### MID-ANNUAL MEETING OF THE ISRAEL NEUROLOGICAL ASSOCIATION

**June 25th, 2008**

Dan Panorama Hotel, Tel-Aviv

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<td>08:00-9:00</td>
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<td>09:00-09:15</td>
<td><strong>VIRULENT COURSE OF CJD IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER</strong>&lt;br&gt;Appel S¹, Chapman J¹, Kahana E², Prohovnik I³, Rosenmann H¹, Cohen OS¹&lt;br&gt;¹Department of Neurology, The Sagol Neuroscience Center, and Chaim Sheba Medical Center affiliated to the Sackler Faculty of Medicine, Tel-Aviv University, Tel-Hashomer, Israel; ²Department of Neurology, Barzilai Medical Center, Ashkelon; ³Departments of Psychiatry and Radiology Mount Sinai Medical Center, New York;</td>
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<td><strong>MECHANISMS OF VESTIBULO-OCULAR REFLEX (VOR) CANCELLATION IN SPINOCEREBELLAR ATAXIA</strong>&lt;br&gt;Gordon CR¹,², Caspi A³, Levite R¹, Zivotofsky AZ³&lt;br&gt;¹Department of Neurology, Meir Medical Center, Kfar Saba; ²Sackler Faculty of Medicine, Tel Aviv University; ³Gonda Multidisciplinary Brain Research Center, Bar Ilan University, Ramat Gan</td>
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<td><strong>INCREASED SEVERITY OVER GENERATIONS OF CMT TYPE 1A</strong>&lt;br&gt;Steiner I¹, Gotkine M², Steiner-Birman B³, Biran I², Silverstein S¹, Abeliovich D¹, Argov Z², Wirguin I³&lt;br&gt;¹Neurological Sciences Unit, Hadassah Mount Scopus; ²Department of Neurology, Hadassah University Hospital, Ein Karem; ³Department of Human Genetics, Hadassah University Hospital, Jerusalem; ³Department of Neurology Soroka Medical Center, Ben Gurion University, Beer Sheva</td>
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4  09:45-10:00  THE IMPACT OF NUTRITIONAL VITAMIN B12, FOLIC ACID, AND FERRUM DEFICIENCY ON SCHOOL PERFORMANCE OF ELEMENTARY SCHOOL CHILDREN
Masalha R1, Afawi Z2, Bolotin A3, Mashal A4, Al-Sayed I1, Ifergane G1, Wirguin I1
1Department of Neurology, Soroka Medical Center, Beer-Sheva; 2Department of Neurology, Sourasky Medical Center, Tel-Aviv; 3Department of Epidemiology; 4Department of Family Medicine, Ben-Gurion University Faculty of Health Sciences, Beer-Sheva.

5  10:00-10:15  EPIDEMIOLOGY OF ISCHEMIC STROKE IN YOUNG PATIENTS
Dorodnicov E, Kahana E, Gelfand A, Milo R
Department of Neurology, Barzilai Medical Center, Ashkelon, Israel; Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva

6  10:15-10:30  TRANSTHYRETIN MUTATIONS IN SPORADIC AMYLOID POLYNEUROPATHY
Dabby R1, Gilad R1, Yarmitsky D2, Sadeh M1
1Department of Neurology, Wolfson Medical Center, Holon, and 2 the Department of Neurology, Rambam Medical Center, Haifa

10:30-11:00  Coffee Break

SECOND SESSION

Chairpersons: Avinoam Reches
Tanya Gurevich

11:00-11:45  Prof. Israel Nelken
Dept. of Neurobiology and the ICNC, Hebrew University, Jerusalem, Israel

WHY DO WE NEED AUDITORY CORTEX?

