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# Adult diagnosis of congenital serine biosynthesis defect: a treatable cause of progressive neuropathy

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## Abstract

A woman with ichthyosis, contractures and progressive neuropathy represents the first case of phosphoserine aminotransferase deficiency diagnosed and treated in an adult. She has novel compound heterozygous mutations in the gene *PSAT1*. Treatment with high dose oral L-serine completely resolved the ichthyosis. Consideration of this diagnosis is important because early treatment with L-serine repletion can halt progression of neurodegeneration and potentially improve neurological disabilities. As exome sequencing becomes more widely implemented in the diagnostic evaluation of progressive neurodegenerative phenotypes, adult neurologists and geneticists will increasingly encounter later onset manifestations of inborn errors of metabolism classically considered in infancy and early childhood.

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Author Contributions

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Conflict of Interest

The authors declare no conflicts of interest.

**Keywords**

Serine; Inborn errors of metabolism; Sphingolipids; Ichthyosis; Progressive neuropathy

## INTRODUCTION

Serine deficiency disorders are a group of inherited neurometabolic diseases caused by dysfunction of serine biosynthetic enzymes. Serine is a nonessential amino acid that is critical for the development and function of the central nervous system.[1] It is synthesized via the phosphorylated pathway by three enzymes (Figure S1): 3-phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase (PSAT), and phosphoserine phosphatase (PSP).

Serine disorders typically present in infancy and can include polyneuropathy, psychomotor retardation, seizures, and microcephaly.[2] However, clinical manifestations vary depending on the severity of the enzymatic defect.[3] Prompt diagnosis is critical, since serine deficiency disorders can be treated with oral L-serine. Treatment can control seizures, restore appropriate growth and development, and improve overall quality of life.[4,5]

In this report, we present an adult patient with a congenital serine biosynthesis defect due to *PSAT1* mutations that manifested as generalized ichthyosis and progressive polyneuropathy leading to severe contractures and sensorineural hearing loss. This represents the first known case of *PSAT1* mutation diagnosed and treated in an adult. Our patient showed resolution of her ichthyosis and improvement in systemic symptoms such as hypertension and amenorrhea after serine supplementation, now of 3 years' duration. Byers et al.[6] described an adult patient with *PSPH* mutation treated with serine whom we also evaluated; common features of their phenotypes included severe axonal neuropathy and contractures.

## MATERIALS AND METHODS

The patient is a 40-year-old woman initially evaluated in the NIH Undiagnosed Diseases Program[7–9] in 2013 when she was 34 years of age. She was enrolled under protocol 76-HG-0238 "Diagnosis and Treatment of Patients with Inborn Errors of Metabolism or Other Genetic Disorders", approved by the National Human Genome Research Institute (NHGRI) Institutional Review Board (IRB). Consent was obtained from the mother, who has guardianship, and the patient.

## RESULTS

### Clinical Report

The patient was born to parents of Chinese and Taiwanese ancestry. The patient's mother is G5P2, with two first trimester miscarriages and a stillborn infant. The mother had primary biliary cirrhosis and anti-mitochondrial antibodies. The patient was noted to have intrauterine growth restriction (term gestation, birthweight at 8$^{th}$ percentile) and microcephaly at birth. She required special education in primary school and had a clumsy gait. She had esotropia as an infant and underwent strabismus repair at age 8 years. At age

13 years, she developed gait difficulty, needed a walker, and progressed to a wheelchair by mid-teenage years. Contractures of her extremities developed at approximately 20 years of age, along with onset of sensorineural hearing loss. She had dry scaling skin since birth which became exacerbated in late teenage years such that she would often complain of generalized pruritus despite multiple topical and oral medications.

Prior evaluations included a muscle biopsy at the age of 14 years, which revealed severe, predominantly type II fiber atrophy, with some type I targetoid fibers. Sural nerve biopsy showed nearly complete loss of myelinated axons. There were no unusual inclusions seen on electron microscopy. Given her prominent ichthyosis, the patient was evaluated for possible Sjögren-Larsson syndrome,[10] but was found to have normal fatty alcohol:NAD oxidoreductase activity.

