennai, INDIA. (3) Sundaram Medical foundation, Chennai, INDIA. (4) Sundaram Medical foundation, Chennai, INDIA.</p>
To contact the author:: lakshmi@mdaindia.org.	<p>Duchenne and Becker muscular dystrophies are X-linked allelic disorders caused due to mutations in the <i>DMD</i> gene. Mutation detection is laborious due to the presence of 79 exons in the <i>DMD</i> gene and carrier analysis complicated due to the heterozygous nature of the X chromosome.</p> <p>The absence of effective treatments has led to develop new approaches for carrier detection and prenatal diagnosis, which are the only ways available to manage and prevent the disease. Several techniques have been tried for carrier analysis using quantitative multiplex PCR (qmPCR), Southern blot, in families where the mutation is identified. Linkage analysis is used in the remainder of the cases without identifiable mutations. Duplication, as well as deletion in carriers is more difficult to quantify. Multiplex Ligation-dependent Probe Amplification (MLPA), a recent technique to detect gene dosage abnormalities, screen for deletions and duplications over the entire length of the gene and has shown to pick up more mutations and useful in carrier analysis.</p> <p>We have studied the carrier status in 13 cases where the patient's mutations were known .Of these 13, 10 were deletions, 2 duplications and 1 point mutation. We used both qmPCR and MLPA to assess the copy number changes and direct sequencing for the case with point mutation. Of the 13 carrier samples, 5 were carrier-negative and 8 were carrier-positive. Both qmPCR and MLPA were useful in picking up copy number changes. However, MLPA was more useful for picking mutations in exons lying outside the hotspot regions, like the exon 2 duplication. In our study we have found five novel deletions and have shown the usefulness of MLPA in picking up rare deletions, duplications and carrier status. This is the first report from India using the technique of MLPA in DMD.</p>

PW1-007	<p>DUCHENNE AND AUTISM: HIGHER THAN EXPECTED ASSOCIATION? BERARDINELLI A¹, ORCESI S¹, ROSSI M¹, MOTTA C¹, GORNI K¹, BALOTTIN U¹ (1) Department of Child Neuropsychiatry Department , IRCCS “C. Mondino” Foundation, University of Pavia, Pavia, ITALY.</p>
<p>To contact the author:: angela.berardinelli@mondino.it.</p>	<p>Duchenne muscular dystrophy (DMD) is an X-linked progressive neuromuscular disorder due to lack of Dystrophin protein in muscle. Dystrophin is mainly concentrated in skeletal and cardiac muscle and less in smooth muscle, its deficiency causing severe progressive motor, respiratory and cardiac impairment. Dystrophin is also in the brain. Boys with Duchenne muscular dystrophy often have also central nervous system involvement such as mental retardation and learning disabilities.</p> <p>Autism is a brain development disorder impairing social interaction and communication and causing restricted and repetitive behavioural patterns, with all symptoms starting before three years of age. This set of signs distinguishes autism from milder autism spectrum disorders (ASDs), including Asperger syndrome. Genetic susceptibility to this condition has been documented.</p> <p>In the past only a single case report has been found about autism and DMD association</p> <p>In the last few years the hypothesis of a significative association between DMD and Autism has been proposed.</p> <p>Based on “ad hoc” chosen items of ADI-R and ADOS scales, both currently being considered the gold standard for autism diagnosis, we retrospectively evaluated the possible relational and communicational impairment and related risk factors in 43 DMD children very well known to our Centre . Only one child (2.3%) was found to be affected by autism , even though we have about 20% children with low IQ and some with depressive traits, speech and emotional problems</p>

