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Abstracts
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Ophtalmoplégie intrinsèque douloureuse révélatrice d'un zona ophtalmique

F. Assal, H. G. Frank, S. von Gunten, M. Chofflon (Genève)

L'association d'une céphalée à une mydriase est une urgence diagnostique évoquant classiquement un anévrisme ou un engagement temporal.

Un homme de 69 ans, connu pour une ancienne tuberculose, un diabète et un lymphome consulte pour une céphalée orbito-temporale droite aiguë et pulsatile. L'examen montre une mydriase droite aréactive à la lumière, à la convergence et à la pilocarpine ainsi qu'une discrète exophtalmie et hyperémie droites. L'AV est de 80% à droite et 60% à gauche. Le reste de l'examen est sans anomalies contributives. L'imagerie cérébrale ne révéle ni anévrisme ni processus expansif. La VS est à 60 mm/hr mais mal interprétable en raison des comorbidités. Le LCR est normal. Au 6ème jour, on note des vésicules dans le territoire du nerf ophtalmique droit. L'analyse virologique de la peau confirme le diagnostic clinique d'herpes zoster.

Les atteintes oculomotrices d'origine zostérienne sont connues, en particulier celles du III et de son contingent parasympathique, par atteinte du ganglion ciliaire, généralement du même côté que l'éruption. L'ophtalmoparésie se manifeste d'emblée ou le plus souvent plusieurs semaines après les lésions cutanées. Le caractère inaugural de la mydriase est, dans ce cas, inhabituel.

Démence, troubles de la marche et «fingerprint-profiles» dans la biopsie de la peau: maladie de Kufs?

H. G. Frank, F. Assal, M. A. Spycher, J. Delavelle, T. Landis (Genève/Zürich)

La forme adulte de céroïde lipofuscinose neuronale (aCLN, maladie de Kufs) est une maladie métabolique dont on distingue deux formes cliniques. L'une associant démence et épilepsie-myoclonies l'autre démence et troubles de la marche. Du point de vue diagnostic le gold standard reste à ce jour l'examen ultrastructural de la biopsie cérébrale.

Nous rapportons le cas d'un patient de 68 ans, qui présente une démence sous-cortico-frontale et une apraxie à la marche évoluant depuis plus de 5 ans. L'IRM cérébrale met en évidence une leucencéphalopathie sus-tentorielle prédominant dans les régions frontales et sous-tentorielle, bilatérale et symétrique. Le bilan métabolique est négatif. La microscopie électronique de la peau du creux axillaire révèle des «fingerprint profiles» (FPs) dans les cellules épithéliales eccrines compatible avec une aCLN. Dans la littérature ces «fingerprint profiles» ont été rapportés dans différents tissus extracérébraux (cellules musculaires striées et lisses et endothéliales) mais le diagnostic reste difficile en raison des faux-positifs et négatifs. Dans notre cas, l'absence des FPs dans d'autres cellules dermales non épithéliales nous a empêché de poser un diagnostic de certitude de aCLN.

La maladie de Kufs est trop rarement observée et le spectre clinique et pathologique semblent trop variable pour définir des critères diagnostiques mais nous aimerions insister sur l'intérêt des biopsies extracérébrales dans ces pathologies.

Stroke in the Swiss elderly

D. H. Benninger, F. R. Herrmann, J. P. Michel, F. Gutzwiller, J. Bogousslavsky (Genève/Zürich/Lausanne)

A population-based study on 921 subjects results in an overall, age- and sex-adjusted stroke prevalence of 7.0% (95%CI: 5.3 - 8.8%) in the Swiss urban population aged 65 years and older, being significantly higher in men than in women (9.2% versus 5.8%, p=0.025). The stroke-free life expectancy for elderly subjects of both sexes amounts to an average 91% of the global remaining life time. This is a useful public health indicator allowing a comparison of the effect of prevention and therapeutic measures and the social and economic impact of stroke among countries and across time within the same areas. Dementia according to DSM-III-R criteria and disability are significantly more prevalent among stroke survivors than in the stroke-free elderly population, 24.2% versus 8.5%, respective, 18.9% versus 6.8%, underlining the close association of stroke with these two major health problems.

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Contribution of neuroimaging findings in a case recovering from global alexia to spelling dyslexia

S. Lanzinger, B. Weder, R. Oettli, Ch. Fretz (St. Gallen)

We report findings in a 67-year-old right-handed man who suffered an ischemic infarction in the territory of the left posterior cerebral artery. The clinical manifestation consisted mainly of total alexia without agraphia. The patient recovered gradually showing, thereafter, the syndrome of spelling dyslexia. In the acute stage [^{99m}Tc]HM-PAO SPECT was characterized by a diminished tracer uptake in the definitely infarcted area and hyperfixation in the region of left forceps major. The two distinct perfusion patterns indicated quite different prognosis for the incriminated brain tissue: at the site of low HM-PAO uptake, at left medio-basal temporal lobe, even ischemic infarction was evinced by MR-imaging at the acute stage. In contrast, the zone of HM-PAO hyperfixation, at white matter of occipito-temporal junction, recovered almost completely as verified by follow-up MR-imaging. We suggest that hyperfixation of HM-PAO delineated potentially salvageable tissue, due to early reperfusion, as observed in recent SPECT studies. Summarizing, our neuroimaging data give further support to the assumption that left forceps major is the critical area for global alexia, whereas spelling dyslexia is due to involvement of left medio-basal temporal lobe.