11:45-12:15  המפללה של טווח ברפואה: בטן
ע"ש חותם ארצי

12:15- 12:45  המפללה של טווח ברפואה: בטן
ע"ש חותם בנין

12:45-13:30  מمجموعة טוסה - שגריר תרבותי מפרספקטריקה של 50
שנה: הפלשים לเฉוללת הרפואה
אולף (堞ראים ח"א) גל גב, תיילה "פרספקט"
13:30-14:30  Lunch Break & Exhibition

THIRD SESSION

Chairpersons: Rafik Masalha  
David Tanne

7  14:30-14:45

**ENDOGENOUS ANALGESIA AND SSNRIS TOWARDS INDIVIDUALLY-TAILORED PAIN THERAPY**
Yarnitsky D, Granovsky Y, Fadel S, Sprecher E, Granot M  
Neurology, Rambam Medical Center & Technion, Haifa, Israel

8  14:45:1500

**DYNAMIC CHANGES OF D-DIMER FOLLOWING ACUTE STROKE**
Shapir L, Gross B  
Department of Neurology, Western Galilee Hospital, Naharia;  
Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa

9  15:00-15:15

**IS HALF ENOUGH? LESSONS FROM APPARENT HETEROZYGOSITY IN ADULT POLYGLUCOSAN BODY DISEASE (APBD)**
Lossos A1, Rozenstein L1, Hagazi N1, Barash V2, Meiner V3, Abramsky O1, Reches A1, Sadeh M4, Rabey JM5, Argov Z1, Rosenmann H1  
1Agnes Ginges Center for Human Neurogenetics and the Departments of Neurology, 2Biochemistry and 3Human Genetics, Hadassah Medical Center, Jerusalem; 4the Department of Neurology, Wolfson Medical Center, Holon; 5the Department of Neurology, Assaf Ha Rofe Medical Center, Zerifin and Sackler School of Medicine, TAU

10  15:15-15:30

**SEVERITY PROGRESSION IN LATE ONSET TAY SACHS**
Korn-Lubetzki I, Steiner-Birmanns B, Zimran A, Elstein D  
Department of Neurology and Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem, Israel

11  15:30-15:45

**SUCCESSFUL AND RAPID IMPROVEMENT OF TARDIVE DYSKINESIA WITH A COMBINATION OF TETRABENAZINE, CLONAZEPAM AND CLOZAPINE AT LOW DOSES**
Prokhorov T, Dobrovnovsky E, Miniovitch A, Klein C, Pollak L, Rabey JM  
Department of Neurology, Assaf Harofeh Medical Center, Zerifin, affiliated to Sackler School of Medicine, Tel Aviv University, Israel
12  15:45-16:00  Lessons Learned from Two Years' Experience in Intravenous Thrombolysis for Acute Ischemic Stroke in the Tel Aviv Medical Center
L. Shopin, A.Y. Gur, N.M. Bornstein
Stroke Unit, Department of Neurology, Tel Aviv Medical Center, The Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

13  16:00-16:15  Neurotrophic Factors Secreting Mesenchymal Stem Cells - A Promising Novel Therapy for Neurodegenerative Diseases
Sadan O1, Bahat-Stroomza M1, Shemesh N2, Cohen Y2, Melamed E1 and Offen D1
1 Laboratory of Neurosciences, FMRC, Department of Neurology, Rabin Medical Center, Sackler Faculty of Medicine, Tel Aviv University; 2The Raymond and Beverly Sackler School of Chemistry, Faculty of Exact Sciences, Tel Aviv University.

16:15-17:00  Clinico-pathological Conference
Discussing Physician: Itzik Wirguin
Pathologist: Yakov Felig

End of Meeting
VIRULENT COURSE OF CJD IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER

Appel S¹, Chapman J¹, Kahana E², Prohovnik I¹, Rosenmann H⁴, Cohen OS¹
¹Department of Neurology, The Sagol Neuroscience Center, and Chaim Sheba Medical Center affiliated to the Sackler Faculty of Medicine, Tel-Aviv University, Tel-Hashomer, Israel ; ²Department of Neurology, Barzilai Medical Center, Ashkelon ; ³Departments of Psychiatry and Radiology Mount Sinai Medical Center, New York ; ⁴Department of Neurology, Hadassah University Hospital, Ein Kerem, Jerusalem

Background: Creutzfeldt-Jakob disease (CJD) is the most common human prion disease. The largest clusters of familial CJD (fCJD) exists in the North African Jews of Libyan origin. Familial Mediterranean fever (FMF) is an inflammatory disease characterized by episode of fever, abdominal pain and arthritis, and is also common in Libyan Jews. Recent evidence suggests a role for inflammatory processes in CJD pathogenesis, indicating that FMF comorbidity may modify the CJD clinical phenotype.

