دوازدهمین سمینار سالیانه

نورومتابولیک

۱۷ و ۱۸ آذر ۱۴۰۱ / اصفهان

کتابچه چکیده مقالات

دوازدهمین سمینار سالیانه نورومتابولیک

Neurotransmitters Disorders & Neuroimaging

Address: Pediatric Neurology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Iranian Neurometabolic Society

2rd floor, Official Building, Mofid Children Hospital, Tehran, 1546815514, Iran Tel & fax: +98 21 22909559

Website: http://Neurometabolic.ir email: Neurometabolic.IRNMD@gmail.com

انجمن علمی نورومتابولیک ایران

تهران، خیابان شریعتی، بالاتر از حسینیه ارشاد، بیمارستان کودکان مفید، ساختمان اداری، ط. دوم، دفتر گروه اعصاب تلفن و فاکس: ۲۲۹۰۹۵۵۹، صندوق پستی: ۱۵۴۶۸۱۵۵۱۴


بسم الله الرحمن الرحيم

فهرست مطالب:

پوستر سمینار

سخن آغازین

خداوند بزرگ را شاکریم که شاهد برگزاری دوازدهمین سمینار سالیانه نورومتابولیک هستیم. سمینار سالیانه نورومتابولیک تابحال هرسال در آذرماه برگزار گردیده و هر سال یک عنوان مرتبط در نظر گرفته شده است. در ۲ سال اخیر به دلیل مشکل پاندمی کرونا مجبور به برگزاری سمینار به صورت مجازی بودیم و امسال پس از فروکش نمودن پاندمی کوید، اولین سالی است که مجددا سمینار سالیانه را به صورت حضوری برگزار می نماییم. امسال برآن شدیم تا سمینار سالیانه را در شهر تاریخی اصفهان برگزار نماییم تا در کنار شرکت در بحث علمی، شرکت کنندگان بتوانند از زیبایی ها و آثار تاریخی شهر اصفهان نیز بازدید نمایند و از همه مهم تر همکاران شاغل در دانشگاه علوم پزشکی اصفهان نیز در این مهم حضور بهم رسانند.

امسال سمینار در ۲ روز برگزار می گردد که روز اول اختصاص به بحث نوروترانسمیترها داده شده و با سخنرانی های کلیدی و معرفی case به بحث و بررسی در این مورد می پردازیم. روز دوم سمینار به بحث Neuroimaging اختصاص دارد و با سخنرانی های کلیدی و پانل های متعدد به معرفی موارد اختصاصی Neuroimaging در هرکدام از شاخه ی بیماری نورومتابولیک می پردازیم.

این سمینار جهت همکاران فوق تخصص مغزواعصاب کودکان ، فوق تخصص غدد و متابولیسم کودکان، فلوهای فوق تخصصی مرتبط با رشته های فوق، متخصصین مغز و اعصاب، همکاران متخصص رادیولوژی، متخصصین ژنتیک پزشکی و متخصصین اطفال برگزار شده و امیدوارم مفید فایده واقع شود.

در پایان از زحمات جناب آقای دکتر اشرفی، جناب اقای دکتر احمدآبادی، جناب آقای دکتر ساکت، اعضای محترم هیئت مدیره انجمن علمی نورومتابولیک ایران، سرکار خانم فرزانه نوربارن و جناب آقای دکتر یقینی و اسپانسرهای محترم سمینار که اگر آن ها حضور نداشتند این سمینار برگزار نمی گردید، صمیمانه سپاسگزارم.

امیدوارم شمارا در اصفهان و دوازدهمین سمینار سالیانه نورومتابولیک ملاقات نمایم.

دکتر پروانه کریم زاده

استاد دانشگاه علوم پزشکی شهید بهشتی

رئیس انجمن علمی نورومتابولیک

درباره ی انجمن

پایه گذاری **انجمن علمی نورومتابولیک ایران** از سال ۱۳۹۱ در بیمارستان کودکان مفید صورت گرفت لیکن فعالیت اصلی انجمن پس از تصویب از سال ۱۳۹۴ آغاز و پی ریزی شد. اهداف انجمن شامل اهداف آموزشی، پژوهشی و درمانی بوده و استراتژی طولانی مدت در راستای اهداف انجمن طراحی شده است. در راستای این اهداف استراتژیک چشم انداز آینده انجمن برای سال ۱۴۰۵ رسیدن به رتبه بهترین و بالاترین انجمن کشور از نقطه نظر پژوهشی و آموزشی می باشد. این انجمن با اعضای تایید شده۷۵ نفری و اعضای در انتظار تایید ۸۰ نفری خود یکی از انجمن های بین رشته ای می باشد که می تواند پاسخگوی قسمتی از نیاز های آموزشی و پژوهشی رشته های مغز و اعصاب، ژنتیک و غدد باشد. ضمن اینکه ارتباط تنگاتنگی با رشته های رادیولوژی، پاتولوژی و علوم تغذیه و طب فیزیکی و توان بخشی دارد.

در رابطه با عملکرد انجمن برگزاری جلسات هفتگی معرفی Case که به صورت مستمر در سه سال اخیر بدون وقفه ادامه یافته است، جلسات ماهیانه نورومتابولیک و نهایتاً ۱۱ دوره کنگره سالیانه نورومتابولیک است که حتی پیش از شروع به کار رسمی انجمن از سال ۱۳۹۱ برگزار گردیده است.

لیست اعضای هیئت مؤسس انجمن: خانم دکتر پروانه کریم زاده، آقای دکتر محمودرضا اشرفی، آقای دکتر فرزاد احمدآبادی، آقای دکتر مسعود هوشمندویژه، آقای دکتر محمدرضاعلایی، آقای دکتر سعید طالبی، خانم دکتر فاطمه سرخیل، خانم دکتر مرجان شکیبا

برنامه دوازدهمین سمینار سالیانه نورومتابولیک ایران

عنوان: Neurotransmitters disorders & Neuroimaging

تاریخ :۱۸ و ۱۷ آذر ماه ۱۴۰۱ (دارای امتیاز بازآموزی)