Unterschiede im neuropsychologischen Leistungsprofil bei Patienten mit persistierenden Beschwerden nach HWS-Distorsion (whiplash associated disorders) und Fibromyalgie

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Einleitung: Bei Late-Whiplash-Patienten und Patienten mit Fibromyalgien finden sich neben der komplexen Schmerzsymptomatik, vegetativen Funktionsstörungen sowie psycho-affektiven Störungen neuropsychologische Defizite mit vorwiegender Beeinflussung der Psychomotorik, deren Aetiologie multifaktoriell bedingt ist. In der vorliegenden Arbeit wurden Unterschiede in bezug auf die neuropsychologische Leistungsfähigkeit zwischen beiden Patientengruppen untersucht.

Methode:
a) Patienten: Es wurden 30 Patienten mit HWS-Distorsion und leichter traumatischer Hirnverletzung, entsprechend den Kriterien des Amerikanischen Kongresses für Rehabilitationsmedizin (21) sowie 20 Patienten mit einem nach ACR-Kriterien diagnostizierten Fibromyalgie-Syndrom (1) neuropsychologisch untersucht.
b) Neuropsychologische Testverfahren: Aufmerksamkeitsfunktionen (Alertness, geteilte Aufmerksamkeit), Lern- und Gedächnisfunktionen (verbale und figurale Lern- und Gedächnisfunktionen), Frontalhirnfunktionen (Frontal-Lobe-Score, verbale und figurale Ideenproduktion, visuell-verbale Interferenzresistenz, motorische Interferenzresistenz- und Impulskontrolle), visuell- und mental-räumliche Funktionen (Objekterkennung sowie mental-räumliche Funktionen).
c) Statistik: Es wurden Gruppenvergleiche der neuropsychologischen Befunde bei Late-Whiplash-Patienten und Fibromyalgie-Patienten durchgeführt. Dabei wurde mit einem Signifikanzniveau von 5% gearbeitet.

Resultate: Unterschiede zwischen den Late-Whiplash-Patienten versus Fibromyalgie zeigten sich im Frontal-Lobe-Score 2, in der motorischen Impulskontrolle, im Stroop 1 sowie der tonischen und phasischen Alertness und im LPS 7. Beide Gruppen unterschieden sich im Frontal-Lobe-Gesamt-Score und in der geteilten Aufmerksamkeit von entsprechenden, der Literatur entnommenen Normwerten.

Conclusion: Es zeigt sich, dass die Late-Whiplash-Patienten schwerere und ausgedehntere neuropsychologische Funktionsstörungen als die Fibromyalgie-Patienten aufweisen. Dabei ist die gemeinsame Pathophysiologie der neuropsychologischen Befunde der Late-Whiplash-Patienten und der Fibromyalgie-Patienten arbeitshypothetisch lediglich für die Nozizeption und die psycho-affektiven Störungen ableitbar. Darüber hinaus muss bei der Gruppe der Late-Whiplash-Patienten angenommen werden, dass die neuropsychologischen Defizite zusätzlich durch diffuse axonal-cerebrale und cervico-cerebrale neuronale Läsionen verursacht sind.

Rezidivierende Retrobulbärneuritiden und ausgedehnte Myelitiden – MS oder Neuromyelitis optica?

G. Rilling, H. P. Ludin (St. Gallen)

Es sollen zwei Patientinnen vorgestellt werden mit rezidivierenden seitenalternierenden Retrobulbärneuritiden und ausgedehnten Myelitiden. Bei der ersten Patientin begann das Leiden mit rezidivierenden Myelitiden, bei der zweiten mit Retrobulbärneuritiden.

Bei beiden Patientinnen zeigte das spinale MRI ausgedehnte, langstreckige Signalalterationen mit deutlichem Kontrastmittel-Enhancement in zumeist cervicaler bzw. cervicothoracaler Lokalisation. Das craniocerebrale MRI ergab zunächst bei beiden Patientinnen keine sicheren pathologischen Herde, bei der ersten Patientin zeigten sich nach mehrjährigem Krankheitsverlauf unklare Läsionen, nicht typisch für eine MS. Der Liquor beider Patientinnen wies eine mässige, vorwiegend lymphocytäre Pleocytose mit einer Zellzahl zwischen 11 und 126/Microliter sowie eine Proteinerhöhung auf, sichere oligoklonale Banden konnten nicht festgestellt werden. Während der «Schübe» fiel bei beiden Patientinnen das ENA-Autoantikörper-Screening positiv aus.