PW1-008	<p><u>EFFECT OF AGE AT INITIATION OF CORTICOSTEROIDS ON AGE AT LOSS OF AMBULATION IN PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY (DMD)</u> PANDYA S¹, FOX D², CIAFALONI E¹, DRUSCHEL C², MOXLEY R¹ (1) University of Rochester, Rochester, USA. (2) New York State Department of Health, Troy, USA.</p>
To contact the author:: shree_pandya@urmc.rochester.edu.	<p>Objective: To determine the effect of age at initiation of corticosteroids on age at loss of ambulation in patients with Duchenne muscular dystrophy (DMD) Background: The hypothesis among clinicians is that earlier the initiation of corticosteroids, the greater the benefit on prolongation of ambulation. No data is available to provide support for this hypothesis. Methods: We retrospectively analyzed data on all boys followed at our site since 1991 to look at the effect of age at initiation of corticosteroids on the age at loss of ambulation. We categorized the boys as follows: 1) Never treated with corticosteroids and 2) treated with corticosteroids. 2) Treated group was subdivided into 3 categories based on age at initiation of steroids as follows: Group a) age 4 to <7 years; b) age 7 to <9 years: c) 9 to <13 years. Results: Complete follow up data was available on 68 boys. 21 boys had never been treated with corticosteroid and ceased ambulation at an average age of 8 years. Of the 47 treated boys: Group a) N =24 initiated treatment at age 6.1(sd 0.7 yrs) and ceased ambulation at age 13.5 (sd 3.3 yrs) Group b) N=14 initiated treatment at age 7.8 (sd 0.6 yrs) and ceased ambulation at age 13.5 (sd 2.5. yrs) Group c) N=9 initiated treatment at age 10.3 (sd 0.6 yrs) and ceased ambulation at age 12.8 (sd 2.5 yrs) The results between the 3 groups categorized by age at initiation of treatment were not statistically significant. This may be due to the small sample sizes. Conclusions: Retrospective data from our site demonstrates a trend that earlier the age (<9yrs) at initiation of corticosteroid the greater the prolongation of ambulation.</p>

PW1-009	<p><u>COMBINED NON-INVASIVE VENTILATION AND MECHANICAL INSUFFLATION-EXSUFFLATION ASSISTANCE IN PEDIATRIC NEUROMUSCULAR DISORDERS WITH HYPERCAPNIC RESPIRATORY INSUFFICIENCY</u></p> <p>PEDEMONTE M¹, OTTONELLO G¹, SCAPOLAN S¹, DOGLIO L¹, BRUNO C¹, MINETTI C¹</p> <p>(1) Istituto Giannina Gaslini, Genova, ITALY.</p>
To contact the author:: marinapedemonte@osp edale-gaslini.ge.it.	<p>Neuromuscular disorders (NMD) are the most important cause of hypercapnic respiratory insufficiency in childhood and respiratory failure is the major cause of morbidity and mortality in NMD. The use of non-invasive ventilation (NIV) in NMD patients can improve the prognosis by correction of hypoventilation and reduction of respiratory work. However, it does not prevent acute respiratory failure during recurrent episodes of pneumonia or atelectasis due to inability to clear airways from secretions.</p> <p>Combined non-invasive ventilation with mechanical insufflation-exsufflation (MI-E), by means of mechanical cough-assistance, can ameliorate these conditions in neuromuscular patients.</p> <p>We have performed a retrospective evaluation of the safety, tolerance and effectiveness of this combined treatment in 27 patients affected by NMD (Duchenne and Becker Muscular Dystrophy=5, Limb Girdle Muscular Dystrophy=1, Spinal Muscular Atrophy=8, Congenital Myopathy=8, Ullrich's Syndrome=4, Congenital Myotonic Dystrophy=1), aging 2 months to 18 years. The follow-up of these patients has been developed through the guideline of the European Neuromuscular Centre and of the American Thoracic Society. All patients used nocturnal NIV and during broncopulmonary acute episodes were treated with MI-E cough-assistance, with a complete resolution. In particular, fourteen patients, who presented severe exacerbations of respiratory conditions with development of pulmonary acute infections and atelectasia, showed a significant improvement after MI-E treatment. Seven patients needed invasive ventilation, only one received tracheotomy, while six were extubated by Bach's protocol.</p> <p>In conclusion, our data indicate the good tolerance and the effectiveness of the combined management of NIV and MI-E in pediatric neuromuscular patients with respiratory insufficiency.</p>