۱۴۰۱/۹/۱۷			
Neurotransmitters disorders			
ردیف	زمان	عنوان	نام سخنران
۱	۸:۵۰-۹:۰۰	**سرود و قرآن**	
۲	۹:۰۰ -۹:۱۰	خیر مقدم	**دکترپروانه کریم زاده**
۳	۹:۱۰-۹:۳۰	کلیات اختلالات نوروترانسمیتری	**دکترپروانه کریم زاده**
۴	۹:۳۰-۹:۵۰	اختلالات حرکتی در نوروترانسمیتر	**دکتر فرزاد احمدآبادی**
۵	۹:۵۰-۱۰:۱۰	بررسیهای آزمایشگاهی در اختلالات نوروترانسمیتری	**دکتر مرجان شکیبا**
Break 10:10- 10:30			
۶	۱۰:۳۰-۱۱:۱۵	پانل اختلالات نوروترانسمیتر مرتبط با متابولیسم آمینو اسید	**دکتر سعید انوری - دکتر ساسان ساکت- دکتر تکتم موسویان-**
۷	۱۱:۱۵-۱۲:۰۰	پانل ژنتیک در نوروترانسمیتر	**دکتر حسین نجم آبادی - دکتر محمد کرامتی پور- دکتر محمد میریونسی**
9	۱۲:۰۰-۱۲:۴۵	پانل وضعیتهای کمبود نوروترانسمیترهای مونو آمینرژیک همراه افزایش فنیل آلانین	**دکتر هدیه صانعی فرد- دکترشاداب صالح پور- دکتر سامان ناهید**
نماز و نهار ۱۲:۴۵ -۱۳:۳۰			
۱۱	۱۳:۳۰-۱۳:۴۵	معرفی مورد	**دکتر پری ناز حبیبی- دکتر مرضیه بابایی**
۱۲	۱۳:۴۵-۱۴:۰۰	معرفی مورد	**دکتر شهرام نصیری**
۱۳	۱۴:۰۰-۱۴:۱۵	معرفی مورد	**دکتر میثم بابائی**

۱۴۰۱/۹/۱۸			
Neuroimaging			
ردیف	زمان	عنوان	نام سخنران
۱	۸:۵۰-۹:۰۰	**سرود و قرآن**	
۲	۹:۰۰-۹:۳۰	MRI in Neurometabolic Disorders	**دکتر محمودرضا اشرفی**
۳	۹:۳۰-۱۰:۰۰	MRS in Neurometabolic disorders	**دکتر الهام رحیمیان**
۴	۱۰:۰۰-۱۰:۳۰	Neuroimaging in Leukodystrophy	**دکترمیترا خلیلی**
Break 10:30-11:00			
۷	۱۱:۰۰-۱۱:۳۰	Neuroimaging in organic acidemia	**دکتر آزیتا توسلی- دکترلادن افشار خاص- دکتر مریم کچوئی**
۸	۱۱:۳۰-۱۲:۰۰	پانل MRI در بیماریهای میتوکندریال	**دکتر شروین بدو- دکتر مرتضی حیدری- دکتر محمد وفائی شاهی**
نماز و نهار ۱۲:۰۰ -۱۳:۰۰			
۹	۱۳:۰۰-۱۳:۱۵	Case Presentation	**دکتر محمدمهدی تقدیری-دکتر یلدا نیلی پور**
۱۰	۱۳:۱۵-۱۳:۳۰	Case Presentation	**دکتر آیدین تبریزی**
۱۱	۱۳:۳۰-۱۴:۰۰	**Ending Ceremony**	---

رئیس سمینار: دکتر پروانه کریم زاده دبیر علمی سمینار:دکتر فرزاد احمدآبادی دبیر اجرایی سمینار: دکترساسان ساکت

برگزار کنندگان و حامیان سمینار

برگزار کنندگان:

- **انجمن علمی نورومتابولیک ایران**

- **دانشگاه علوم پزشکی اصفهان**

- **انجمن علمی اعصاب کودکان ایران**

- **دانشگاه علوم پزشکی شهید بهشتی تهران**

	حامیان	رتبه
۱.	شرکت شفایاب گستر	طلایی
۲.	آزمایشگاه فرزانگان	طلایی
۳.	شرکت پرتو طب حقیقت	نقره ای
۴.	شرکت اشبال شیمی	نقره ای
۵.	شرکت داروسازی مداوا	نقره ای
۶.	شرکت مدیسا آرا گستر	برنزی
۷.	شرکت کوبل دارو	برنزی
۸.	شرکت زیست تخمیر	برنزی
۹.	شرکت اهران تجارت	برنزی
۱۰.	شرکت سامان دارو سلامت	برنزی
۱۱.	شرکت روژین فارمد	برنزی


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آزمایشگاه فرزانگان: مرکز تخصصی غربالگری و تشخیص بیماری‌های متابولیک ارثی

دپارتمان فوق تخصصی متابولیک آزمایشگاه تشخیص طبی فرزانگان با بیش از ده سال تجربه در زمینه غربالگری و تشخیص بیماری‌های متابولیک ارثی، در حال ارائه خدمات تخصصی به مراکز درمانی و آزمایشگاهی در عمده نقاط کشور می باشد.

آزمایشگاه فرزانگان با بهره‌گیری از کادر متخصص و مجرب و همچنین با به کارگیری تجهیزات پیشرفته و مدرن آزمایشگاهی نظیر LC-MS/MS و GC-MS به عنوان اولین آزمایشگاه Biochemical Genetics درکشور شناخته می‌شود که کاملترین مجموعه تست‌های تشخیصی در حوزه بیماریهای متابولیک ارثی را دارا می باشد. یادآور می‌شود آزمایشگاه فرزانگان به عنوان همکار معاونت بهداشتی جهت اجرای برنامه کشوری غربالگری بیماری‌های متابولیک ارثی نوزادان و مرکز تایید تشخیص این برنامه انتخاب گردیده است.

از جمله رویکردهای نوین آزمایشگاه فرزانگان می‌توان به موارد زیر اشاره نمود:

۱- ترغیب پزشکان جهت درخواست تست های تشخیصی به جای تست‌های غربالگری برای بیماران علامت‌دار
۲- استفاده از جدیدترین روشها جهت اندازه گیری مجموعه کامل آنالیت های قابل اندازه‌گیری و جایگزینی روش‌های نوین

(به عنوان مثال اندازه‌گیری پروفایل کامل اسیدهای آمینه به روش نوین LC-MS/MS به جای روش سنتی HPLC)

۳- ارتباط نزدیک متخصصین بیوشیمی این مرکز با پزشکان متخصص و ارائه تفسیر جامع جهت تسهیل و تسریع روند تشخیص
۴- ارائه خدمات قابل اطمینان، سریع و منصفانه با رعایت اصول اخلاق حرفه‌ای
۵- تلاش در راستای جوابدهی دقیق در زمینه تشخیص بیماری‌های متابولیک ارثی، جلب رضایت بیماران و پزشکان

قابل ذکر است مدیریت این مرکز در راستای دستیابی به اهداف فوق متعهد به استقرار، اجرا و بهبود مستمر الزامات سیستم مدیریت کیفیت بر مبنای استانداردهای INSO-ISO-15189: 1393 و ISO 9001: 2015 و آزمایشگاه‌های پزشکی ویرایش سال ۱۳۹۷ آزمایشگاه مرجع سلامت است و همچنین پذیرای نظرات، انتقادات و پیشنهادات اساتید و همکاران عزیز می‌باشد.