Unter einer «Schubtherapie» mit Solumedrol bildeten sich jeweils – vorübergehend – die Symptome zurück. Bei beiden Patientinnen musste wegen rezidivierender Symptome Cyclophosphamid in einer Dosierung von 100 mg täglich eingesetzt werden.

Une famille avec myopathie myotonique proximale (PROMM)

A. Kohler, P. Burkhard, S. Hefft, G. P. Pizzolato, M. R. Magistris (Genève)

La myopathie myotonique proximale, ou PROMM, de la terminologie anglaise Proximal Myotonic Myopathy, est une maladie autosomale dominante caractérisée par une faiblesse proximale, une myotonie, parfois une cataracte et des troubles du rythme cardiaque. Elle se différencie de la maladie de Steinert par le caractère proximal de la faiblesse, l'absence d'atteinte faciale, l'absence d'expansion anormale du triplet CTG sur le chromosome 19.

Trois patients d'une même famille présentent une parésie proximale lentement progressive depuis l'âge de 40 ans. Un seul présente une myotonie clinique depuis l'âge de 20 ans. L'analyse génétique révèle un nombre normal de triplet CTG. L'EMG montre des décharges myotoniques diffuses. Une biopsie musculaire montre des fibres anisométriques, la présence de fibres lobulées et de noyaux centraux.

En conclusion, la myopathie myotonique proximale peut se présenter comme une myopathie des ceintures, ou comme une myotonie suggérant une maladie de Steinert. L'EMG est particulièrement utile, puisqu'il montre des décharges myotoniques même chez les patients sans myotonie clinique. La myopathie myotonique proximale est une entité différente de la maladie de Steinert. Le déficit génétique n'est pas connu actuellement.

Stiffness on exercise (Brody's syndrome): from clinical to genetic abnormalities in a Swiss family

Th. Kuntzer, F. Ochsner, C. Naegeli, R. C. Janzer (Lausanne)

Brody's syndrome is a rare, possibly underrecognised, inherited error of muscle function. It is characterized by stiffness of muscles after exercise, due to reduced Ca^{2+}-ATPase activities in the sarcoplasmic reticulum.

We report 2 brothers in whom symptoms dated back to childhood. They had the same range of activities as their peers, but could not do them as quickly because they found that with effort their muscles «tightened up». Examination of patients revealed no weakness nor myotonia. Exercise such as opening and closing hands or eyes induced progressive stiffening, some pain in the exercised muscles, and increasing difficulty relaxing them. Patient 1 had an associated Gitelman's syndrome, a recently recognized cause of permanent hypokalemia with mutation of the renal thiazide-sensitive Na-C1 cotransporter on chromosome 16. A normal biochemical profile was obtained in patient 2. In both patients, serum CK was slightly increased, and electromyography showed normal motor unit potentials and no myotonic discharges. The McManis exercise test was normal.

The muscle biopsy showed a minimal change myopathy. Surprisingly, the immunohistochemical expression of SERCA 1 and 2 was normal. The search of defects in the ATP2a1 on chromosome 16p12.1-12.2 encoding SERCA1 (the fast-twitch skeletal muscle sarcoplasmic reticulum Ca^{2+}-ATPase), shows the Pro789 to Leu mutation which cosegragates with this syndrome (David MacLennan, Toronto, Canada).

In conclusion, this study (i) helps to recognize and distinguish clinical syndromes with stiffness of muscles on exercise and (ii) underscores the limitation of the available commercially antibodies to SERCA1 and 2 to diagnose this treatable syndrome since Ca^{2+}-ATPase can be present but inactive.

Epidermolysis bullosa und Muskeldystrophie infolge Plectinmangel

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1996 wurde gezeigt, dass die seltene Konstellation einer seit Geburt bestehenden Epidermolysis bullosa simplex und später auftretender Muskeldystrophie (EB-MD) auf mangelnder Expression von Plectin beruht. Plectin ist für die Verankerung zytoskelettärer Strukturen in Keratozyten und Muskelfasern notwendig. Wir berichten über eine Probandin, die seit Geburt an einer Epidermolysis bullosa an mechanisch exponierten Stellen leidet. Die körperliche Aktivität war deshalb stark eingeschränkt.