PW1-010	<p>DIAGNOSTIC UTILITY OF SKIN BIOPSY IN DYSTROPHINOPATHIES SHARMA M¹, TANVEER N², SARKAR C³, GULATI G⁴, KALRA K⁵, SINGH S⁶, BHATIA R⁷ (1) AIIMS, DEPARTMENT OF PATHOLOGY, New DELHI, INDIA. (2) AIIMS, DEPARTMENT OF PATHOLOGY, New DELHI, INDIA. (3) AIIMS, DEPARTMENT OF PATHOLOGY, NEW DELHI, INDIA. (4) AIIMS, DEPARTMENT OF PEDIATRICS, NEW DELHI, INDIA. (5) AIIMS, DEPARTMENT OF PEDIATRICS, NEW DELHI, INDIA. (6) AIIMS, DEPARTMENT OF NEUROLOGY, NEW DELHI, INDIA. (7) AIIMS, DEPARTMENT OF NEUROLOGY, NEW DELHI, INDIA.</p>
To contact the author:: sharmamehar@yahoo.co.in.	<p>Objectives: To elucidate the role of skin biopsy in the diagnosis of dystrophinopathies. Study design: Paired skin and muscle biopsies from 39 cases of Duchenne muscular dystrophy, 4 cases of Becker muscular dystrophy and 37 controls were studied. Immunostaining for dystrophin (Dys1, 2, 3) and utrophin was done on frozen sections of the cases and controls and their staining pattern in skin biopsies was compared with corresponding muscle biopsies.</p> <p>Results: Immunostaining for Dys1, 2 and 3 was negative in the skin biopsies of all patients (39/39, 100%) who were diagnosed as DMD and was weakly expressed in BMD patients (4/4, 100%). Dys1, 2, 3 were strongly expressed in the arrector pili muscles of 35 controls patients (94.6%) but was weakly expressed in 2 controls. Utrophin was expressed on the arrector pili muscles of all test patients (39/39, 100%) but was also expressed in controls (30/37, 81.1%).</p> <p>Conclusion: Our study suggests that skin biopsy is very useful for the diagnosis of Duchenne/ Becker's muscular dystrophy. It can be a useful adjunct/replacement for muscle biopsy in the diagnosis of these cases especially in end stage muscle diseases where muscle is replaced by fat infiltration, and as a screening test for the diagnosis before genetic studies. In future it can be used as a routine test in the follow up of these cases after gene therapy, as it is easy to perform and can be repeated frequently. Our findings also suggest that punch biopsy is better than open skin biopsy.</p>

PW1-011	<p><u>TEST-RETEST RELIABILITY OF DUAL ENERGY XRAY ABSORPTIOMETRY (DEXA) MEASUREMENTS IN PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY (DMD)</u> PANDYA S¹, DILEK N¹, MARTENS W¹, MOXLEY R¹ (1) University of Rochester, Rochester, USA.</p>
<p>To contact the author:: shree_pandaya@urmc.rochester.edu.</p>	<p>Objective: To establish the test- retest reliability of DEXA measurements in patients with DMD. Background: DEXA measurements are frequently used as an outcome measure in therapeutic trials of DMD to document changes in lean body mass. There is no data available in the literature documenting the reliability of these measurements. Methods: We performed repeated DEXA measurements on a single day on two separate visits on 12 boys with DMD participating in clinical trials at our site. The measurements were made with instrumentation and software from the Lunar corporation, Madison WI. Results: Demographic data: Age 6.6 (sd 0.9), Height 114cm (sd 7.4) Weight 20.4 kg (sd 3.0) All patients were ambulatory at the time of testing. The Intra class correlations (ICC) for the measurements of DEXA total, DEXA Bone Mineral Content (BMC), DEXA Fat, and DEXA Lean Body Mass (LBM) were: Visit 1: DEXA Total 0.99, DEXA BMC 0.97, DEXA Fat 0.99 and DEXA LBM 0.97 Visit 2: DEXA Total 0.97, DEXA BMC 0.98, DEXA Fat 0.99 and DEXA LBM 0.91. Conclusions: All the ICC's were greater than .90 which denotes excellent reliability. This also allows for the calculations of the minimal clinically important difference for natural history studies and therapeutic trials.</p>