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معرفی مرکز تحقیقات تصویربرداری حقیقت

مرکز تحقیقات تصویربرداری پزشکی حقیقت(خصوصی)، با بهره گیری از امکانات، نرم افزارها و دستگاه های مرکز تصویربرداری پزشکی حقیقت، تجربه های علمی و ارزشمند اعضای شورای پژوهشی، متخصصین، اعضای هیات علمی و دانشجویان دکتری و مقاطع تحصیلات تکمیلی، به دنبال گسترش تحقیقات در زمینه تصویربرداری و حوزه های مرتبط است. این مرکز تصویربرداری، با سابقه خدمت ۱۴ ساله تا کنون بالغ بر ۱۰۰ هزار خدمت تصویربرداری اعم از MRI، CT Scan، و سایر مدالیته های تصویربرداری به هموطنان ارائه نموده است و با دسترسی به اطلاعات مرتبط به این تصویربرداری ها، دارای بانک بزرگ اطلاعاتی تصویربرداری، در حوزه های تشنج،بیماریهای نورومتابولیک و بیماریهای مادرزادی ، تومور های مغز و نخاع، بیماری های عروقی مغز، بیماری های نخاعی و... می باشد و تحقیقات خود را بر پایه این بانک بزرگ اطلاعاتی قرار داده و برای جستجو در این بانک بزرگ، نرم افزاری را طراحی کرده که قابلیت جستجو بین تصاویر و اطلاعات ثبت شده و دسته بندی اطلاعات را دارد.

لازم به ذکر است که، این مرکز تحقیقات به پشتوانه محققین داخل و خارج از کشور، به جدید ترین و بروز ترین نرم افزار های تشخیصی دسترسی دارد و علاوه بر توانایی تولید علم به روز، زمینه همکاری با مراکز تحقیقات خارج از کشور و تولیدات مشترک را با آن ها فراهم می کند.

علاوه بر این بانک اطلاعاتی دقیق و کاملی، بالغ بر ۳۰ هزار پرونده، از بیماران سرطان پستان در این مرکز گرد آوری شده که قابل استفاده توسط پژوهشگران علاقه مند به حیطه تصویربرداری سرطان پستان در کشور می باشد.

در زمینه "Advanced Neuro -imaging ,related softwares and pre-surgical Imaging" این مرکز تحقیقات، در ایران پیشرو بوده و بانک اطلاعاتی بزرگی، شامل شرح حال بیماران، انواع

تصویربرداری های تخصصی مغز و post-processing صورت گرفته بر این دیتا ها و پاتولوژی و در نهایت نتیجه حاصل از جراحی در این بیماران را در اختیار دارد. بدین ترتیب این مرکز تحقیقات با فراهم آوری زیرساخت های لازم بنا دارد، زمینه همکاری با پژوهشگران حیطه تصویربرداری پزشکی را فراهم کند.

تعهد ما، تامین، حفظ و ارتقای سلامت جامعه، و ارتقای اطلاعات و دانش به روز در حیطه تصویربرداری، تبیین نقش تصویربرداری در تشخیص بیماری های نادر از طریق تحقیقات مبتنی بر شواهد علمی، مشارکت بیماران، و آموزش و توانمند سازی پژوهشگران می باشد.

این مرکز قصد دارد که با انجام پژوهش های کاربردی و انتشار آن در حیطه تصویربرداری با تاکید بر اصل "تکیه بر شواهد علمی و روشمندی علمی" و با حمایت پژوهشگران و همکاری با مراکز تحقیقات داخلی و خارجی، همگام با مراکز تحقیقات تصویربرداری پزشکی مطرح جهان قدم بردارد و بدین ترتیب مراکز درمانی، پزشکان، جراحان و بیماران گرانقدر، از تولیدات علمی و نرم افزاری حاصل از این تحقیقات در جهت تشخیص به موقع بیماری ها و بهبود آن بهره ببرند.

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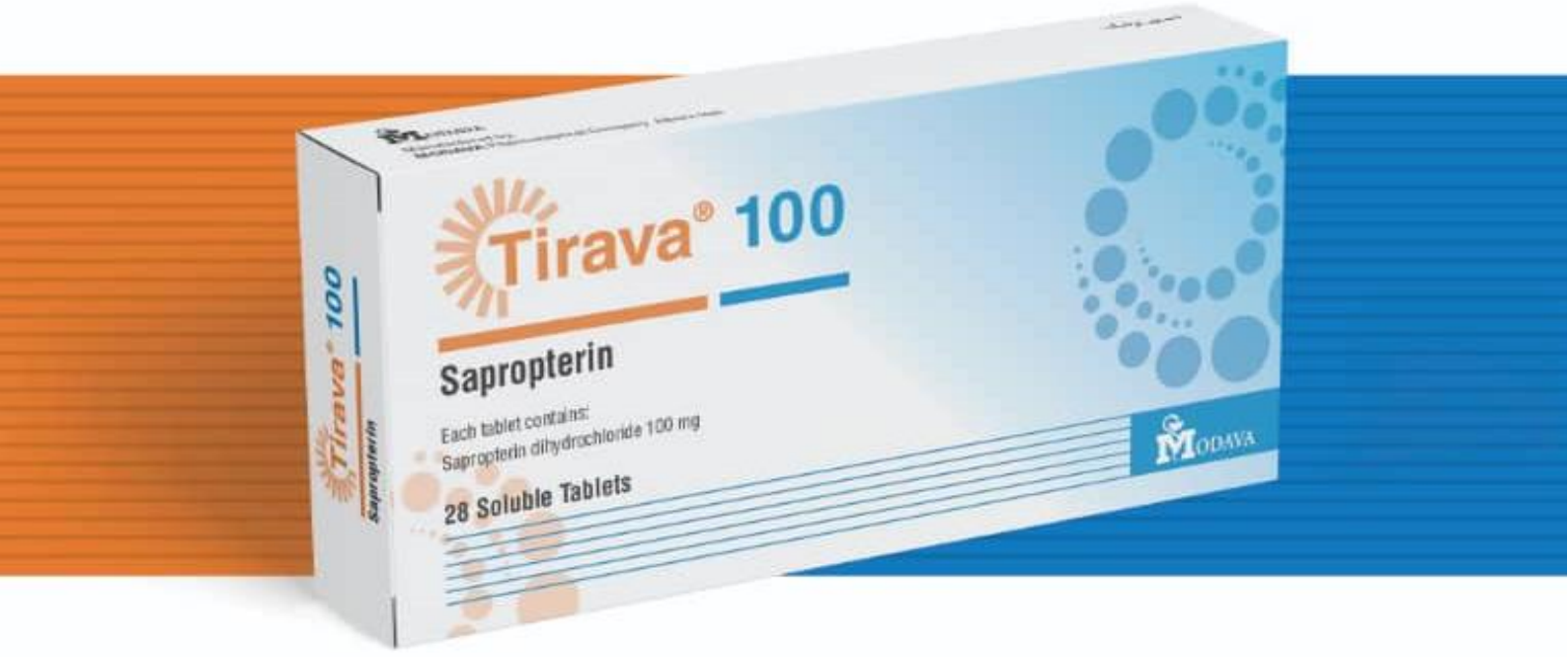