Erste Symptome einer Muskelaffektion mit Schmerzen wurden mit 13-14 Jahren realisiert, ein Jahr später wurde eine Ptose festgestellt, in der Folge Schwäche im Schultergürtelbereich. Klinisch lagen im Alter von 16 Jahren deutliche proximal betonte Schwächen der Arme und Beine, der Hals- sowie Gesichtsmuskulatur vor. CK-Werte waren zehnfach erhöht. Zusatzuntersuchungen ergaben keine Hinweise für Polyneuropathie, Kardiomyopathie oder Beteiligung der zerebralen weissen Substanz. Muskelbioptisch sprachen Kaliberschwankungen, internalisierte Kerne, «fibre splitting» und fokale Nekrosen für einen dystrophen Prozess. Die Befundkonstellation war vereinbar mit einem Plectinmangel, der immunhistochemisch bestätigt wurde.

Verschiedenen Arbeitsgruppen ist es kürzlich gelungen, bei EB-MD Mutationen im Plectingen auf Chromosom 8q.24 nachzuweisen. EB-MD wird autosomal-rezessiv vererbt.

Prognostic role of muscle biopsy in polymyositis: evaluation of T-cell oligoclonality and T-cell subset distribution

R. C. Janzer, C. Marin, Th. Kuntzer (Lausanne)

Muscle biopsy in patients with polymyositis is considered not to be able to predict the response to treatment. Recent findings indicate that in a certain number of polymyositis cases an oligoclonal T-cell population is present. We therefore tested in 17 patients with polymyositis (12 responders «RPM» and 5 non-responders «NRPM») and 7 control cases, the hypothesis that the presence of T-cell oligoclonality as assessed by PCR for the T-cell receptor γ-gene rearrangement correlates with a bad response to treatment. In parallel, the role of lymphocyte subsets and their size of accumulation was reevaluated morphometrically.

We found in 6 of 17 muscle biopsies from patients with polymyositis, but in no control muscles, an oligoclonal T-cell population. However, there was no significant correlation with the response to treatment. T-cell oligoclonality was strongly correlated with long duration of the symptoms prior to biopsy. In the 12 RPM, total CD3+ T-cells and the CD8+ subset showed an equal distribution between endomysial and perimysial sites, whereas in the 5 NRPM a higher concentration of CD3+ and CD8+ T-cells was observed in the endomysium. Number and distribution of CD4+ T-cells and macrophages showed no significant difference.

These results indicate that in NRPM the localisation of CD3+ and CD8+ T-cells is predominantly endomysial, as compared to a more diffuse infiltration pattern in RPM. T-cell oligoclonality is not a prognostic factor and correlates with long duration of the illness. If these findings will be corroborated by larger series, the muscle biopsy might be a predictor of treatment response an eventually justify an early, more aggressive therapy in selected cases.

Familial cardiomyopathy and distal myopathy with abnormal desmin accumulation and migration

A. Lobrinus, R. C. Janzer, Th. Kuntzer (Lausanne)

Desminopathies form a heterogeneous group of myopathies characterised by pathological aggregations of desmin.

We report on a family where mother and daughter suffer from cardiomyopathy and distal myopathy. Early symptoms were related to atrioventricar block in both patients at the same age, but the mother developed later a severe heart failure which needed heart transplantation at the age of 56 years. Distal amyotrophy and weakness of distal upper and lower limbs appeared progressively in their twenties, with a further slow progression of the disease leading to bilateral foot drops in the forties of the mother. Lower limbs CT scans revealed non-homogeneous focal atrophy of predominantly distal muscles. Skeletal muscle biosies and explanted heart were characterised by inclusion bodies that expressed strongly desmin and alpha-B-cristallin and weakly dystrophin and ubiquitin.

Ultrastructurally, most inclusions corresponded to non-membrane bound granulo-filamentous material with disruption of myofibrils. An immunoblot analysis showed two desmin bands, the first at 53 kD and the second at 49 kD.

In conclusion, this study of a distinct subtype of desminopathy underscores that skeletal and heart muscles share in common very similar muscle changes with abnormal desmin migration that may correspond to a defective desmin.

Charcot-Marie-Tooth (CMT) neuropathy in a large CMT2 Swiss family

B. Leemann, R. Lettry-Trouillat, Th. Kuntzer (Lausanne)

A large Swiss family is reported, based on clinical (onset of symptoms, degree of atrophy of muscles, functional disability), electrophysiological and nerve biopsy findings.

In this family of 35 members, originating from the Fribourg Canton, 13 cases were found to be affected. Onset of the first functional manifestations was in the first decade in 30% of cases and before the age of 20 years in 40% of cases. The predominant clinical signs were ankle instability with repeated sprains, cramps and carpal tunnel syndrome. One of the patients was normal on clinical examination, the others presented pes cavus or absent ankle jerk reflexes. Functional disability was mild in all the affected members, but 3 were unable to work.

Motor nerve conduction velocity was variably reduced, and was >35 and <50 m/s in the median nerve for all patients. Sensory potentials were abnormal in 3 out of 3 cases, even when there was no clinical sensory loss. Needle electromyography recruitment was reduced in distal muscles for all patients. One patient had light and electron microscopy examination of a radial nerve biopsy, that showed an axonal neuropathy (JM Vallat, Limoges).