Objective: To investigate whether comorbid FMF affects the course of CJD.

Methods: The Israeli Registry of Neurological Disease includes 372 CJD patients, 236 of them with fCJD and 136 with sCJD. We reviewed all patients files and found 3 patients with FMF-CJD comorbidity, who were compared to the 369 patients without FMF. The two groups were compared for demographic and clinical parameters using the non-parametric Mann Whitney U test.

Results: The 3 FMF patients (2 fCJD, 1 sCJD) had disease durations of 3.5, 1 and 2.5 months, significantly shorter than in the non-FMF patients (median 5.6, p=0.02). Disease onset was also at an earlier age in the FMF patients (41, 57 and 54 years) when compared to non-FMF patients (median 62, p=0.02).

Conclusions: Co-morbidity of FMF and JCD may lead to a younger age of onset and a shorter disease duration, probably due to activation of pro-inflammatory factors determining the course of CJD. This finding, while limited by small sample size, adds support to recent suggestions of inflammatory mechanisms involved in the pathogenesis of prion diseases.
Background: The Vestibulo-Ocular Reflex (VOR) mechanism triggers eye movements as a result of head motion in order to keep the gaze stationary relative to the world. However, in order to shift the direction of the gaze along with head motion, the VOR mechanism must be overridden ("cancelled"). Two mechanisms have been proposed to explain this cancellation: a reduction of the VOR gain or activation of smooth pursuit eye movements in the opposite direction.

Objectives: To evaluate VOR cancellation in spinocerebellar ataxia type 3 (SCA-3) and episodic ataxia type 2 (EA-2) patients, who are known to have abnormal smooth pursuit but very different vestibular and cerebellar symptomatology.

Methods: We studied smooth pursuit eye movements, VOR response to head thrusts, visually enhanced VOR and VOR cancellation using the magnetic search coil technique in six SCA-3 and four EA-2 patients.

Results: Abnormal VOR was found in 2 of the 4 EA-2 patients and all of the SCA-3 patients. All subjects possessed residual VOR, although when tested using head-thrusts it was almost negligible in the SCA-3 patients. The EA-2 patients showed essentially no smooth pursuit and the SCA-3 patients had poor smooth pursuit. However, for all patients the gain during VOR cancellation was comparable to normals.

Conclusions: Smooth pursuit cancellation of the VOR cannot be the sole mechanism utilized in overriding the VOR in SCA-3 and EA-2 patients. The present findings could also be useful to discern different types of ataxia.

Disclosure: Authors reports no conflicts of interest.
**INCREASED SEVERITY OVER GENERATIONS OF CMT TYPE 1A**

Steiner I1, Gotkine M2, Steiner-Birmanns B3, Biran I2, Silverstein S4, Abeliovich D4, Argov Z2, Wirguin I5

1Neurological Sciences Unit, Hadassah mount Scopus; 2Department of Neurology, Hadassah University Hospital, Ein Karem; 3Department of Neurology Shaare Zedek Hospital; 4Department of Human Genetics, Hadassah University Hospital; Jerusalem, 5Department of Neurology Soroka Medical Center, Ben Gurion University, Beer Sheva

**Background:** Charcot-Marie-Tooth type 1A (CMT1A) is an autosomal dominant polyneuropathy due to a 1.5 Mb tandem duplication in chromosome 17p11.2, containing the PMP22 gene. This mutation is not modified during inheritance.

**Objectives:** We set forth to test the hypothesis that in a subgroup of CMT1A patients there is clinical anticipation, namely an increase in disease severity over generations.

**Methods:** Thirty-nine CMT1A mutation-positive patients in 16 families and 23 parent-offspring pairs were evaluated. This included 14 families with 2 generations and 2 families with 3 generations. Age of presentation was assessed by interviewing the patients and clinical severity was measured using the CMT neuropathy score (CMTNS).

