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Membrane trafficking in neurodevelopmental disorders – new insight and therapeutic implications

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Abstract

Introduction: Membrane trafficking processes are essential for cell viability and basic functions, as well as for interactions between the cell interior and the surrounding environment.

Purpose: This article focuses on the review of specific subgroup of inherited neurodevelopmental disorders caused by membrane trafficking dysfunction. The possibility of innovative therapeutic approaches based on selective effects on membrane trafficking processes is also discussed.

State of knowledge: Most previously published reviews are lists of multi-organ diseases related to membrane trafficking dysfunction that are grouped by damaged genes/proteins or

by single dominant clinical symptom. No review that focused exclusively on the subgroup of neurodevelopmental diseases related to membrane trafficking defects and their differential diagnosis useful in clinical practice, could be identified.

Conclusions: Neurodevelopmental diseases related to membrane trafficking defects constitute a significant still growing group of rare/ultra-rare disorders which, due to the spectrum of symptoms, require differentiation from the more common neurogenetic syndromes with different pathomechanisms of the disease, but also related to intellectual disability, autism, epilepsy or neurodegenerative processes. The design of innovative drugs based on selective effects on membrane trafficking processes creates wide opportunities for precise, targeted therapeutic intervention, with a significantly minimized risk of its ineffectiveness or side effects.

Keywords: membrane trafficking, vesicle trafficking, neurodevelopmental disorders, inborn genetic disorders, nanoparticle, drug delivery

Introduction: General aspects of membrane trafficking

Membrane trafficking are essential processes to maintain critical cellular functions. This group includes processes associated with the movement of cargo using membrane-bound transport vesicles (vesicular trafficking) and is divided into two pathways (1, 2):

- Exocytosis – movement of cargo (including mainly newly synthesized molecules) from the endoplasmic reticulum (ER) through the Golgi apparatus (GA) to the cell membrane or extracellular compartment;
- Endocytosis – opposite movement of cargo (including mainly nutrients or intracellular material for recycling or degradation) from the plasma membrane into the cell.

Generally process of membrane trafficking could be divided into following steps (2):

1) selection of cargo from resident proteins in the donor compartment;
2) formation of transport vesicle with encapsulation of cargo-bound adaptors and specific changes in its membrane;
3) vesicle movements to the target compartment;
4) membrane tethering via cooperation with RAB proteins;
5) docking and membrane fusion mediated by SNARE protein complexes.

In connection with the above steps, the following families of vesicle trafficking proteins can be distinguished (1-3):

- COAT protein complex – group of proteins assisting in the collection and concentration of cargo vesicle with three main coat proteins:
    - Clathrin – clathrin coating is needed to initiate endocytosis from the plasma membrane to endosomal compartments and GA;
    - Coat protein I (COPI) – COPI coating is associated with retrograde transport within GA and ER;
    - Coat protein II (COPII) – COPII coating mediates anterograde transport within GA and ER during exocytosis;
- ADAPTOR-related protein complex – group of cargo adaptors with specific binding sites recognizing and capturing a dedicated cargo to the vesicles forming:
    - Sec24 – cargo adaptor with multiple binding sites to capture various proteins excreted from ER and transported to GA;
    - AP1-AP5 – group of cargo adaptors binding to different intracellular membranes (mainly associated with endosomes);
- CALVEOLIN proteins – a family of small proteins with particular structural role in the formation of caveolae by polymerization during the transport of vesicles from GA;
- RAB proteins – a large family of small soluble Ras-related proteins in the brain related to the recognition and regulation of vesicle transport to a specific target;
- TBC proteins – group of proteins with a highly conserved TBC domain, functioning as GTPase activating proteins (GAPs) and promoting conversion from GTP to GDP form of RAB proteins;

- TRAFFICKING PROTEIN PARTICLE (TRAPP) complex – group of proteins associated with vesicle fusion and vesicle transport to the targeted intracellular membrane;
- VACUOLAR PROTEIN SORTING (VPS) complex – complex of proteins involved in segregation of intracellular molecules into distinct organelles, especially in cooperation with the SNARE complex;
- SNARE complex – a group of proteins that mediate vesicle fusion, which can be divided into two subgroups depending on their location in the cellular compartment:
    - target SNARE (t-SNAREs) – associated with the target membranes, mainly nerve terminal membranes and playing significant role in the processes of neurotransmission (main t-SNAREs: syntaxins and SNAP-25 are the core of SNARE complex and are related to calcium independent fusion of synaptic vesicles (syntaxins) and vesicle docking and fusion in special active zones on the cell membrane (SNAP-25));
    - vesicle SNARE (v-SNAREs) – incorporated into the vesicle membranes for further processes of vesicle docking and fusion.