Early age at onset and greatly reduced motor responses were predictive of a more severe disease course; the earlier the onset the more reduced the amplitude of motor responses and the higher the functional disability tended to be after an equivalent disease duration.

Genetic analyses are under way, but this family does not cosegragates with PMP22, PO or connexin 32 genes.

Metalloproteinases MMP-9 and MMP-2 in sural nerve biopsies of inflammatory and non-inflammatory polyneuropathies

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Introduction: Matrix metalloproteinases are a family of zinc containing enzymes that play an important role in inflammation and tissue degradation. Gelatinases (MMP-9 and MMP-2) have been implicated in the disruption of the blood-brain and blood-nerve barrier. We studied the expression of gelatinases by immunohistochemistry in sural nerve biopsies from patients with inflammatory and non inflammtory polyneuropathies.

Methods: Tissue sections of 11 sural nerve biopsies were stained for MMP-2 and MMP-9. 5 patients had vasculitic neuropathies, 4 chronic inflammatory demyelinating polyneuropathies (CIDP) and 2 non-inflammatory polyneuropathies (1 alcohol induced, 1 drug toxicity).

Results: Perineurium and endothelium were positive for MMP-2 in all tissue sections. MMP-9 positive cells could be detected in vessel walls, infiltrates, epineurium and endoneurium of vasculitic neuropathies. In CIDP, MMP-9 positive cells were prominent in vessel walls. In noninflammatory controls we could only detect a few MMP-9 positive cells in circulation and adhering to vessel walls. Double staining with CD3/DC68 indicates that the infiltrating cells are T-cells and macrophages.

Conclusion: MMP-9 seems to play an important role in inflammatory peripheral neuropathy probably as a means of nerve tissue invasion by inflammatory cells.

Etiologie inhabituelle d'une compression du nerf médian dans la traversée du tunnel carpien: un fibrosarcome malin (malignant peripheral nerve sheath tumor «MPST»)

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La compression du nerf médian dans la traversée du tunnel carpien est la neuropathie par enclavement la plus fréquemment diagnostiquée dans un laboratoire d'électrophysiologie clinique.

Une étiologie est rarement déterminée, l'étiquette «idiopathique» se rencontre le plus souvent dans la littérature hormis de rares causes reconnues telles qu'une malformation vasculaire ou musculo-tendineuse, une chondrocalcinose, etc.

Un processus malin n'est relevé qu'exeptionnellement. Birche en 1994 dans le cadre des «MPNST» ne cite que 5 cas documentés, et d'une manière générale la prévalence des «MPNST» dans la population générale est de 0.001%, la proportion des néoplasies médianes rarissimes.

A propos d'une observation privilégiée, les auteurs, dans le descriptif clinique, détaillent les différents fascicules sensitifs lésés, complété par une appréciation électrophysiologique minutieuse qui étudie les composants sensitivo-moteurs pathologiques du nerf médian.

Les tergiversations histologiques (tumeur maligne d'un faisceau nerveux, histiocytome fibreux malin, tumeur maligne pléomorphe épithéloïde, schwannome malin et enfin fibrosarcome de grade intermédiaire) rendent compte de la difficulté à déterminer la nature exacte du processus, expansif afin de planifier correctement l'approche thérapeutique, exérèse étendue, amputation de l'avant-bras et/ou radiothérapie palliative.

Out-patients unit for neuromuscular disorders: a new experience in Lausanne

R. Lettry-Trouillat, Th. Kuntzer (Lausanne)

During the last 3 years, 167 patients and their relatives were examined and investigated in a new consultation devoted to neuromuscular disorders (except for ALS), partially funded by the ASRM (Association Suisse Romande contre la Myopathie). 75% of the patients were new, 20% of the patients were directly referred from the association of patients (ASRM) and 18% of patients were not ill but wanted to know if they were carried the disease gene of an affected family member.

The patients belonged to 4 categories: Group 1 includes cases with an acquired neuromuscular disorder (10%). Group 2 includes those cases with an inherited neuropathy (28%). Group 3 includes patients with inherited myopathy or neuronopathy (52%). Group 4 includes patients with predominant mylagia with no clinical sign of muscle weakness (8%). Diagnosis were based on clinical, biochemical, electrophysiological grounds, study of biopsy and genetic analyses. Whenever possible total management was applied to the patients. Collaborative studies were possible with other services, at the CHUV (pathology, R.C. Janzer; genetic, D. Schorderet; biochemistry, O. Boulat; cardiology, J.J. Goy; rehabilitation, R. Frischknecht; ophalmology, F. Borruat; pneumology, J. Fitting), Inselspital (J.M. Burgunder and S. Liechti), HUG (M. Morris), CMU (C. Bader), INSERM 153, Paris (K. Schwartz), INSERM U289, Paris (E. LeGern, A. Brice) and Genethon, Evry.