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References
1. Epilepsia. 2010; 51(6): 958-967.
2. Novel Treatment of Epilepsy. 2011;14.
3. Lacosamide, FDA label 2019; Reference ID: 4447215.

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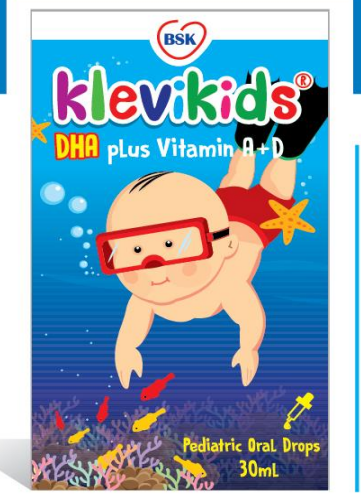

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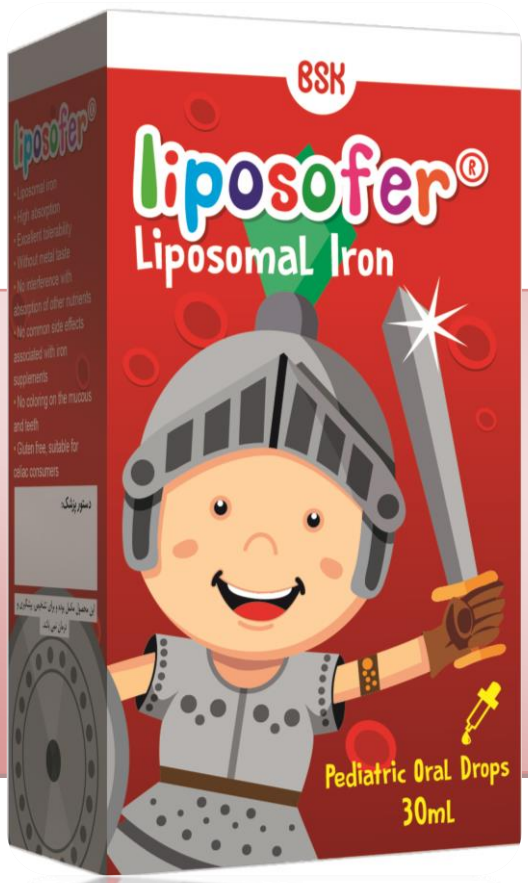

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Probiotic Blend: 10^9 CFU

Other Ingredients:
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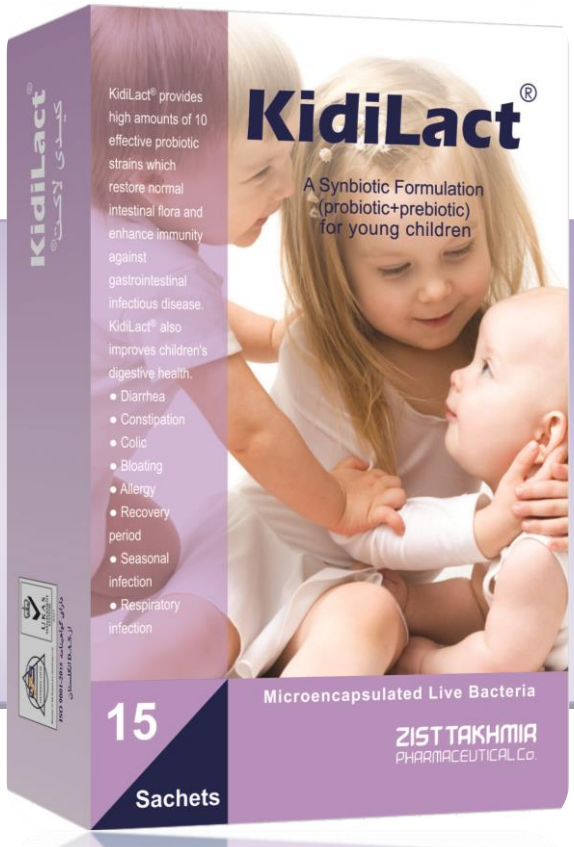

Abstracts

Neurotransmitter Disorders in Pediatric Neurology Patients

Parvaneh Karimzadeh MD, Professor of Pediatric Neurology, Shahid Beheshti University of Medical Sciences, Mofid Children Hospital, Tehran/Iran

Neurotransmitters are substances which neurons use to communicate with one another and with their target tissues in the process of synaptic transmission (neurotransmission). Neurotransmitters are synthetized in and released from nerve endings into the synaptic cleft.From there, neurotransmitters bind to receptor proteins in the cellular membrane of the target tissue.The target tissue gets excited, inhibited, or functionally modified in some other way.

There are more than 40 neurotransmitters in the human nervous system; some of the most important are acetylcholine, norepinephrine, dopamine, gamma-aminobutyric acid (GABA), glutamate, serotonin, and histamine.