Objectives of review

The phenomenon of membrane trafficking covers the level of the cellular and subcellular membranes and is a significant process in regulating the location and distribution of exogenous and endogenous molecules (4). The above processes are particularly important in the proper development and functioning of the human nervous system, and their disorders lead to a number of specific brain malformations and neurodevelopmental diseases associated with intellectual disability, neurotransmission disorders and neurodegenerative processes (1, 2). Altered membrane transport is also one of the most common causes of the development of drug resistance due to reduced drug uptake by membrane transporters, changes in subcellular pH or disturbances in the synaptic vesicle cycle (1, 4).

Most previously published reviews are lists of multi-organ diseases grouped by damaged genes/proteins or by single dominant clinical symptom (1, 2, 5, 6). Our review, in contrast to above-mentioned reviews, focuses exclusively on neurodevelopmental diseases and their differential diagnosis. Additionally, practical division into four categories of clinical neurodevelopmental syndromes was used, along with a detailed comparison of neurological symptoms in each subgroup. The final summary of each category takes into account the

differential diagnosis with other neurogenetic syndromes more frequently encountered in clinical practice, with completely different pathomechanisms.

At the same time, new dedicated therapeutic possibilities for neurodevelopmental diseases related to vesicular trafficking defects, resulting directly from their molecular basis, were discussed.

Overview

New insights into membrane trafficking in neurodevelopmental disorders

More than 300 causative genes of human diseases related to vesicular trafficking defects have been identified (1). Vesicle trafficking is a ubiquitous and significant process in all human tissues, however, a tissue-specific phenotype of defects in this cellular machinery has been noticed. This phenomenon could be associated with: 1) tissue-specific expression of the trafficking components, 2) activity of the complete turnover of surface proteins and membranes over a specified time period; 3) nature of the causative mutation (complete/partial loss-of function, overexpression/gain-of-function) (1, 2).

Tissue-specific phenotypes of human diseases related to vesicular trafficking defects usually include neurological abnormalities, hypopigmentation and disturbances in cell-mediated immune response. This indicates the particular importance of polarised cell involvement (i.e. neurons, neutrophils, migrating or developing cells) and disturbances in the apical and basolateral trafficking in the development of the clinical presentation of the vesicular trafficking related diseases (6).

In the case of inherited neurological disorders caused by membrane trafficking dysfunction, certain distinctive features should be emphasized that render neuronal cells particularly sensitive to this type of dysfunction: their postmitotic nature and large size, ultra-specialization of trafficking in dendrites, extended neurite processes, including synaptic vesicle cycle constituting the basis for neurotransmission (1, 5). The post-mitotic nature of neurons requires an extremely efficient clearance system to prevent the accumulation of neurotoxic, misfolded or damaged proteins (5). Neurons are particularly sensitive to defects in lysosomal and autophagic degradation pathways, which lead to the development of protein aggregates with their neurotoxicity and further progression to neurodegenerative processes (5). The ultra-specialization of trafficking in dendrites is important from the early stage of brain development, and its disturbances could lead to specific congenital brain malformation or the development of intellectual disability or autism spectrum disorders (7). Neurotransmission disorders caused by defects in the synaptic vesicle cycle may result in the development of

early-onset developmental and epileptic encephalopathies characterized by drug-resistant seizures and severe intellectual disability (1).

Lists of selected diseases from the above-mentioned groups of neurodevelopmental disorders are presented in the tables:

- intellectual disabilities - this group consists mainly of X-linked intellectual disability with varying degrees of cognitive dysfunction (mild to severe), with coexisting macrocephaly and mild dysmorphic features resembling spectrum of *FMR1*-related disorders or Cohen's syndrome (→ Table 1);
- early onset developmental and epileptic encephalopathies mainly associated with dysfunction of clathrin-mediated endocytosis and SNARE complex, with a phenotypic spectrum of symptoms including severe intellectual dysfunction, drug-resistant and polymorphic seizures with characteristic EEG patterns (→ Table 2);
- specific brain malformation – mainly heterotopias and pontocerebellar hypoplasias (→ Table 3a-3b);
- progressive neurodegenerative disorders with complex clinical presentation and specific CNS abnormalities that should be differentiated from the classic group of metabolic disorders (neuronal ceroid lipofuscinoses, mitochondrial disorders or sulfite oxidase deficiency (→ Table 4).