Based on our experience, several points can be stressed: (i) such consultations are time consuming for patients (necessity of knowing the extension of the disease, scoring the deficits and discussing genetic counseling), that wouldnit be possible without grants from ASRM. (ii) Special attention should be paid to patients with no diagnosis since diagnostic tools change rapidly in this field. Gathering patients in one center has the double advantage of knowing which is the most recent diagnostic tool or treatment and to gain confidence in those rare disorders. (iii) Progressive motor deficits need repeated rehabilitation care which is to be developed. (iv) Finally, this consultation wouldnit be settled up without the invaluable cooperation of many groups in Switzerland and France.

Levodopa responsive familial Parkinsonian syndrome: correlation of clinical, molecular-genetic, imaging and neuropathological findings

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In some cases, Parkinson's disease is encountered in families, where it is usually transmitted in an autosomal dominant fashion. We present clinical and autopsy findings in a patient successfully treated with levodopa. The family history suggested Parkinson's syndrome with autosomal dominant inheritance. The patient first noticed a slowness of movement with tremor and clumsiness of his right hand at about 60 years of age. Five years later a resting tremor, slight bradykinesia and rigidity was found on the right. He responded well to levodopa. A SPECT scan was performed after the injection of β-CIT, a ligand for dopamine reuptake sites, and a bilateral asymmetric signal decrease was found. In one of his cousins, who also suffered from a levodopa-responsive Parkinson syndrome, a β-CIT SPECT showed a similar pattern. No Synuclein gene mutation was found in DNA extracted from peripheral blood. The patient died after a car accident. The autopsy showed no gross atrophy of the brain. The histological findings confirmed the diagnosis of Parkinson's disease and showed extra-neuronal deposits of melanin pigment in the SN as well as several typical Lewy bodies and «pale bodies». In addition conspicuous smaller eosinophilic, rod-like inclusions were present in several neurons of the SN. The Lewy bodies and the rod-shaped inclusions were immunoreactive for ubiquitin. Occasionally intraneuronal inclusions imunoreactive for α-B-crystallin were detected. There was marked cytoplasmic α-B-crystallin staining of numerous oligodendrocytes in the SN and elsewhere.

In conclusion, we present a case of hereditary Parkinson's disease, not linked to a known synuclein gene mutation with typical clinical and histological features. The search for the responsible mutation is important for deeper understanding of Parkinson's disease in general.

Hépatite fulminante associée à la tolcapone

P. Burkhard, L. Spahr, A. Hadengue, L. Rubbia-Brandt, F. Assal, T. Landis (Genève)

La tolcapone (Tasmar®) est un inhibiteur de la catéchol-O-méthyltransférase récemment commercialisé pour le traitement de la maladie de Parkinson, qui se révèle être efficace et bien toléré. Occasionnellement, le médicament peut induire une élévation transitoire des transaminases hépatiques, mais, à ce jour, aucun cas de toxicité hépatique sévère n'a été rapporté.

Une patiente de 74 ans est connue pour une maladie de Parkinson classique était traitée par lévodopa/bensérazide, amantadine et étiléfrine en raison d'une hypotension orthostatique. Elle était également sous un traitement chronique d'oxazépam, et amiloride/hydrochlorothiazide. Un traitement de tolcapone 2x 100 mg/j est introduit. Neuf semaines plus tard, elle développe une asthénie, un ictère et elle est hospitalisée à la suite d'une chute. A l'admission, elle présente, outre un syndrome parkinsonien akinéto-rigide et trémulant modéré, une somnolence, un ictère franc. Le bilan biologique montre une élévation massive des transaminases et des troubles de la crase. Un examen hémodynamique hépatique relève une hypertension portale et la biopsie confirme une hépatite aiguë sévère d'allure médicamenteuse. Un bilan à visée étiologique est négatif, en dehors de stigmates sérologiques d'une ancienne hépatite A. La proximité temporelle entre l'introduction de la tolcapone et l'hépatite suggère fortement une relation causale. L'évolution est défavorable et la patiente décède en coma hépatique 14 jours après son admission.

A notre connaissance, il s'agit du premier cas de toxicité hépatique létale associée à la tolcapone. Le mécanisme semble être dose-indépendant et idiosyncrasique. Un contrôle régulier de la fonction hépatique apparaît indispensable après l'introduction d'un traitement de tolcapone.

Changes in cerebral activity induced by thalamic and pallidal stimulation for Parkinson's disease

E. Taub, G. Künig, K. L. Leenders, J. Siegfried (Zürich)

To study how deep brain stimulation alleviates parkinsonism, we used $H_2{}^{15}O$-PET to detect changes in rCBF induced by stimulation of the nucleus ventro-intermedius (Vim), the nucleus ventro-oralis posterior (Vop), and the globus pallidus internus (Gpi).