Cutaneous examination (Figure 1) showed generalized xerotic skin with fine scaling and areas with a shiny and atrophic texture. Ichthyosiform scaling was more pronounced over her upper forearms, hands, lower abdomen, and upper thighs. She had significant nail dystrophy on the bilateral first digits of the hands and feet and right index finger. Hair abnormalities, including trichoschisis and trichorrhexis nodosa, were seen when hair shafts were examined from a tuft of shortened hair on the vertex scalp. She had patchy alopecia of the occipital scalp.

At age 38 years, her neurological examination was notable for microcephaly (HC 50.6 cm, <1 percentile, −3.5 SD) and facial dysmorphisms with micrognathia and depressed nasal bridge. She had a very jovial disposition and responded appropriately to simple questions and commands. Extraocular movements were full, but her visual pursuit was not smooth. She had retinal (macular) lesions bilaterally with preserved vision. These consisted of deep small (~300 micron) scattered white spots with indistinct borders within the arcades, symmetric bilaterally. Vasculature was normal. She had weakness of eye closure bilaterally and moderate to severe spastic dysarthria. She was fit initially with bilateral hearing aids at age 20. Audiologic assessment revealed a bilateral severe to profound sensorineural hearing loss. Absence of otoacoustic emissions supported a cochlear contribution, although involvement of the auditory nervous system could not be ruled out because severity of the pure-tone hearing loss prevented characterization of central auditory pathways.

The patient was in a wheelchair with spastic quadriparesis and fixed contractures of her hands and knees. She had marked distal atrophy and weakness, and contractures of upper and lower extremities (Figure 1). Her arm strength proximally was quite good while her leg strength was minimal to absent. She had bilateral hip, knee, and ankle fixed contractures. She had mild elbow flexion contractures. Her ankles were in equinovarus posturing and could be passively ranged to supination a quarter of the range with very little pronation. She could raise her arms above shoulder level and extend her elbows against gravity. Her wrists were flexed bilaterally with fixed contractures at the proximal interphalangeal and distal interphalangeal joints. She could not passively extend her fingers. Her upper extremities remained remarkably functional despite her hand contractures. She fed herself with an adaptive spoon but was otherwise dependent for all activities of daily living.

Her deep tendon reflexes were absent. She had absent pain and temperature sensation distally in all extremities, absent vibration even at proximal joints, and could only sense vibration at the spinous midthoracic spine for upper extremities and at hips for lower extremities.

## Neurodiagnostic testing

Brain MRI showed some atrophy which was stable over time (Figure S3). Long-term video electroencephalogram showed a normal background but was notable for 1-2 second diffuse bursts of rhythmic theta/delta activity during wakefulness. At times, there were embedded spikes in the bursts of slowing with variable maxima. There was also frequent quasi-rhythmic theta activity during wakefulness seen in the central/vertex region occurring for up to 15 seconds.

## Biochemical and Molecular Data

Research-based exome sequencing revealed compound heterozygous pathogenic variants in *PSAT1* (NM_058179.2:c.467C>T; p.Thr156Met and c.43G>C; p.Ala15Pro); the patient's clinical phenotype was consistent with phosphoserine aminotransferase deficiency (PSATD).[4,12] The p.Thr156Met variant is rare (24/282,878 alleles in gnomAD[13] v2.1.1), occurs at a residue conserved through evolution (Figure S4), and is predicted pathogenic by several in silico algorithms (deleterious by SIFT[14], probably damaging by Polyphen-2[15], Phred-scaled CADD[16] score 26.5). The p.Ala15Pro variant is rare (12/258,286 in gnomAD v2.1.1), occurs at a residue conserved through evolution (Figure S5), and is predicted pathogenic by in silico algorithms (deleterious by SIFT, probably damaging by Polyphen-2, Phred-scaled CADD score 32). The p.Ala15Pro was recently demonstrated to be a loss of function variant.[17]Additionally, plasma amino acid measurements confirmed a functional effect on PSAT1 function, given the low fasting serine concentration at 21 μmol/L (normal range 63-187); glycine was normal at 160 μmol/L (normal range 126-490). In retrospect, at age 26 years a plasma serine concentration was 43 μmol/L, just below the reference range (44-180) for that lab (non-fasting samples may decrease sensitivity.) Cerebrospinal fluid (CSF) amino acid analysis showed low serine at 3.8 μmol/L (reference range 18.3-52.2). CSF glycine and CSF organic acid profiles were normal. Serum vitamin B12 level was normal. Her CSF neurotransmitters showed low 5-hydroxyindoleacetic Acid (5-HIAA) at 41 nmol/L (reference range 67-140) and low homovanillic Acid (HVA) at 102 nmol/L (reference range 145-324), with normal 3-O-methyldopa, tetrahydrobiopterin and neopterin, as well as 5-methyltetrahydrofolate.