PW1-012	<p><u>EFFECT OF SPINAL SURGERY ON THE LUNG FUNCTION IN DUCHENNE MUSCULAR DYSTROPHY</u> RAUSCENT H¹, BERARD C³, HUMBERTCLAUDE V², GAUTHERON V⁴, RICHELME C¹ (1) Maladies Neuromusculaires Pédiatriques, centre Hospitalier Archet 2, 06202 Nice Cedex 3, Nice, FRANCE. (2) Neuropédiatrie, Institut Saint Pierre, 34250 Palavas les Flots, Palavas les Flots, FRANCE. (3) Rééducation Pédiatrique L'ESCALE Centre Hospitalier Lyon-Sud, 69495 PIERRE BENITE Cedex, Lyon, FRANCE. (4) Rééducation Pédiatrique Centre Hospitalier Nord, 42055 Saint-Etienne Cedex 2, Saint Etienne, FRANCE.</p>
To contact the author:: rauscent.h@chu-nice.fr.	<p>Concerning multidisciplinary care of Duchenne Muscular Dystrophy (DMD), the prevention of scoliosis remains a priority. Spinal surgery is considered as the treatment of choice and early instrumentation and fusion are widely proposed. The objectives of surgery are to improve the comfort and quality of life of the patient and to prevent the degradation of their respiratory function. Nevertheless, the effect of spinal surgery on respiratory function is still controversial. We intended then to study, retrospectively, the loss of forced vital capacity in 64 DMD patients born between 1970 and 1990, and we followed up on average 9 years after they lost deambulation. The average time before the onset of arthrodesis was 4 years for the surgery group comprising 52 patients. Our study (which covered 4 french departments) did not show any improvement in the lung function arising from surgery. The annual forced vital capacity decrease was the same in the 52 patients operated before (5,12%/year) and after the spinal fusion (5,89%/year) on as for the 12 patients not operated on. Consequently, our study showed that no improvement in respiratory function could be expected from surgery. There is therefore no argument in favour of advising patients to accept surgery. Our results are consistent with other recent studies, which consider the question of whether systematic and early spinal surgery should still be widely proposed. Furthermore, recent studies report that 25% of patients with DMD would suffer from a moderate and non progressive scoliosis, that is likely to be improved by the early introduction of corticosteroids.</p>

PW1-013	<p><u>DUCHENNE MUSCLE ACTIVITY EVALUATION AND MUSCLE FUNCTION PRESERVATION: IS A PROPHYLACTIC STRATEGY FEASIBLE?</u> SBLENDORIO V¹, PALMIERI B¹, FERRARI A², PIETROBELLI A³ (1) University of Modena, Modena, ITALY. (2) S. Maria Nuova Hospital, Reggio Emilia, ITALY. (3) Verona University Medical School, Verona, ITALY.</p>
To contact the author:: valeriasbl@hotmail.com.	<p>Abstract. Duchenne muscular dystrophy yields pervasive and progressive muscle mass loss. In the current measures relating to the monitoring of disease progression is relevant: 1) the type of scale used; 2) the clinical significance of the attribute being measured and 3) the mathematical properties of the data provided. The high prevalence of obesity at an early stage of this pathology could result not only from reduced physical activity, but may also involve low resting energy expenditure (REE), abnormal nutrient utilization, or overfeeding. This muscle weakness may be attenuated by regular, low-intensity exercise. However, there is a critical lack of data to support appropriate exercise prescription. Because inappropriate activity may exacerbate the dystrophic process, a systematic analysis of muscle function to determine potential exercise load thresholds to avoid injury in dystrophic mice and dogs, and then in human is recommended.</p>