Table 1. Intellectual disabilities caused by disorders in vesicle-mediated trafficking

Disease	Intellectual developmental disorder, X-linked 41	Intellectual developmental disorder, X-linked 72	Intellectual developmental disorder, X-linked 50	Intellectual developmental disorder, autosomal recessive 13	Intellectual developmental disorder, autosomal recessive 52
MIM number	300849	300271	300115	613192	616887
ORPHA code	ORPHA:777	ORPHA:777	ORPHA:777	ORPHA:88616	ORPHA:88616
Causative gene(s)	*GDI1*	*RAB39B*	*SYN1*	*TRAPPC9*	*LMAN2L*
Inheritance	XLD	XLR	XL	AR	AR
Protein function	vesicular trafficking, RAB-GDP dissociation inhibitor	vesicular trafficking, small GTPase	tethering/clustering synaptic vesicles, synaptic phosphoprotein	ER-to-Golgi trafficking, TRAPP complex member	glycoprotein transport from ER
Anthropometric features					
Microcephaly	-	-	-	+	-
Macrocephaly	-	+	+ (mild)	-	-
Short stature	-	-	+	-	-
Obesity	-	-	-	+ (truncal)	-
Dysmorphic features					
	-	long face	-	short, smooth philtrum, hyper/hypotelorism, cleft lip, prominent central incisors, short neck, long, thin fingers	-
Cognitive skills					
Developmental delay	+	+	+	+	+
Severity of intellectual dysfunction	mild to severe	mild to severe	moderate to severe	moderate to severe	severe

Speech delay/limitations	-	+	+	+	-
Neurodevelopmental features					
Hypotonia	+	-	-	-	-
Seizures	+ (absence)	+	-	+	+ (remission by 5 yr)
Abnormal eye contact	-	-	+	-	-
Autistic features	-	+	+	-	-
Hyperactivity/attention deficits	-	+	-	+	-
Happy disposition	-	-	-	+	-
Stereotypic movements	+	+	-	-	-
Brain imagination					
Cerebral atrophy	-	-	+ (frontal regions)	-	-
Thin corpus callosum	-	-	-	+	-
White matter abnormalities	-	-	-	+	-
Cerebellar vermis hypoplasia	-	-	-	+	-
Clinical spectrum of differential diagnosis – classical syndromes					
	other MRXS and XLID	Fragile X syndrome (*FMR1*) MACID (*NFIB*) other MRXS	other MRXS and XLID	Cohen syndrome (*VPS13B*)	DEE32 (*KCNA2*) *SCNA2*-related disorders

DEE – Developmental and Epileptic Encephalopathy; ER – Endoplasmic Reticulum; MACID – Macrocephaly Acquired with Impaired Intellectual Development; MRXS – Mental Retardation X-Linked Syndrome; TRAPP – Trafficking Protein Particle; XLID – X-Linked Intellectual Developmental Disorder

Table 2. Early onset developmental and epileptic encephalopathies caused by disorders in vesicle-mediated trafficking

Disease	Intellectual developmental disorder autosomal dominant 60 with seizures	Developmental and epileptic encephalopathy 48	Developmental and epileptic encephalopathy 49	Developmental and epileptic encephalopathy 21	Developmental and epileptic encephalopathy 4	Epilepsy X-linked with variable learning disabilities and behaviour disorders	Developmental and epileptic encephalopathy 53	Progressive myoclonic epilepsy 6
MIM number	618587	617276	617281	615833	612164	300491	617389	614018
ORPHA code	ORPHA:1942	ORPHA:442835	-	ORPHA:442835	ORPHA:599373	ORPHA:85294	ORPHA:1934	ORPHA:280620
Causative gene(s)	*AP2M1*	*AP3B2*	*DENND5A*	*NECAP1*	*STXBP1*	*SYN1*	*SYNJ1*	*GORS2*
Inheritance	AD	AR	AR	AR	AD, AR	XL	AR	AR
Protein function	clathrin-mediated endocytosis, ADAPTOR-related protein complex	clathrin-mediated endocytosis, ADAPTOR-related protein complex	Golgi trafficking, RAB GTPase	clathrin-mediated endocytosis, ADAPTOR-related protein complex	synaptic vesicle docking and fusion, SNARE complex	tethering/ clustering of synaptic vesicles, RAB-related protein	clathrin-mediated endocytosis, COAT protein complex	ER-to-Golgi trafficking, SNARE complex
Head circumferences								
Microcephaly	-	+	+	-	-	-	-	-
Macrocephaly	-	-	-	-	-	+	-	-
Dysmorphic features								
	-	protruding eyes	coarse facies, frontal bossing, large ears, prominent nose, open mouth	scaphocephaly	-	-	-	-
Cognitive skills								
Developmental delay	+	+	+	+	+	+	+	-

