Effectiveness of L-serine dietary supplementation in children with a GRIN2B loss-of-function mutation: n-of-1 series

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Assess the potential efficay of L-serine dietary supplementation in patients children with a GRIN2B LoS mutation.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON51542

Source
ToetsingOnline

Brief title
Serine-GRIN2B

Condition

- Metabolic and nutritional disorders congenital

Synonym
GRIN2B deficiency

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Metakids;Vriendenloterij

Intervention

Keyword: GRIN2B, L-serine, NMDAR, N-of-1

Outcome measures

Primary outcome

PRPP (Perceive-Recall-Plan-Perform) assessment

Secondary outcome

• Goal Attainment Scaling (GAS)

• If epilepsy: seizure control (seizure log book)

• EEG

• Sleep (sleep log book)

• Irritability (Brief Irritability Test)

• Bowel movement assessment (Bristol stool scale)

• Language (MacArthur)

• Quality of Life (PedsQL)

Study description

Background summary

Loss-of-function (LoF) mutations in GRIN2B result in neurologic abnormalities due to N-methyl-D-aspartate receptor (NMDAR) dysfunction. In vitro experiments showed that the naturally occurring coagonist D-serine restores function to GluN2B (mutation)-containing NMDARs. In a 5 years old patient with a missense mutation in GRIN2B with a Rett-like syndrome with severe encephalopathy notable improvements in motor and cognitive performance and communication were observed after L-serine dietary supplementation. Thus, L-serine supplementation, which has proven safe and well-tolerated in patients with inborn errors of serine biosynthesis, offers a therapeutic strategy for patients with GRIN2B deficiency, previously considered untreatable and for which there exist no other options.

Study objective

Assess the potential efficay of L-serine dietary supplementation in patients children with a GRIN2B LoS mutation.

Study design

A series of prospective double-blind randomized and placebo-controlled multiple cross-over, single centre studies within a participant (multiple n-of-1 trials).

Intervention

Each patient receives multiple blocks consisting of 4 time daily L-serine (500 mg/kg/day) alternated with placebo and washout periods.

Study burden and risks

No treatment is available for this severely affected patient group. There is an unmet medical need to treat this severe encephalopathy and other neurological conditions. L-serine is a semi-essential amino acid that is found in normal diet and is naturally synthesized by humans. L-serine intake has shown no adverse events to date. A recent study demonstrated that L-serine supplementation might ameliorate motor and cognitive performance in GRIN2B-related encephalopathy. Because of the major impact on quality of life, early innervation is necessary. Therefore paediatric patients with GRIN2B deficiency are necessary to include. Risk for subject participating in this trial consist of additional blood draw. As the clinical trial enables a potential treatment for patients that lack treatment options, we will expect that the benefits substantially outweigh the burden of participation.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)
Newborns
Premature newborns (<37 weeks pregnancy)

Inclusion criteria

1) The patient or the parent(s)/legal guardian(s) must provide written informed consent before start of the study;
2) Male and female patients with confirmed GRIN2B LoF mutation;
3) >=37 weeks, <=18 years
4) Able to travel to the study site.

Exclusion criteria

1) Has taken L-serine supplement within 30 days prior to enrolment;
2) The patient has received another investigational product within 30 days prior to enrolment;
3) Known hypersensitivity reactions, intolerance or adverse reactions to L-serine or the inactive ingredients;
4) The patient is unwilling or, in the investigator*s opinion, unable to adhere to the requirements of the study;
5) The patient is unable to swallow powder and has no other enteral access (e.g. gastrostomy);
6) Any condition or abnormality which may, in the opinion of the investigator, compromise the safety of patients.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-10-2022
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	L-serine
Generic name:	L-serine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	30-06-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-08-2022
Application type:	First submission

Review commission: METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2022-000241-32-NL
CCMO	NL80290.018.22