PW1-014

**PRESERVATION OF NEUROMUSCULAR SPINDLES IN A SEVERELY AFFECTED
ADULT DUCHENNE MUSCULAR DYSTROPHY PATIENT.**

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Duchenne muscular dystrophy (DMD) is characterized by a progressive destruction and ultimate disappearance of the skeletal muscle parenchyma, which is replaced by adipose and fibrous connective tissue. Previous reports about the involvement of neuromuscular spindles in this pathological process were controversial, but were done mainly in young patients. Here, we report the case of a severely affected DMD patient, 27 years old, in which neuromuscular spindles were preserved in spite of the completely or almost completely disappearance of the extrafusal myofibers. Well-preserved neuromuscular spindles were observed in biopsies of the biceps brachii and a forearm muscle. The well-preserved intrafusal myofibers showed absence of dystrophin but also utrophin, evidencing that their preservation was not due to an over-expression of this last protein. To our knowledge, this is the first report of neuromuscular spindle preservation in a so old and severely affected DMD patient. It would be interesting to elucidate the mechanism by which intrafusal myofibers can be preserved in DMD, in spite of the completely destruction of the extrafusal myofibers. On the other hand, the fact that neuromuscular spindles can be preserved in severely affected DMD patients appears as important for the therapeutic possibility of restoring the lost myofibers by cell-based tissue-engineering strategies. We want to point-up that therapeutic strategies aiming to restore extrafusal myofibers in degenerating muscles may provide little benefit if the mechanisms of proprioception are not preserved.

PW1-015	<p>EVALUATION OF PATHOLOGICAL PATTERN IN EARLY STAGE OF DUCHENNE MUSCULAR DYSTROPHY (DMD) BY GAIT ANALYSIS DOGLIO L¹, PERNIGOTTI I¹, TACCHINO C¹, PEDEMONTE M¹, SCAPOLAN S¹, BRUNO C¹, MINETTI C¹ (1) Istituto Giannina Gaslini, Genova, ITALY.</p>
To contact the author:: lucadoglio@gmail.com.	<p>DMD patients walk with a non-physiological pattern showing a initially weakness of antigravitary muscles, followed by loss of walking capability. Initially, DMD patients do not show clinical signs of pathological pattern, that become manifest with the grown and the progression of illness. Aim of our study was to analyze the pathological pattern in early stage of DMD patients by Gait Analysis, a technique which analyses the human walking, allowing the comparison of kinematics and kinetics data in the same and among different patients.</p> <p>We have performed Gait Analysis in 10 DMD patients (aged from 5 to 7 years) and in 10 healthy matched control age group. All patients have been evaluated according to the following items: range of motion analysis, Gowers test, capability of run for 10 meters, walking on tip-toe and heel, and functional HAMA test. All patients were not taking any drug.</p> <p>All patients were able to perform all the items requested, but by Gait Analysis we showed that in the DMD group early pathological signs were present. In all patients, pelvis showed the most important modification in term of improvement of movements on the coronal and transversal plane, probably due to a compensation of gluteus weakness. In 4 patients our data showed an increase of drop-foot. Hip and knee did not show any significant alteration in early stage.</p> <p>Our study indicates that Gait Analysis is a useful tool in detecting early modification of the walking pattern of DMD patients, and may help us to choose further clinical and rehabilitation programs.</p>