**Results:** In 21/23 parent-child pairs and 14/16 families, there was an earlier age of presentation in children of genetically affected parents. The mean age of onset in the progeny was 12.61 years compared to 41.22 years in the parent generation, (p<0.001). Mean severity in the younger generation was slightly higher than that of the parent generation. When corrected for the age difference, the trend for a worse phenotype in the younger generation became statistically significant (p<0.02, Wilcoxon signed rank test).

**Conclusions:** Our findings suggest that in a subgroup of CMT1A patients there is an increase in clinical severity over generations. The mechanism responsible for this observation remains unknown. Our findings should be validated on a larger cohort of CMT1A families.
THE IMPACT OF NUTRITIONAL VITAMIN B12, FOLIC ACID, AND FERRUM DEFICIENCY ON SCHOOL PERFORMANCE OF ELEMENTARY SCHOOL CHILDREN

Masalha R1, Afawi Z2, Bolotin A3, Mashal A4, Al-Sayed I1, Ifergane G1, Wirguin I1

1Department of Neurology, Soroka Medical Center, Beer-Sheva, 2Department of Neurology, Sourasky Medical Center, Tel-Aviv, 3Department of Epidemiology; 4Department of Family Medicine, Ben-Gurion University Faculty of Health Sciences, Beer-Sheva.

Background: Deficiencies of nutrients such as vitamin B12, folic acid and iron are frequently associated with impairment of memory, concentration and learning ability. Deficiencies of these micronutrients are very rare in Western countries, whereas they are common in developing countries.

Objective: This study was carried out to determine the impact of vitamin B12 deficiency, folic acid deficiency and/or anemia on the academic achievement of elementary school children from a low socio-economic population, i.e., impoverished Bedouin population living in southern Israel.

Design: Sixty-seven elementary school children, 9-11 years of age, were randomly tested. Serum levels of vitamin B12, folic acid, and hemoglobin were measured using automated chemi-luminescence systems. An individual questionnaire was filled out for each student, which included information on number of meat meals consumed per week, the number of people in the family and information about the father’s employment status.

Results: Significant positive correlations were observed between the number of meat meals consumed per week, low vitamin B12 levels and attainment of low marks in school, respectively. There was a negative correlation between the total number of family members and the attainment of low marks in school. No correlation between anemia or low folic acid levels and school performance was observed.

Conclusions: Despite the small sample number, results indicate a high prevalence of vitamin B12 deficiency among these elementary school children, which could be linked to inadequate meat meal intake. This ultimately affected school performance of these children.
**EPIDEMIOLOGY OF ISCHEMIC STROKE IN YOUNG PATIENTS**

Dorodnicov E, Kahana E, Gelfand A, Milo R

Department of Neurology, Barzilai Medical Center, Ashkelon, Israel; Faculty of Health Sciences, Ben-Gurion University of the Negev, Israel

**Background:** The incidence of ischemic stroke in young patients is increasing. Risk factors may vary for young and old patients. Important stroke risk factors in young patients include cardiogenic emboli, coagulopathies, and arterial dissection. In addition, genetic and socio-economic factors may affect the incidence of stroke. Previous studies showed that ethnicity may affect the risk of stroke in Israel’s heterogenous population.

**Objective:** To evaluate stroke incidence and risk factors in young stroke patients of both Ashkenazi (A) and non-Ashkenazi (NA) origin.

**Methods:** We retrospectively reviewed the clinical and epidemiological data of all young ischemic stroke patients (age 18-50) admitted to the Barzilai Medical Center in Ashkelon, between 2003-2007. Population at risk was derived from the Central Bureau of Statistics. Statistical analysis was performed using Student's t-test.