18 patients were studied (6 with stimulation at each site). They took antiparkinsonian medications up to the day of scanning. Images were obtained with stimulation off and on, both at rest and during motor activity. rCBF changes were analyzed by statistical parametric mapping. Clinical effects were assessed by neurological examination.

Results
Clinical: Both Vim and Vop stimulation reduced contralateral tremor, as well as rigidity and akinesia. GPi stimulation reduced contralateral rigidity and akinesia. PET: Vim stimulation lessened rCBF in the ipsilateral precentral gyrus and contralateral cerebellum ($p<0.001$); Vop stimulation had similar effects. GPi stimulation at rest increased rCBF in the ipsilateral precentral gyrus ($p<0.001$); GPi stimulation during motor activity increased rCBF in the contralateral cerebellum ($p<0.005$).

Thalamic and pallidal stimulation thus affect the activity of motor brain areas (motor cortex, cerebellum) in opposite directions-deactivation and activation, respectively. This makes physiological sense, as the GPi-thalamic projection is inhibitory. It remains to be explained how thalamic and pallidal stimulation nevertheless confer similar clinical benefits.

Parkinsonism and chronic subdural hematomas

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Subdural hematomas may be associated with various movement disorders. According to our experience worsening of preexistent movement disorders or new movement disorders occur in about 2% of patients with chronic subdural hematomas (CSH).

We describe three patients with parkinsonian syndromes caused or aggravated by CSHs. The first patient was a 63-year-old man with de novo asymmetric parkinsonian symptoms.

Levodopa treatment was ineffective. The second patient was a 70-year-old man with drug induced parkinsonism. He suffered from deterioration of his movement disorder for two weeks. The third patient, a 82-year-old man had idiopathic Parkinson's disease. CSHs were detected on computed tomography scans in all three patients. Evacuation and drainage of the hematoma resulted in disappearance or amelioration of the parkinsonian syndromes in each case.

There was no history of recent trauma in two of our patients. Diagnostic evaluations appear to be delayed in patients with preexistent movement disorders. The findings of our report and review of the literature suggest that in patients with CSH-related parkinsonian syndromes usually a favourable outcome is achieved after appropriate surgical treatment.

Disturbed functional brain interactions during somatosensory discrimination in Parkinson's disease

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Somatosensory discrimination of oblong rectangular parallelepipeds was studied in a group of healthy volunteers and patients with Parkinson's disease using regional cerebral blood flow (rCBF) measurements by PET and ^{15}O labelled water [$H_2{}^{15}O$]. In addition, a 6-[^{18}F]-fluoro-L-dopa (FDOPA PET) scan was performed in the patients. On categorical comparisons, task induced rCBF increases were deficient in sensorimotor cortex of both hemispheres in the parkinsonian patients, and, in particular, in right medial and dorsolateral prefrontal cortex in a subgroup of patients with low FDOPA-uptake in caudate nucleus. Additionally, in a principal component (PC) analysis of the rCBF data, without a priori assumption, three patterns were revealed that differentiated patients from controls. These PCs were classified according to the supposed pattern function. PC A represented a bihemispheric array of areas known to be involved in tactile exploration with a right hemispheric preponderance. The shift of the interrelated areas to the right hemisphere, in parallel to sucessful task performance, suggested explicit information processing. PC B delineated a subcortical-cortical interrelation emphasizing the importance of outflow from subcortical relay nodes to prefrontal cortex, being of significance for working memory. PC C contained temporo-parieto-occipital association cortices on both sides, suggesting intermodal somatosensory-visual information transfer for final shape discrimination.

Zirkadiane molekulare Rhythmen in der Substantia nigra: Erklärung der schlafinduzierten Besserung der Parkinsonsymptomatik (sleep benefit)?

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Zirkadiane Schwankungen der Symptomausprägung bei M. Parkinson mit Zunahme der Beschwerden gegen Abend sind ein bekanntes Phänomen. 10-50% der Parkinson-Kranken zeigen zudem eine ausgeprägte subjektive Besserung der Symptomatik direkt nach dem Erwachen (sleep benefit), die bis zu einigen Stunden anhält. Bisherige Erklärungsversuche dieser Reaktion, wie beispielsweise durch pharmakodynamische Phänomene oder Dopaminspeicherung während des Schlafes sind unvollständig.

Um die Rolle zirkadianer endogener Faktoren im Hinblick auf den «sleep benefit» abzuklären, wurde die Expression verschiedener Neuropeptide und Neurotransmitter in der Substantia nigra der Ratte mittels in situ-Hybridisierung untersucht. Eine ausgeprägte zirkadiane Rhythmik der Expression der Tyrosinhydroxylase, des Dopamin-synthetisierenden Schlüsselenzyms, konnte beobachtet werden: die Expression war tagsüber zunehmend verstärkt mit einem Beginn in den frühen Morgenstunden und einem Maximum am Spätnachmittag.