PW1-016	<p><u>COGNITIVE EVOKED POTENTIALS AND NEUROPSYCHOLOGY TEST IN DUCHENNE MUSCULAR DYSTROPHY PATIENTS</u> ESQUITIN N¹, ESCOBAR RE¹, MIRANDA A¹, ESCOBAR MG¹, CORAL R², RODRIGUEZ M², VELASQUEZ AC² (1) Instituto Nacional de Rehabilitacion, México, MEXICO. (2) Centro Medico Nacional Siglo XXI, México, MEXICO.</p>
<p>To contact the author:: rescobarmx@yahoo.com .mx.</p>	<p>Duchenne muscular dystrophy is a neuromuscular disease genetically inherited X-linked condition with progressive physical disability. The exact functional role of the dystrophin in the brain is unknown, but their absence is associated with a downward shift in intelligence quotients (IQ). P300 makes an objective estimation of the cognition disorders related with central nervous system <u>Objective:</u> To examine the relation between cognitive evoked potentials (P300 potentials) and neuropsychological dysfunction in patients with Duchenne muscular dystrophy (DMD). <u>Method:</u> this was a prospective, comparative and descriptive study. P300 potentials and neuropsychological test (Standford- Binet) results were obtained from 31 DMD patients and 30 healthy control boys. Mean age was 9.44 (2.25). Full Intelligence Quotients (IQ) were estimated for patients and control group. Statistic Analysis were made with Man Whitney Test and Chi square to compare IQ and P300, significance (p>0.05). <u>Results:</u> The mean IQ values were 93.21 (10.39) DMD patient group and 107.54 (9.24) in the control group (p=0.000) both are in the normal IQ. Mean P300 values in Pz were 314.75 in the DMD group and 311.50 in the control group (p=0.730). There was no significant correlation between parameters in each group. The most affected area in the was numeric reasoning (p=0.001), conceptual thinking (p=0.002), memory (p=0.003), reasoning (p=0.005), social intelligence (p=0.033) and visuomotor area (p=0.051). <u>Conclusion:</u> there is no correlation statistically significant between the P300 component and the IQ. The values were normal in both groups. The majority of the patients in the Duchenne group had normal intelligence. Systematic alterations in neuropsychological test results were found to be statistically significant.</p>

PW1-017	<p><u>DUCHENNE/BECKER MUSCULAR DYSTROPHY: AN ASYMPTOMATIC CASE REPORT</u> FERREIRO V¹, GILIBERTO F², MUÑIZ GARCIA N², FRANCIPANE L¹, MARCESE D³, ROQUE M³, FRECHTEL G¹, SZIJAN I² (1) División de Genética - Hospital de Clínicas- Universidad de Buenos Aires, Buenos Aires, ARGENTINA. (2) Cátedra de Genética y Biología Molecular - Facultad de Farmacia y Bioquímica - Universidad de Buenos Aires, Buenos Aires, ARGENTINA. (3) Cátedra de Biología Celular y Molecular - Facultad de Ciencias Médicas - Universidad de Cuyo, Mendoza, ARGENTINA.</p>
To contact the author:: lifrancipane@hotmail.com.	<p>The severe Duchenne muscular dystrophy (DMD) and the milder Becker muscular dystrophy (BMD) are characterized by progressive muscular degeneration. Both are caused by mutations in the dystrophin gene (Xp21.2). Two thirds of patients show intragenic deletions of one to several exons, the remaining cases arise from genomic duplication or microrearrangements. The reading frame rule explains the two different phenotypes resulting from mutations in the same gene. Clinical progression of the disease can be predicted by whether the deletion maintains (in frame-BMD) or disrupts (out of frame-DMD) the translational reading frame of the dystrophin gene. This hypothesis explains the phenotypic differences observed in approximately 92% of the DMD/BMD cases. We report a Becker muscular dystrophy family with one 5-year-old affected patient and his 69-year-old asymptomatic grandfather. Dystrophin gene multiplex PCR and MLPA analyses showed that both males carry an in-frame deletion of exons 45-55. Molecular analysis of different tissues and elevated serum creatin kinase (CK) levels, ruled out a germline mosaicism in the grandfather. Segregation analysis revealed two additional asymptomatic boys with the same deletion and 4 deletion-carrier females. These results show that the deletion of exons 45-55 found in the family is associated with a mild or asymptomatic phenotype. Our findings support previous prediction of being exons 45-55 the optimal multiexon skipping target in antisense gene therapy to transform the Duchenne muscular dystrophy phenotype into a Becker or even asymptomatic phenotype. The screening of 170 DMD-deletions, already analysed by us, resulted in the finding of 45% of them being included in the region of exons 45-55. Therefore, the patients with these deletions would be benefited with the antisense therapy to acquire a mild or even asymptomatic phenotype.</p>