Excitatory neurotransmitters cause depolarization of the postsynaptic cells and generate an action potential; for example, acetylcholine stimulates muscle contraction. Inhibitory synapses cause hyperpolarization of the target cells, leading them farther from the action potential threshold, thus inhibiting their action; for example, GABA inhibits involuntary movements.

Pediatric Neurotransmitter Diseases (PNDs), Patients with PNDs typically present in infancy or early childhood, though presentation can occur at any age.

Monoamine neurotransmitter disorders,are important genetic syndromes that cause disturbances in catecholamine (dopamine, noradrenaline and adrenaline) and serotonin homeostasis.These disorders result in aberrant monoamine synthesis, metabolism and transport.The clinical phenotypes are predominantly neurological, and symptoms resemble other childhood neurological disorders, such as dystonic or dyskinetic cerebral palsy, hypoxic ischemic encephalopathy and movement disorders.Monoamine neurotransmitter disorders are under-recognized and often misdiagnosed.DiagnosisRequires detailed clinical assessment, cerebrospinal fluid neurotransmitter analysis and further supportive diagnostic investigations.The treatment is usually mechanism-based, with the aim to reverse disturbances of monoamine synthesis and/or metabolism. Therapeutic intervention can lead to complete resolution of motor symptoms in some conditions improve quality of life in others.

Common symptoms seen in this group of conditions are:

Encephalopathy, developmental delay, developmental regression, central hypotonia, peripheral hypertonia, autonomic dysfunction, diurnal variation in sy

mptoms with severity worsening later in the day, seizures, and abnormal movements (unilateral or asymmetric limb dystonia, progressive gait dysfunction, hypokinesia, rigidity, postural tremor, involuntary tongue thrusting, oculogyric crises, myoclonus, and chorea).

'Red flag' symptoms of monoamine neurotransmitter disorders include diurnal variation of symptoms, a mixed movement disorder, autonomic disturbance, involvement of the eyes (ptosis, oculogyric crisis) and levodopa responsiveness.Analysis of CSF neurotransmitter levels aids identification of the specific monoamine pathway defect and is vital for accurate diagnosis of most primary neurotransmitter disorders and selection of appropriate disease-specific pharmacotherapy.Discoveries of novel genetic defects and biomarkers in monoamine neurotransmitter disorders, together with novel disease models, will improve our understanding of pathophysiological mechanisms and facilitate the development of new treatments.

Abnormal Movements in Neurotransmitter Disorders

F Ahmadabadi ,Mofid Childrens Hospital, SBMU

Neurotransmitter disorders are defects of neurotransmitter metabolism releasing and transport. Neurologic symptoms associated with them are broad and range from extremely mild and subtle alterations in mood or gait to a classic exercise-induced dystonic gait. In others neurologic symptoms are often more severe even life threatening

They include defects of catecholamine (dopamine, epinephrine and norepinephrine), serotonin, biopterin, glycine, pyridoxine and gamma amino butyric acid (GABA) metabolism.

Two cofactors are required for the synthesis of dopamine and serotonin: tetrahydrobiopterin and pyridoxal 5′-phosphate The cerebrospinal fluid (CSF) diagnostic metabolites used for diagnosis of defects of tetrahydrobiopterin metabolism are tetrahydrobiopterin, biopterin, and neopterin.

Movement disorders are an important group of neurological diseases in children. They include developmental movement disorders, hyperkinetic movement disorders, hypokinetic movement disorders, and paroxysmal movement disorders. Many movement disorders may also be associated with other neurological diseases, such as epilepsy or neurometabolic diseases. Neurotransmitter diseases are another group of neurological diseases that may be associated with different movement disorders in children.

We will try to introduce some of mentioned disorders and their movement problems .

For example, AADC deficiency can cause movement disorders in patients of all ages, from newborns to adults.

Common movement disorders reported in AADC deficiency are Dyskinesia, Bradykinesia ,tremor ,Dystonia, myoclonus and oculogyric crisis.

Neuroimaging in leukodystrophy

Mitra Khalili, Radiology Department , Mofid Children Hospital, Shahid Beheshti University of Medical Science

Disorders that mainly affect the white matter are generally referred to as "leukoencephalopathy" or "white matter disorders" . leukodystrophies are defined as inherited disorders affecting the white matter of central nervous system with or without peripheral nervous system involvement.

White matter disorders in children are extensive, complex and challenging to learn. Before interpreting to white matter disorder, myelination milestone should be considered.It is important to know in six months of life T1 weighted imaging is the best sequence for evaluating myelination and T2 weighted sequence is useful after that.

Imaging especially MRI have a key role in imaging and help for correct diagnosis besides clinical and laboratory findings. Some sequences such as long TR sequences and diffusion weighted imaging are the most important sequences for definition of lesions. Use of intravenous contrast and MR spectroscopy maybe helpful in some situation. Having an approach in MRI is essential to lessen differential diagnosis. The first step is defining subcortical or deep white matter involvement. In the setting of sub cortical involvement concomitant macrocephaly and deep gray matter involvement are helpful distinguishing factors. In deep white matter disorders, involvement of thalamus and brain stem are important clues for differential diagnosis. In this presentation , there is a cased-based review in different leukodystrophies in pediatrics.

Glutaric aciduria type 1

Azita Tavasoli, Pediatric Neurologist, IUMS

Glutaric aciduria type 1 (GA1) is a rare neurometabolic disorder of lysine, hydroxylysine and tryptophan metabolism caused by deficiency of the mitochondrial enzyme, glutaryl CoA dehydrogenase (GCDH). This deficiency results in accumulation of the neurotoxic products of glutaric acid: glutaconic acid, 3-hydroxyglutaric acid and glutarylcarnitine. The disorder have a world-wide birth prevalence of 1 in 100,000. The clinical presentation is very variable, even within families . Macrocephaly is present at birth or shortly after birth in most cases. Untreated individuals usually develop acute encephalopathic crises with neurological deterioration and regression during the first 3 years of life that are triggered by infectious diseases, vaccinations, and surgery. These crises result in bilateral striatal necrosis with dystonia, orofacial dyskinesia, and choreathetosis. In some patients, neurologic disease may develop without clinically apparent crises. *Late onset* GA1 refers to diagnosis after 6 years of life and symptoms are nonspecific, including headache, memory loss, dysarthria, weakness, epilepsy and difficulty with co ordination.