Severity of intellectual dysfunction	moderate	severe to profound	profound	profound	severe to profound	variable	profound	mild
Speech delay/limitations	+	+	+	+	+	+	+	+
Seizures								
Type of seizures	• absence; • myoclonic; • atonic; • tonic-clonic;	• subtle neonatal; • infantile spasms; • generalized; • tonic-clonic;	• tonic; • myoclonic; • tonic-clonic; • startle induced;	• clonic; • tonic-clonic; • hemispasms; • blank stare; • apnea;	• tonic-clonic; • tonic • myoclonic; • absence; • atonic; • focal dyscognitive; • fever induced;	• complex partial; • water induced • fever induced; • nocturnal; • secondary generalized;	• tonic; • tonic-clonic; • myoclonic • eye-blinking;	• tonic-clonic; • absence • atonic
Drug resistance	-	+	-	+	+	-	+	-
Age of onset	1-4 yr	0-9 mo	neonatal period	0-3 mo	neonatal – infancy period	first two decades	0-6 mo	first decade
EEG abnormalities	• background slowing; • multifocal spike-wave discharges;	hypsarrhythmia	• background slowing; • generalized spike-wave discharges;	• generalized slowing; • burst-suppression pattern;	• hypsarrhyth-mia; • burst-suppression pattern; • multifocal discharges;	abnormalities in temporal region	• background slowing; • multifocal epileptic activity; • hypsarrhyth-mia;	• active generalized spike and wave and polyspike pattern • photosensitivity
Additional neurodevelopmental features								
Hypotonia	-	+ axial	-	+ axial	+	-	+	-
Hypertonia	-	+ peripheral	+ peripheral	+ peripheral	+ peripheral	-	+ peripheral	-
Abnormal eye contact/	-	+	+/-	+	+	-	+	-

movements								
Movement disorders	ataxia	dyskinesias	myoclonus	-	tremor	-	-	action myoclonus, progressive ataxia, tremor
Autistic features	+	-	-	-	+	+	-	-
Behavioral abnormalities	+	-	-	-	+	+	-	-
Sleep disorders	-	+	-	-	-	-	-	-
Brain imagination								
Cerebral atrophy	-	+	-	+	+	-	-	+
Corpus callosum abnormalities	-	+ thin	+ dysgenesis	+ thin	+ thin	-	+ thin	-
White matter abnormalities	-	+	-	-	-	-	-	-
Cerebellar abnormalities	-	+ atrophy	+ Dandy-Walker malformation	-	-	-	-	+ atrophy
Hydrocephalus/ ventriculomegaly	-	-	+	-	-	-	-	-
Intracranial calcifications	-	-	+	-	-	-	-	-
Other specific	-	-	partially fused thalami	delayed myelination	delayed myelination	-	-	-
Clinical spectrum of differential diagnosis – classical syndromes								
	other DEE	other DEE	*GLRA1*-related hyperekplexia, other DEE	other DEE presenting as Ohtahara syndrome	*MECP2*-related disorders, *SCN1A*-related disorders	*SCN1A*-related disorders	other DEE	neurodegenera-tive disorders with progressive ataxia

DEE – Developmental and Epileptic Encephalopathy; ER – Endoplasmic Reticulum

Table 3a. Heterotopias caused by disorders in vesicle-mediated trafficking

HETEROTOPIAS			
Disease	Periventricular nodular heterotopia 8	Periventricular heterotopia with microcephaly	Bilateral temporooccipital polymicrogyria
MIM number	618185	608097	612691
ORPHA code	ORPHA:98892	ORPHA:98892	-
Causative gene(s)	*ARF1*	*ARFGEF2*	*FIG4*
Inheritance	AD	AR	AR
Protein function	COPI coat assembly, COAT protein complex	trans-Golgi vesicle and membrane trafficking	endosomal trafficking
Head circumferences			
Microcephaly	+	+ progressive	-
Neurodevelopmental features			
Developmental delay	+	+ severe	-
Speech delay/limitations	+	-	-
Seizures	+	+	+
Spasticity	+	+	-
Behavioral abnormalities	+	-	+
Hypotonia	-	+	-
Abnormal eye contact/ movements	-	+	-
Brain imagination			
Cerebral abnormalities	+ cerebral underdevelopment cortical thinning delayed myelination	-	-
Corpus callosum abnormalities	-	+ thin	-
White matter abnormalities	+ diminished volume	-	-
Cerebellar abnormalities	+ vermis atrophy	-	-