## Treatment

At age 37, the patient began high dose oral L-serine repletion at approximately 100 mg/kg/day, given as 1.5 grams three times daily. The dose was extrapolated from childhood treatment cases.[1,5,18–21] There is also evidence of dosing in adults with hereditary sensory neuropathy type 1 (HSAN1).[22–24] The patient's plasma serine level normalized, but then declined as her urinary serine excretion increased. Over time, the plasma serine level returned to the reference range without any change in dosing (Figure S2). Given her spinal canal stenosis, we were unable to confirm a post-treatment therapeutic CSF serine level

despite attempts at repeat lumbar puncture under fluoroscopic guidance. The patient has tolerated the serine well without side-effects.

Her skin manifestations markedly improved, including her ichthyosis, trichorrhexis, and onychodystrophy (Figure 2.) This has greatly enhanced her quality of life, since the pruritus had been unrelenting despite maximal medical therapy with associated sedative side effects. Her hypertension resolved such that her antihypertensives have been weaned (she was on amlodipine 10 mg twice daily and metoprolol 25 mg daily, now only on amlodipine 5 mg daily). She seemed more alert and more vocal. Prior to treatment from a gynecologic perspective, she had been anovulatory having only one to four menses per year and had been given medroxyprogesterone acetate to induce withdrawal bleeds. Upon serine repletion, she had three spontaneous menses in a seven-month span. However at the age of 39 years she was diagnosed with primary ovarian insufficiency (POI) in the setting of secondary amenorrhea for >4 months and two follicle stimulating hormone (FSH) values in the menopausal range at least one month apart with normal prolactin and normal thyroid function.[25] This diagnosis was supported by the patient's vasomotor symptoms of hot flushes and additional laboratory findings of undetectable inhibin B and antimullerian hormone (AMH) with menopausal range estradiol levels. Evaluation of potential etiologies of POI including karyotype, *FMR1* premutation testing, and testing for adrenal antibodies, failed to identify a cause. Given the negative POI work-up in this patient, serine biosynthesis deficiency as a cause of POI could not be excluded. Also likely exacerbated by her immobility and low estrogen levels related to POI, the patient was found to have osteoporosis (BMD measured at femur T-score of −3.6) for which she has been started on a bisphosphonate.

Profound sensorineural hearing loss persisted with declining benefit from hearing aids. The patient was evaluated for a cochlear implant and underwent this procedure for the right ear. After cochlear implantation, her ability to comprehend daily conversation has improved significantly and there are plans for a contralateral cochlear implant.

Nerve conduction electrodiagnostic studies showed a severe axonal sensorimotor neuropathy with a possible demyelinating component. In her initial study at 34 years of age, facial motor nerve conduction (MNC) had the only recordable response with normal amplitude and prolonged distal latency. In her subsequent study at age 39 years, the facial MNC was unchanged. A study of the median MNC, recording from forearm (flexor carpi radialis) obtained low amplitude response with slow conduction velocity that was not obtained on her initial study. Additional MNC studies on proximal arm muscles (axillary nerve, musculocutaneous nerve) were performed and showed prolonged distal latencies. No responses to any of the sensory nerves nor motor nerves in the legs were obtained in either study. Needle EMG of proximal arm muscles showed chronic neurogenic changes with a reduced number of motor units activated.