GA1 can be suspected by clinical presentation or neuroimaging findings. The typical widening of Sylvian fissures with micrencephalic macrocephaly is suggestive. CT can show early frontotemporal atrophy with enlarged pretemporal subarachnoid spaces and the Sylvian fissures often showing a “batwing” configuration. Other findings include: hypoattenuation of the lentiform nuclei and cerebral hemispheric white matter, ventricular dilatation, generalized cerebral atrophy, and communicating hydrocephalus. widening of the subarachnoid space can lead to tension on bridging veins which in turn are more susceptible to rupture, even after minor trauma, leading to subdural hematomas. This may trigger an evaluation for child abuse. The key to correct diagnosis is the recognition of other imaging characteristics of GA 1. Diagnosis relies on the identification of glutaric and 3-hydroxyglutaric acid in urine along with plasma glutarylcarnitine and confirms by genetic study. Metabolic treatment, consisting of low lysine diet, carnitine supplementation, and intensified emergency treatment during catabolism, is effective treatment and improves neurologic outcome in those individuals diagnosed early.

Neuroimaging approach to Inborn Errors of Metabolism

Mahmoud Reza Ashrafi, Professor of Pediatric Neurology, Children's Medical Center, Pediatrics Center of Excellence. Tehran University of Medical Sciences

Sir Archibald Edward Garrod (25 November 1857 – 28 March 1936) introduced the concept of Inborn Errors of Metabolism (IEM) at the turn of the 20th century (1908) in Royal College of Physicians of London. Around 1000 genetic defects related to Synthesis, Metabolism, Transport and Storage of biochemical compounds have been identified.

The role of neuroimaging in Inborn Errors of Metabolism (IEM) is manifold, and includes : raising the possibility of a metabolic disease process, narrowing down the differential diagnoses based on pattern recognition, occasionally providing a specific diagnosis and role in prognostication and follow-up . Early diagnosis is crucial in many of these conditions to prevent or minimize brain damage. Whilst many of the neuroimaging features are nonspecific, certain disorders demonstrate specific patterns due to selective vulnerability of different structures to different insults. Along with clinical and biochemical profile, neuroimaging thus plays a pivotal role in differentiating metabolic disorders from other causes, in providing a differential diagnosis or suggesting a metabolic pathway derangement, and on occasion also helps make a specific diagnosis. This allows initiation of targeted metabolic and genetic work up and treatment. Neuroradiological features of many IEM overlap and are stage-dependent.

Patients occasionally show distinctive patterns of central nervous system involvement in magnetic resonance imaging (MRI).These patterns may characterize some disorders, especially during the early stages, or they can show guiding characteristics, or reveal non-specific changes.In later phases, the MRI findings are similar for most IEM with neurological involvement, often presenting diffuse loss of brain tissue. For this reason, it is important to perform brain MRI early in the course of the disease, when some key features are more evident.

Pyridoxine-dependent epilepsy: a case report

salman baratzadeh rofoogar, MD [1];**Parvaneh Karimzadeh**,MD[2];**Meisam Babaei**, MD[3*]

pyridoxine-dependent epilepsy: a case report

salman baratzadeh rofoogar, MD [1];Parvaneh Karimzadeh**,**MD[2];Meisam Babaei, MD**[3*]**

Introduction:

Pyridoxine-dependent epilepsy (PDE) is a rare autosomal recessive encephalopathy due to mutations in the ALDH7A1 that present in early childhoodwith recurrent seizures that resistant to thecommon antiseizure medications but often responded to pyridoxine.

Case presentation:

Here we report a 6-year-old female patient presented to our hospital with status epilepticus. Her seizures were started since neonatal period often by status clinical feature.Similar clinical presentation lead to death in hertwo siblings. Her seizures could not be controlled with appropriate antiseizure treatment but there was good response to Pyridoxine trial. The diagnosis of PDE was considered and genetic study revealed ALDH7A1 gene mutation,a homozygous missense mutation. By pyridoxine administration, there was dramatic response and significant decrease in her seizures, and

Conclusion:

As a result, PDE should be considered especially in positive history of recurrent status epilepticus and poor response to treatment.

Key words:

Pyridoxine dependent epilepsy, children

Methylmalonic academia and brain imaging findings

Dr Ladan Afsharkhas,Pediatric Neurologist,IUMS

Methylmalonic acidemia (MMA) is a lethal, severe, heterogeneous disorder of methylmalonate and cobalamin (cbl; vitamin B12) metabolism with a poor prognosis.Defects in methylmalonyl-CoA mutase (MCM) or its coenzyme, cobalamin, lead to the accumulation of methylmalonic acid, which is characteristic of MMA.Common features of the isolated MMA are failure to thrive, developmental delay, megaloblastic anemia, and neurologic dysfunction. Those genetic forms with mutations of Mut0, cblA, and cblB, often present in the first days to weeks of life with poor feeding, dehydration,increasing lethargy, emesis, and hypotonia. Metabolic acidosis and secondary hyperammonemia, may be catastrophic. Mild forms of MMA may present later in infancy or in childhood with hypoglycemia, acidosis, seizures, and lethargy.A patient with cblC disease can present early in infancy with signs and symptoms of metabolic decompensation, in later childhood, or in adulthood with myopathy, lower-extremity paresthesias, and thrombosis as a result of elevated plasma homocysteine. Other their features are optic atrophy, progressive pigmentary retinopathy, nystagmus, strabismus, and worsening vision. They may also exhibit hydrocephalus and microcephaly.
Brain MRI may reveal pathology of the basal ganglia and white matter. Some children with MMA have delayed myelin development or dysplasia.The most common imaging findings in the MMA patients are subcortical white matter changes, periventricular white matter changes,ventricular dilation and cerebral atrophy.The autopsies have shown brain atrophy, reactive gliosis, hypomyelination, multifocal cerebellar hemorrhage, and depletion or hypodevelopment of the cerebellar external granule cells in older children. Treatment of known MMA is directed toward stopping catabolism and restricting protein intake and hydroxocobalamin.

Key words: Brain imaging,Methylmalonic acidemia,

MRI findings in mitochondrial disorders

Mohammad Vafaee-Shahi
Reza Shervinbadv
Morteza Heydari
Associate professor of Pediatric Neurology

Primary mitochondrial disorder (PMD) is caused by pathogenic variants in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) that commonly affect the pediatric central nervous system (CNS), lacking pathognomonic imaging findings. At neuroimaging, PMD findings vary widely. Certain PMDs have typical neuroimaging features and may evolve during the course of the disease that include Leigh, MELAS, POLG-RDs, Kearns-Sayre,Leber hereditary optic neuropathy (LHON),Pyruvate dehydrogenase (PDH) complex deficiency, CoQ10 deficiency and Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL).