**Results:** Among 2530 ischemic stroke events, 104 (4%) occurred in young patients (29 in A and 75 in NA). Age-specific incidence in Ashkelon city was 20.4/100,000 in A origin (n=20) and 34.1/100,000 in NA (n=44) (z=1.927, p<0.06). Mean age at first stroke was 43.8±5.8. Median number of risk factors was 3 for NA and 2 for A patients. Most common risk factors were smoking (60%), dyslipidemia (48%) and hypertension (48%) in NA, hypertension (59%) and smoking (48%) in A. Hypertension, diabetes mellitus and smoking were more common in males than females (57%, 40%, 68% vs. 43%, 8%, 31% respectively), while coagulopathies were more frequent in females (13% vs. 4.5%). Cardiac abnormalities accounted for 8% of all strokes. Only 17% of the 45 patients treated for dyslipidemia at the time of the event were adequately controlled. Ten percent were treated with t-PA, compared with 2.6% of all stroke patients.

**Conclusion:** Most patients with young-onset ischemic stroke have risk factors seen also in older populations; however, they have higher chance of receiving t-PA. Differences in stroke incidence and risk factors exist between Ashkenazi and non-Ashkenazi patients. Women were more likely to have coagulopathies, and less likely to have diabetes mellitus than men. The higher incidence of stroke and number of modifiable risk factors in NA young stroke victims, and the uncontrolled dyslipidemia, call for better education and prevention in young patients with stroke risk factors.
TRANSTHYRETIN MUTATIONS IN SPORADIC AMYLOID POLYNEUROPATHY

Dabby R1, Gilad R1, Yarnitsky D2, Sadeh M1
1Department of Neurology, Wolfson Medical Center, Holon, and 2 the Department of Neurology, Rambam Medical Center, Haifa

Objectives. To describe clinical and molecular genetic findings in 3 patients with sporadic amyloid polyneuropathy.

Background. Transthyretin (TTR) familial amyloid polyneuropathy is the most common form of autosomal dominant amyloid neuropathy. It is caused by mutations in transthyretin, a plasma transport protein for thyroid hormone and retinol-binding protein/vitamin A. It bears a fatal outcome within 10 years after onset of symptoms.

Methods. All patients underwent nerve conduction studies (NCS), nerve biopsies with Congo red stain and immunostain for TTR, followed by sequencing of the coding regions of the TTR gene.

Results. All 3 patients showed axonal neuropathy in NCS. Nerve biopsies revealed axonal loss with amyloid deposits that were negative with TTR stain. However, molecular genetic studies disclosed mutations in the TTR gene in all (2 with the common mutation Val30Met, a one with a rare though previously described Phe33Leu transition). In one patient the diagnosis was delayed in several years, and she died from malabsorption before orthotopic liver transplantation was available.

Conclusions. Late diagnosis in non-familial cases delays adequate potentially life-saving treatment. DNA analysis for TTR- familial amyloid polyneuropathy should be considered in patients with a progressive neuropathy of unknown etiology, especially when associated with autonomic dysfunction, even if TTR stain is negative.
Aim of Investigation: SSNRIs attenuate pain by elevating noradrenaline and serotonin central transmission, enhancing activity in pain inhibitory pathways. Activity of these pathways can be assessed in the lab before and during treatment by the DNIC paradigm, allowing assessment of the individual's pain modulation profile. We aimed to find out whether DNIC efficiency is improved by Duloxetine, and whether this effect depends on the pre-treatment DNIC state.

Methods: A randomized double blind placebo controlled cross-over design was performed on 40 healthy volunteers aged 21-38 yrs, using Duloxetine 60 mg once a day for one week, and non active placebo, with one week washout in-between treatments (20 volunteers did not complete the second week due to administrative reasons). DNIC paradigm, tested at baseline and after each of the treatments, consisted of administration of two painful stimuli, a test-pain delivered by contact heat, and a 'conditioning' pain induced by hot water immersion of the other hand. The DNIC efficiency was calculated as the difference between pain perceptions induced by the test-pain when given alone, and when given concomitantly with the conditioning one.

Results: Mixed model ANOVA on treatment, DNIC efficiency at pre-treatment, and their interaction, indicated a significant interaction (P=0.0082), and only a weak trend for treatment alone (P=0.0896). Tukey tests indicated that Duloxetine treatment was only significantly effective for the low pre-treatment DNIC group (pre-treatment vs. Duloxetine treatment DNIC score, 0.15 vs. 19.35, P<0.05), and not for the high pre-treatment DNIC group (32.50 vs. 29.26, NS), with placebo ineffective for either group.