Parkinson-Erkrankte leiden unter einer stark herabgesetzten endogenen Dopamin-Produktion (<10-20%). Wir schliessen aus unseren Daten, dass morgens, wenn das Aktivitätsniveau des Dopaminsystems noch niedrig ist, die in Gang kommende endogene Restproduktion zur Besserung der Symptomatik ausreicht, während der tagsüber höhere Dopamin-Bedarf nicht mehr gedeckt werden kann. Der «sleep benefit» ist also zumindest teilweise auch als Folge der tageszeitlich unterschiedlichen Dopaminproduktion zu werten.

Lymphedema, lymphatic microangiopathy and increased lymphatic and interstitial pressure in a patient with Parkinson's disease

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New microvascular findings of a female patient with Parkinson's disease and lower leg edema are presented. The network of lymph capillaries was visualized by fluorescence microlymphography at the distal tibia on both legs. 0.01 ml of FITC-Dextran 150'000 was injected into the subepidermal layer of the skin. The examination was registered using fluorescence video microscopy. Morphologic details were recorded in a 62x final magnification. Dynamic pressure within the lymph capillaries and the interstitial tissue of the skin were measured by a servo-nulling micropressure system (IPM, San Diego) in supine position at the malleolar region of the right leg.

Microlymphography revealed a maximum spread of the fluorescent contrast medium in the microlymphatics with 17 mm on the left leg and 18 mm on the right leg (Controls <12mm). The detailed capillary morphology showed abundant cut-offs, capillary fragments, changes in capillary diameters (mean 107 mm, range 83-188 mm) and increased leakiness of the capillaries. The microlymphatic as well as the interstitial pressures of the skin were increased (27.1 mmHg, resp. 15.5 mmHg). The increased interstitial and microlymphatic pressure are the result of an insufficient venous and lymphatic drainage due to the impairment of the calf muscle function during walking in Parkinson's disease. Manual lymph drainge and compression therapy in combination with improvement of the calf muscle function resulted in regression of the edema.

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Adenosine A2a receptors in the striatum: mRNA distribution in normal brain and in an animal model of Parkinson's disease

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Adenosine is a well-known extracellular neuromodulator. Several recent evidences suggest an important physiological function of adenosine A2a receptors (A2aR) in the striatum. Stimulation of striatal A2aR induces depression of locomotor activity. In order to better understand the function of A2aR in the mammalian striatum we have compared its gene expression in different mammalian species (cat, mouse, rat, human) using hybridization histochemistry with a S35-labelled radioactive oligonucleotide probe. A2a receptor gene expression was further investigated after lesion of the rat substantia nigra with 6-OH-dopamine, a well-known animal model of Parkinson's disease. The results showed high expression of A2aR mRNA only in the medium sized GABA- and enkephalinergic striatal cells in all examined species. In the rat striatum, expression of A2a receptors was not significantly changed after lesion of the dopaminergic pathways with 6-OH-dopamine in spite of up-regulation of enkephalin mRNA. These results confirm the important function of A2aR in the mammalian basal ganglia. The absence of modulation of A2a receptor gene expression in the 6-OH-Dopamine speaks against a dependency on dopaminergic innervation. The unaltered inhibitory function of A2aR on motor activity in spite of dopamine depletion could be partly responsible for the depression of locomotor activity observed in Parkinson's disease. A2aR antagonists could be new antiparkinson agents.

A family with mitochondrial encephalomyopathy with mutation of the T9883C gene

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The clinical manifestation of mitochondrial encephalomyopathy is very heterogenous. We present a swiss family (n=20) in which we found in 9 persons of the first and second generation evidence of mitochondrial encephalomyopathy. The main clinical symptoms were gait difficulties (n=9), exercise induced myalgia/cramps (n=7) and stuttering (n=5). In the neurological examination we found spasticity and ataxia (n=9), calf atrophy (n=4), sensory disorder (n=3) and eye movement disorder (n=3).

Two patients have been electrophysiologically examined. in both cases we found pathological MEP and in one case pathological SSEP and mild peripheral neuropathy. The brain MRI of this two patients were normal. In one biopsy of M. vastus lateralis were found paracristalline inclusion bodies.

Molecular genetic analysis showed a T to C point mutation of mitochonrial DNA at position 8993. This gene encodes the ATPase-6 complex V of the respiratory chain.

Conclusion: The point mutation T8993C we detected in the presented family seems to be a milder variant of the more frequent T8993G mutation, found in Leigh-Disease and NARP-Syndrome. These findings underline the heterogenity of the mitochondrial encephalomyopathy.