In the appropriate clinical setting, the following imaging features may indicate the possibility of a PMD: neuroimaging combinations of signal intensity changes in the basal ganglia, thalamus, brainstem, cortex, white matter (leukodystrophy), cerebellum, or spinal cord; calcification especially in the basal ganglia; white matter cavitation; cerebral and cerebellar atrophy; myelination delay orhypomyelination; callosal agenesis or dysgenesis;subependymal cysts; optic nerve atrophy;cerebral edema (cytotoxic and vasogenic); andcertain abnormal MR spectroscopy findingsinclude lactate and succinate peaks.

The most common imaging findings observed in individuals with Leigh syndrome are bilateral lesions in the basal ganglia, especially in the striatum (caudate nucleus and putamen), diencephalon (mainly the medial aspect of the thalamus), and brainstem (substantia nigra, oculomotor nuclei, periaqueductal gray matter, and inferior olivary nuclei). Less common locations include those in the white matter, cortex, cerebellum, and spinal cord. The purpose of this lecture is explaining of characteristic MRI finding in mitochondrial disorders.

Impact of MRS in neurometabolic disorders

Elham.Rahimian M.D Neuroradiologist .Haghighat research and imaging center.

With consideration to the information provided by MRS about brain metabolism and neurometabolic disorders ,MRS has proven itself to be a useful tool in diagnosis and monitoring the treatment process of neurometabolic disorders .In particularly in the early stages of disease process ,MRS often appears to be more sensitive than conventional MRI. Two types of spectroscopic abnormalities are seen in the neurometabolic disorders which affect mostly white matter disorders and deep gray matter.

1-process -specific spectroscopic abnormalities ,related to delayed maturation and tissue damage ,in this group delayed myelination reflects in MRS as metabolite levels are younger age than patients age .However MRS has limited value in this group due to wide normal variations .In Demyelinating disorders it is primarily myelin sheath that is lost with secondary axon damage .in the H1 MRS decrease in the NAA levels occur and based on disease stage it has remarkable variation. However in the active phase of demyelination, there is Choline rise representing enhanced membrane lipid turn over. Also myelin loss causes protein and lipid peak at 0.9-1.3 ppm as well as lactate rise .Gliosis is evaluated based on mIns levels. In neurodegenerative disorders involving white matter NAA decrease in Cortexes in more than Demyelinating disorders and occurs before remarkable atrophy. In hypomlyeinating disorders there is reduced Choline levels due to reduced white matter density. In the Mitochondrial disorders which target the energy metabolism such as Leigh syndrome ,NARP syndrome MEALS ,MERRF and Krearns sayre syndrome ,Mostly morphological abnormalities are diagnostic . However there is lactate and alanine rise but it is unequivocal. There is correlation between CSF lactate and Lactate rise in MRS. In hyperammonemia of any origin shows changes directly related to high level of Ammonium as glutamine rise .

2-**Disease -specific spectroscopic changes** ,directly related to the particular disorder under investigation. In this group specific metabolites are accumulated due to inborn errors of metabolism which manifests as specific spectral pattern. In this group , Canavan disease with remarkable rise in NAA peak ,Salla disease and sever infantile sialic acid storage disease are characterized by accumulation of N-acetyl-neuraminic acid (sialic acid).In MSUD there is Lactate rise in acute metabolic crise and accumulation of branched -chain amino acids and Keto acids around 0.9ppm.Also in NKHG there is rise in the Glycine signal at 3.55 ppm and short and long TE. In SDHD ,there is rise in the succinate peak resonance at 2.40 ppm.

Considering to all above MRS can be useful tool in early diagnosis and treatment monitoring in neurometabolic disorders .

Propionic acidemia

Maryam Kachoei -Pediatric Neurologist

Propionic acidemia(PA) is a rare metabolic disorder which is characterized by deficiency of propionyl-CoA carboxylase. Symptoms most commonly become apparent during the first weeks of life and may include hypo/hyperglycemia, ketosis, hyperammonaemia, and even multi-organ failure.
Patients with PA canalso develop long-term complications. Organs with high energy demands are those most affected, including the nervous system (encephalopathy, abnormal movement, epilepsy, psychomotor delay, involvement of the basal ganglia, and optic nerve atrophy), the heart (cardiomyopathy, arrhythmia, long QT interval), the skeletal muscles (myopathy), etc. Long-term complications independent of acute decompensationepisodes can increase morbidity and mortality. Propionic acidemia is inherited in an autosomal recessive pattern.Neuropathologic findings in this disorder have not been characterized, but white matter spongiosis in neonates is seen, most prominently at the junction of gray-white matter of the temporal cortex, and also at the tracts of midbrain, pons, and medulla . There is a report of hemorrhage in the basal ganglia in a patient with propionic acidemia, probably due to increase in sensitivity of endothelial cells to toxic insults.Neuroimaging findings of neonates revealsdiffuse edema and signal irregularities in the cerebral white matterwith sparing of the basal ganglia. ·
In older childrenhyperintense lesions in basal ganglia (mainly in the putamen and caudate) is seen and abnormal signal intensity and edema in the cerberal and cerebellar cortices are less common.

In MR spectroscopytypical pattern during acute decompensation may include decreased NAA and glutamateand glutamine level and increased lactate level.