Hydrocephalus/ ventriculomegaly	-	-	+
Other specific	+ periventricular nodular heterotopia	+ periventricular nodular heterotopia	+ temporo-occipital polymicrogyria

COPI - Coat Protein I

Table 3b. Pontocerebellar hypoplasias caused by disorders in vesicle-mediated trafficking

PONTOCEREBELLAR HYPOPLASIAS			
Disease	Pontocerebellar hypoplasia type 11	Pontocerebellar hypoplasia type 2E	Pontocerebellar hypoplasia type 13
MIM number	617695	615851	618606
ORPHA code	ORPHA:611247	ORPHA:247198	ORPHA:613267
Causative gene(s)	*TBC1D23*	*VPS53*	*VPS51*
Inheritance	AR	AR	AR
Protein function	vesicle tethering TBC protein	trans-Golgi vesicle and membrane trafficking VPS complex	trans-Golgi vesicle and membrane trafficking VPS complex
Head circumferences			
Microcephaly	+	+ progressive	+
Neurodevelopmental features			
Developmental delay	+ severe	+ severe	+
Speech delay/limitations	+	+	+
Cerebellar ataxia	+	-	+
Seizures	+	+	+
Spasticity	+	+	-
Behavioral abnormalities	+	+	-
Autistic features	+	-	-
Hypotonia	+	+	+
Abnormal eye contact/ movements	+	+	+
Brain imagination			

Cerebral abnormalities	+ cortical hypoplasia	+ progressive atrophy	+ atrophy
Corpus callosum abnormalities	+ hypoplasia	+ thin	+ thin
White matter abnormalities	-	-	+ periventricular abnormalities reduced volume
Cerebellar abnormalities	+ pontocerebellar hypoplasia	+ progressive atrophy	+ pontocerebellar hypoplasia progressive atrophy Dandy-Walker variant
Hydrocephalus/ ventriculomegaly	-	-	+
Laboratory abnormalities			
Abnormal liver enzymes	-	-	+
Hypoglycosylation of serum transferrin	-	-	+
Clinical spectrum of differential diagnosis – classical syndromes			
	MECP2-related disorders, other PCH	other PCH	congenital disorders of glycosylation

PCH – Pontocerebellar Hypoplasia; VPS - Vacuolar Protein Sorting

Table 4. Progressive neurodegenerative diseases caused by disorders in vesicle-mediated trafficking

Disease	Lopes-Maciel-Rodan syndrome	Neurodevelopmental disorder with ataxic gait, absent speech and decreased cortical white matter	Neurodevelopmental disorder with microcephaly, epilepsy and brain atrophy	Early-onset progressive encephalopathy with brain atrophy and spasticity	Childhood-onset striatonigral degeneration
MIM number	617435	617807	617862	614139	617054
ORPHA code	-	-	-	-	ORPHA:497906
Causative gene(s)	*HTT*	*RAB11B*	*TRAPPC6B*	*TRAPPC12*	*VAC14*
Inheritance	AR	AD	AR	AR	AR
Protein function	endocytosis, interaction with clathrin-binding protein HIP1	vesicular trafficking, small GTPase	ER-to-Golgi trafficking, TRAPP complex member	ER-to-Golgi trafficking, TRAPP complex member	endosomal trafficking
Anthropometric features					
Microcephaly	-	+	+	+	-
Dysmorphic features					
	-	tented mouth tapering fingers simian crease overriding toes	-	-	-
Cognitive skills					
Developmental delay	+	+	+	+	-
Severity of intellectual dysfunction	severe	severe to profound	severe	severe	regression
Speech delay/limitations	+	+	+	+	+
Neurodevelopmental features					
Hypotonia	+ truncal	+	-	+ truncal	-
Spasticity	+	+	-	+ appendicular	+