Conclusions: The higher effect found in individuals with less efficient DNIC suggests these individuals are more likely to benefit clinically from this medication. Less efficient DNIC is (i) associated with presence of idiopathic pain syndromes, and (ii) predicts development of chronic post operative pain. Measuring DNIC before use of Duloxetine, in order to predict whether it will or will not be beneficial to the specific patient, is a first step towards individually tailored therapy in pain medicine.
DYNAMIC CHANGES OF D-DIMER FOLLOWING ACUTE STROKE

Shapir L, Gross B
Department of Neurology, Western Galilee Hospital, Naharia; Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa Israel

Background: Various coagulation abnormalities according to stroke subtypes have been reported. The true relationship between plasma D-dimer and acute stroke remains uncertain.

Purpose: To investigate whether systemic D-dimer activation occurs after intracerebral hemorrhage (ICH) and after acute ischemic stroke. To find the association between plasma D-dimer levels and stroke with different etiologies and whether its level may predict the clinical outcome.

Methods: 96 consecutive patients with acute stroke were recruited. Plasma D-dimer levels were determined on admission, 24 hours, one week and 3 months after the acute event. Stroke subtype was determined by CT and according to TOAST criteria. Stroke severity was evaluated by NIHSS.

Results: Average level of plasma D-dimer after acute stroke was elevated and returned to normal range after 3 months.

D-dimer levels were higher in patients with intracerebral hemorrhage than in those with infarction. Patients with infarction had higher levels than those with normal brain CT on admission. The levels were higher on admission, after 24 hours, and after one week (P<0.021). The percent of patients with plasma D-dimer level above the normal range on admission with intracerebral hemorrhage was higher than the percent of patients with brain infarction and with TIA. D-dimer values average was higher upon admission and after 24 hours when the infarction was due to occlusion of large vessels, and decreased when territory became smaller. In lacunar stroke, D-dimer levels increased after 7 days. D-dimer returned to normal level after 3 months.

The percent of patients with high plasma level of D-dimer correlates both to the severity of stroke and to the mortality (p=0.039, P=0.017 respectively).

Conclusions: D-dimer levels associate with stroke etiology, size of the damaged area, and stroke severity during the acute phase. D-dimer return to the normal range at 3 months. Increased plasma D-dimer levels following acute stroke associate with early complication and high mortality.
IS HALF ENOUGH?
LESSONS FROM APPARENT HETEROZYGOSITY IN ADULT POLYGLUCOSAN BODY DISEASE (APBD)

Lossos A1, Rozenstein L1, Hagazi N1, Barash V2, Meiner V3, Abramsky O1, Reches A1, Sadeh M4, Rabey JM5, Argov Z1, Rosenmann H1

1Agnes Ginges Center for Human Neurogenetics and the Departments of Neurology, 2Biochemistry and 3Human Genetics, Hadassah Medical Center, Jerusalem; 4the Department of Neurology, Wolfson Medical Center, Holon, and 5the Department of Neurology, Assaf Ha Rofe Medical Center, Zerifin and Sackler School of Medicine, TAU.

Objectives. To describe molecular and phenotypic findings in 16 Ashkenazi Jewish (AJ) patients with APBD.

Background. APBD is a late-onset slowly progressive disorder manifested by pyramidal tetraparesis, polyneuropathy, cognitive impairment and neurogenic bladder associated with neuronal accumulation of polyglucosan bodies. Reduced glycogen branching enzyme (GBE) activity and homozygous p.Y329S mutation in the GBE1 have been previously shown by us to segregate with the disease phenotype in AJ families corresponding to an autosomal recessive mode of inheritance.

Methods. Diagnosis was based on the typical clinical and pathological findings. GBE activity was assayed on skin fibroblasts or peripheral blood lymphocytes. Genotyping was performed on genomic DNA implementing restriction enzyme analyses and sequencing the coding and flanking regions.