Without appropriate treatment, coma and death may result.During acute episodes, the treatment of infants with propionic acidemia may require fluid therapy; measures to provide appropriate nutritional intake (e.g., intravenous glucose, with and without intravenous lipids); and other supportive measures as required. In infants with severe disease (e.g., severe acidosis, hyperammonemia), treatment may require hemodialysis.Prevention of primary manifestations Individualized dietary management to restrict propiogenic substrates; nasogastric or gastrostomy feeding as needed; increased caloric intake during illness to prevent catabolism; and continued multidisciplinary care with metabolic specialists. Medications may include: –L-carnitine supplementation; –oral metronidazole to reduce propionate production by gut bacteria; and/or N- carbamoylglutamate. Orthotopic liver transplantation (OLT) may be indicated in those with frequent metabolic decompensations, uncontrollable hyperammonemia, and/or restricted growth

Gamma-Aminobutyric Acid Transaminase Deficiency

Dr.Saeed Anvari -Pediatric Neurologist -Social Security Organisation

γ-Aminobutyric acid (*gamma*-aminobutyric acid), or **GABA** , is the chief inhibitory neurotransmitter in the developmentally mature mammalian central nervous system. Its principal role is reducing neuronal excitability throughout the nervous system. GABA is sold as a dietary supplement in many countries. It has been traditionally thought that exogenous GABA (taken as a supplement) doesn't cross the blood-brain barrier, however data obtained from more current research[3] describes the notion as being unclear pending further research. The carboxylate form of GABA is **γ-aminobutyrate**. Two general classes of GABA receptor are known,

- $GABA_A$ in which the receptor is part of a ligand-gated ion channel complex
- $GABA_B$ metabotropic receptors, which are G protein-coupled receptors that open or close ion channels via intermediaries (G proteins). Neurons that produce GABA as their output are called **GABAergic** neurons, and have chiefly inhibitory action at receptors in the adult vertebrate.

GABA is an inhibitory transmitter in the mature brain. its actions were thought to be primarily excitatory in the developing brain. GABA derived primarily from glutamate, the major excitatory neurotransmitter. GABA transaminase deficiency is a rare, autosomal-recessive disorder characterized by abnormal development, seizures, and high levels of CSF GABA betaalanine, both of which are also elevated in serum. characterized by a severe neonatal-infantile epileptic encephalopathy (manifesting with symptoms such as seizures, hypotonia, hyperreflexia and developmental delay) and growth acceleration . Onset occurs in the neonatal/infantile period. The phenotype of GABA-T deficiency is more severe than what is seen in succinic semialdehyde dehydrogenase (SSADH) deficiency. Although some patients have survived infancy but with severe neurodevelopmental impairment including myoclonic seizures and choreoathetosis. caused by a mutation in the *ABAT* gene (16p13.2) encoding mitochondrial 4-aminobutyrate aminotransferase (GABA-T). GABA-T is responsible for catalyzing the conversion of gamma-aminobutyrate to succinate semialdehyde in the GABA metabolic pathway. GABA-T is responsible for catalyzing the conversion of gamma-aminobutyrate to succinate semialdehyde in the GABA metabolic pathway.

UNDEFINED NEUROTRANSMITTER DEFICIENCY STATES

Because patients with neurotransmitter deficiency disorders caused by tyrosine hydroxylase or BH4 deficiency have been deficient for prolonged periods before treatment, they can be extremely sensitive to initiation of neurotransmitter precursors. These include patients with a wide variety of movement disorder phenotypes, encephalopathy, or seizures.

APPROACH TO TREATMENT IN PATIENTS WITH NEUROTRANSMITTER DEFICIENCY STATES

- ❑ Starting with extremely conservative dosages, increasing the dosage slowly during weeks or months, and ensuring that peripheral aromatic L-amino acid decarboxylase is fully blocked by providing ample carbidopa can make the transition to treatment much easier. The rate or degree to which children respond depends on a variety of factors, including age at diagnosis, specific disorder and mutation, presence or absence of associated hyperphenylalaninemia, and presence or absence of central BH4 deficiency. In general, optimism about improvement is warranted

Aminoacidneurotransmitteres

Dr.Toktam Mousavian -Pediatric Neurologist

Neurotransmitters are **chemical messengers that your body can't function without**. Their job is to carry chemical signals (“messages”) from one neuron (nerve cell) to the next target cell. The next target cell can be another nerve cell, a muscle cell or a gland The neurotransmitter systems can be divided into mainly inhibitoryaminoacidergic [-aminobutyric acid (GABA) and glycine], excitatory aminoacidergic (as- partate and glutamate), cholinergic (acetylcholine), monoaminergic (mainly adrenaline, noradrenaline, dopamine, and serotonin), andpurinergic (adenosine and adenosine mono-, di-, and triphosphate). A rapidly growing list of peptides are also considered putative neurotransmitters. GABA is formed from glutamic acid by glutamic acid decarboxylase. It is catabolized into succinic acid through the sequential action of two mi- tochondrial enzymes, GABA transaminase and suc- cinicsemialdehyde dehydrogenase.

All these enzymes require pyridoxal phosphate as a coenzyme. Pyridoxal phosphate also intervenes in the synthesis of dopamineand serotonin and in many other pathways including the glycine cleavage system.

A major inhibitory neurotransmitter, GABA is present in high concentration in the central nervous system, predominantly in the gray matter. GABA modulates brain activity by binding to sodium-independent, high-affinity, mostly GABA receptors.

GLYCINE, a non-essential amino acid, is an intermediate in many metabolic processes but also one of the major inhibitory neurotransmitters in the central nervous system. The inhibitory glycine receptors are mostly found in the brain stem and spinal cord. GLUTAMATE is the major excitatory neurotransmitter in the brain. Its function requires rapid uptake to replenish intracellular neuronal pools following extra cellular release.

- Neurotransmitter related disorders
- Broad spectrum
- Defect in production
- Transport
- Release and reuptake

Disorders of Neurotransmission

inborn Errors of Gamma Amino Butyric Acid Metabolism

Gamma Amino Butyric Acid Transaminase Deficiency Succinic Semialdehyde Dehydrogenase Deficiency

inborn Defects of Receptors and Transporters of Neurotransmitters

HyperekplexiaGABA Receptor MutationMitochondrial Glutamate Transporter Defect

Inborn Errors of Monoamine Metabolism

Tyrosine Hydroxylase Deficiency , Aromatic L-Aminoacid Decarboxylase Deficiency , Dopamine β-Hydroxylase Deficiency , Monoamine Oxidase-A Deficiency , Guanosine Triphosphate Cyclohydrolase-I Deficiency

inborn Disorders Involving Pyridoxine and Pyridoxal Phosphate

Pyridoxine-Responsive Epilepsy ,Pyridox(am)ine 5'-Phosphate Oxidase Deficiency

Mild gait or mood abnormality to classic exercise induced dystonic gait and infantile onset parkinsonism and sever in BH4 d. global DD .fluctuation tone and eye movement abnormality encephalopathy ataxia seizure

- But in aminoacidneurotramsmitter dysfunction (gaba glutamate glycine): more difficult to characterize due to breadth of function: seizure ataxia hypotonia oculomotor dyspraxia ddelay