Seizures	+	+	+	+	-
Abnormal eye contact	-	+	-	+	-
Movement disorders	+ dystonia bradykinesia tremor gait instability abnormal hand movements	+ dystonia ataxic gait	+ ataxia tremor	+ dystonia myoclonus	+ gait instability dystonia abnormal involuntary movement
Behavioral abnormalities	+	+	+	-	-
Sleep disturbances	+	-	-	-	-
Poor feeding	+	+	-	+	+
Brain imagination					
Cerebral atrophy	+	+/- thin brainstem	+ cortical brainstem	+ cortical	-
Thin corpus callosum	-	+	+	+ agenesis	-
White matter abnormalities	-	+	-	-	-
Cerebellar abnormalities	+ atrophy	+ vermis hypoplasia	+ atrophy	-	-
Other specific	+ caudate atrophy	+ partial rhombencephalosynapsis	-	+ pontine hypoplasia simplified frontal gyri	+ abnormal signal in striatum
Clinical spectrum of differential diagnosis – classical syndromes					
	FXTAS Sulfite oxidase deficiency HSD10 mitochondrial	CLN	Angelman syndrome MRXSCH	PCH Microcephaly with simplified gyral pattern Pseudo-TORCH	Early-onset dystonia-parkinsonism syndromes *KCNA4*-related

	disease	syndrome	disorder

CLN – Neuronal Ceroid Lipofuscinosis; ER – Endoplasmic Reticulum; FXTAS – Fragile X Tremor/Ataxia Syndrome; MRXSCH – X-linked syndromic intellectual developmental disorder Christianson type; PCH – Pontocerebellar Hypoplasia; TRAPP – Trafficking Protein Particle

New therapeutic implications in neurodevelopmental disorders related to membrane trafficking defects

Effective treatment of a specific disease is possible if there are available drugs which antagonize the pathological processes and causes of the disease, as well as normalize biological states of affected tissues (4). However, the targeted action of a dedicated drug on a specific organ is usually influenced by the complexity of the cellular network, disturbances in pH and the effectiveness of efflux pump proteins, or the activity of enzymes or the host immune response (4).

Targeting a specific gene, receptor, ion channel or enzyme with a particular molecule that reacts with these effectors may be a more efficient way to overcome these barriers.

A perfect example is transferrin, which has the ability to effectively direct polyethylene glycol coated nanoparticles containing certain drugs into brain tissue (4, 6). The brain absorbs iron from transferrin after internalization via the transferrin receptor across the blood-brain barrier. Additionally, internalization via a clathrin-dependent endocytic process allows partial avoidance of recognition by efflux transporters, which are highly concentrated in the blood-brain barrier, and thus elimination of the drug from brain tissue (4, 6). Riboflavin works analogously to transferrin, which may be an excellent solution for creating an effective dedicated treatment for mitochondrial diseases with a dominant brain involvement and neurological symptoms (4, 6).

Glycosylphosphatidylinositol (GPI)-anchored proteins are related to clathrin- and caveolin-independent endocytosis (4, 8). GPI-linked proteins are incorporated slowly into cells, with a half-time up to minutes or hours (8). Their uptake is not blocked by perturbations typical for the process of clathrin-coated-pit formation and they can enter the cell via multiple pathways (8). These features allow for their wide clinical application, including gene therapy, immune therapy, cancer therapy, and vaccinations (9). It may also be an effective therapeutic solution for neurodevelopmental disorders of lipid transport and metabolism (1).

The mitochondria-targeted coenzyme Q10 (CoQ10) nanodelivery system is an innovative solution that enables precise targeting of mitochondria and delivery of CoQ10 in appropriate amounts to these organelles (4, 10). This new miktoarm-based carrier provides a suitable means of CoQ10 delivery to mitochondria without loss of drug effectiveness (10). This novel mitochondria-targeted nanocarrier could be widely used as a readily reproducible drug delivery procedure for many neurodevelopmental disorders with involvement of mitochondria or other intracellular organelles (10).

Conclusions

Neurodevelopmental diseases related to membrane trafficking defects are a growing group of diseases due to the identification of newer genes related to membrane-trafficking processes. They constitute a significant group of rare or ultra-rare diseases which, due to the spectrum of symptoms, require differentiation from the more common neurogenetic syndromes with different pathomechanisms of the disease, but also related to intellectual disability, autism, epilepsy or neurodegenerative processes.

The design of innovative drugs based on selective effects on membrane trafficking processes creates wide opportunities for precise, targeted therapeutic intervention, with a significantly minimized risk of its ineffectiveness or side effects.

Author Contribution Statement

Conceptualization M.P.; methodology M.P.; resources M.P.; writing - rough preparation M.P.; writing - review and editing M.P. All authors have read and agreed with the published version of the manuscript.

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