Results. All 16 patients fulfilled the essential diagnostic requirements and had a very low GBE activity. Molecular analysis identified p.Y329S homozygosity in 10 patients, p.Y329S/L224P compound heterozygosity in 1 patient, and apparent p.Y329S heterozygosity in 5 additional patients.

Conclusions. All APBD patients of AJ origin manifest reduced GBE activity. While 60% of these patients carry a homozygous p.Y329S mutation, apparent heterozygosity with no disease causing mutation on the other allele is observed in 30%. Given the typical autosomal recessive inheritance of APBD, such heterozygosity may result either from a yet undetected mutation outside the known coding/regulatory region or from a complex chromosomal rearrangement. Alternatively, association with a known GBE1 polymorphisms or double heterozygosity for an additional mutation in another neuronally-important gene is proposed. Studies in progress will hopefully resolve this important issue.
SEVERITY PROGRESSION IN LATE ONSET TAY SACHS

Korn-Lubetzki I, Steiner-Birmanns B, Zimran A, Elstein D
Department of Neurology and Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem, Israel

Objectives: To test neurocognitive function and track disease severity progression in patients with Late-onset Tay-Sachs (LOTS) disease.

Background: LOTS is an ultra rare lysosomal storage disorder. The disease affects mostly motor functions but cerebellar, psychiatric and cognitive features may be present. Oral substrate reduction and chaperone therapy are potential therapeutic options under investigation. There is a need to define clinically relevant outcome measures of possible therapeutic interventions.

Methods: LOTS severity score relating to six disease specific clinical domains was assessed twelve patients at first examination and at follow up in 5. Ten patients underwent cognitive evaluation at least once (Mindstreams Neurotrax system). Six sub-scores and a Global Cognitive Score were tabulated.

Results: All patients were Ashkenazi Jewish, mean age 41.1 (range 25-66) years. All have genotype G269S/4 bp insertion exon 11 (1278insTATC), and residual hexosaminidase A levels (< 10%). LOTS Severity Score was initially mild in 6 patients, moderate in 5, and severe in one. At follow up deterioration was observed in all tested patients. Global cognitive score was below normal in 8/10 patients, with verbal and executive functions most affected.

Conclusions: Cognitive score in conjunction with a disease specific severity score may be appropriate and clinically relevant as a tool for follow-up of clinically relevant outcome measurements.
SUCCESSFUL AND RAPID IMPROVEMENT OF TARDIVE DYSKINESIA WITH A COMBINATION OF TETRABENAZINE, CLONAZEPAM AND CLOZAPINE AT LOWDOSES

Prokhorov T, Dobronevsky E, Miniovitch A, Klein C, Pollak L, Rabey JM
Department of Neurology, Assaf Harofeh Medical Center, Zerifin, affiliated to Sackler School of Medicine, Tel Aviv University, Israel

Objective: To apply a protocol utilizing tetrrabenazine (TBZ), clozapine (CLOZ) and clonazepam (CLONAZ) simultaneously for the treatment of tardive dyskinesia (TD) patients.

Background: TD is a complex involuntary movement disorder affecting about 23% of neuroleptic treated patients and about 34% of those who abandon medication (emergent dyskinesias) (Woerner et al, 1991, Yassa and Jeste, 1992). Treatment of the condition is quite disappointing and there is no single drug that is considered 100% effective in rapidly abating the symptoms.

Methods: Six patients with severe TD that was not successfully controlled by the treating psychiatrist were referred to our clinic for treatment (mean age 51.5; 3 male and 3 women; 4 schizophrenics (2 paranoidal type, 2 affective type); 1 bipolar disease, 1 borderline. They were being treated with neurolopetics (classic 3 of them; risperidone 2; olanzapine 1) and developed severe neck and buccolingual dyskinesias that seriously affected their quality of life. In the clinic, all of them were treated simultaneously with TBZ (mean dose 141.6 mg); CLONAZ (mean dose 4.3 mg), CLOZ (mean dose 125 mg). In parallel we stopped the offending medication.

Results: Within 1 week we observed a very impressive recovery of the symptomatology and within 1 month all the patients were free of symptoms. The mean observation period was 4 years.

Conclusions: Although in the past TBZ, and CLOZ were reported to be useful for TD, the early combination of 3 drugs (adding CLONAZ) produced a rapid and effective option for the management of this incapacitating syndrome.
LESSONS LEARNED FROM TWO YEARS’ EXPERIENCE IN INTRAVENOUS THROMBOLYSIS FOR ACUTE ISCHEMIC STROKE IN THE TEL AVIV MEDICAL CENTER

L. Shopin, A.Y. Gur, N.M. Bornstein
Stroke Unit, Department of Neurology, Tel Aviv Medical Center, The Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

Background: Intravenous thrombolytic therapy (ITT) is widely recommended as standard treatment for acute (≤3 hours) ischemic stroke in most clinical practice guidelines. The Israeli experience with ITT is still limited. We describe our 2-year experience (2006-2007) with intravenous tissue plasminogen activator (IV tPA) in the management of 58 patients with acute ischemic stroke. We present demographic data, the most important timing details (from symptom onset to emergency room [ER], ER to CT scan, ER to IV tPA, symptom onset to IV tPA), stroke severity, hemorrhagic complications, mortality, and early outcome.

Methods: Internal carotid artery (ICA) occlusion has been recently associated with poor clinical outcome in patients with acute ischemic stroke treated with IV tPA. The impact of severe ICA stenosis (70-99%) on thrombolysis response is undetermined. We compared early clinical outcome after IV tPA of 31 patients with stroke in the middle cerebral artery with and without severe ICA stenosis. Carotid Doppler and/or CT angiography were performed in all of them. National Institute of Health Stroke Scale (NIHSS) scores were recorded before and 7 days after thrombolysis: a decrease ≥4 points indicated neurological improvement.

Results: Our data demonstrate fairly similar parameters of IV tPA treatment compared to other centers based on the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST) registry, and suggest that patients with severe ICA stenosis might be less likely to benefit from IV tPA. This information may be useful in: (1) the optimization of ITT in patients with acute ischemic stroke, and (2) the planning of ITT in other Israeli hospitals. We propose that an extracranial carotid evaluation should be performed in patients with acute ischemic stroke before deciding on interventions such as thrombolysis (intravenous, intra-arterial) or thrombectomy.
Background: Stem cells based therapy is a promising frontier for the treatment of neurodegenerative disease. In our lab, we developed a novel protocol that induces rat and human bone marrow derived mesenchymal stem cells into neurotrophic factors (NTFs) secreting cells, thus combining stem cells based therapy with the NTF based neuroprotection. These cells produce and secrete factors as brain derived neurotrophic factor (BDNF), glial cell derived neurotrophic factor (GDNF), vasculoendothelial growth factor (VEGF) as others. Our studies demonstrated that the NTFs secreting cells migrate toward striatal lesions as well as protect against toxin-induced lesion.

Methods: Human or rat derived MSCs went through our two phases medium based induction media. Migratory behavior was examined by transplanting the cells away from a quinolinic acid induced striatal lesion, a rat model for Huntington's disease, and tracking the cells in vivo by serial MRI scans following by histology. An efficacy study was conducted on the 6-hydroxy-dopamine induced lesion, a rat model for Parkinson's disease. The cells were transplanted on the day of 6OHDA administration and amphetamine induced rotations were measured as a primary behavioral index. We further measured dopamine levels ex vivo by HPLC.

Results: Induced cells migrated along the internal capsule into the QA-induced lesion as demonstrated by high-resolution 3D MR images and by histology. When transplanted posterior to the 6OHDA lesion, the NTFs secreting cells attenuated amphetamine induced rotations by 45% (2.16±0.37 vs. 4.74±1.07 in the control group). Biochemical analysis demonstrated an 300% elevation of the dopamine levels post cellular treatment (21.3±3% vs. 63±16%) as measured by HPLC.

Discussion: We therefore conclude that the induced mesenchymal stem cells have a therapeutic potential for neurodegenerative processes and diseases, both by the NTFs secretion and by the migratory ability toward the diseased tissue.