## DISCUSSION

There is limited data about the treatment of serine deficiency (Tables S1 and S2), especially in milder phenotypes diagnosed in adulthood.[6] All previously reported treatments of PSAT1 deficiency have been in children.[4,12]

The first patients identified with PSAT deficiency were siblings, an older male followed by a female, born to nonconsanguineous parents.[4] Although treatment with serine and glycine was initiated at 11 weeks, the male infant died at age 7 months. His younger sister was treated within 24 hours of life; clinical results included head circumference catch-up and normal growth and development at age 3 years. The striking contrast in outcomes for these siblings emphasizes the importance of early diagnosis and treatment for patients with serine deficiency. Brassier et al.[12] reported a male with PSAT deficiency who began treatment at age 3 months; this improved his spasticity, and serine plasma and CSF values were normalized. However, at age 5.5 years, the patient was bedridden with small head circumference and no psychomotor progress.

The mechanism of the central and peripheral neurological manifestations of serine deficiency disorders is not well understood. Serine is a substrate in the rate-limiting step of the biosynthesis of sphingolipids, which are essential for normal neural tissue function. Recent work has suggested that limited serine availability might result in an overall decrease in sphingolipids[1] or in phospholipids.[26] Another possible mechanism is an increase in atypical sphingolipids, which may be neurotoxic. When insufficient serine is available for sphingolipid biosynthesis, non-canonical substrates are utilized, resulting in the production of atypical sphingolipids.[18,27] The neurological phenotype seen in serine-deficient patients may thus be explained by the combination of impaired neural tissue function due to a shortage of sphingolipids and the neurotoxic effects of atypical sphingolipids. Recent work highlights the importance of serine metabolism in macular disease.[11]

Inborn errors of metabolism should be considered when evaluating adults with progressive polyneuropathy, given that disorders of serine biosynthesis are treatable.[6,20] It is also important to consider other neuro-ichthyotic syndromes[28] especially potentially treatable ones, such as Refsum disease which can respond to restriction of dietary phytanic acid, or MEDNIK syndrome (intellectual disability, ichthyosis, hearing loss, peripheral neuropathy, enteropathy, and keratoderma) due to a defect in copper metabolism, which is treatable by zinc supplementation.[29]

Our patient has been receiving serine repletion for three years with normalized plasma levels. Unfortunately, we were unable to measure CSF serine level on treatment to assess adequacy of current dosing regimen. The patient’s integumentary problems fully resolved, as well as some of her systemic features such as her hypertension. She has been neurologically stable, including no progression of her neuropathy on repeat nerve conduction testing, with the caveat that she already had severe neuropathy at onset of treatment. She underwent cochlear implant with good results even though serine deficiency may have affected the central auditory pathway.

Despite an adult diagnosis and treatment onset, our patient experienced stabilization of neurological regression and resolution of skin manifestations and hypertension with treatment. This suggests that in adult patients presenting with ichthyosis, polyneuropathy, joint contractures, developmental delay, and microcephaly, it is prudent to consider late presentations of inborn errors of metabolism. Since plasma levels of serine can be normal, especially in non-fasting samples, serine deficiency disorders can be clinically missed. Furthermore, genetic testing is necessary to confirm the specific serine synthesis enzyme affected. As exome sequencing is becoming more readily available, the phenotypic spectrum of previously classical childhood onset disorders will continue to expand.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## REFERENCES

1. El-Hattab AW. Serine biosynthesis and transport defects. Mol Genet Metab 2016; 118(3): 153–9. [PubMed: 27161889]
2. van der Crabben SN, Verhoeven-Duif NM, Brilstra EH, et al. An update on serine deficiency disorders. J Inherit Metab Dis 2013; 36(4): 613–9. [PubMed: 23463425]
3. El-Hattab AW, Shaheen R, Hertecant J, et al. On the phenotypic spectrum of serine biosynthesis defects. J Inherit Metab Dis 2016; 39(3): 373–81. [PubMed: 26960553]
4. Hart CE, Race V, Achouri Y, et al. Phosphoserine aminotransferase deficiency: a novel disorder of the serine biosynthesis pathway. Am J Hum Genet 2007; 80(5): 931–7. [PubMed: 17436247]
5. Tabatabaie L, Klomp LW, Berger R, de Koning TJ. L-serine synthesis in the central nervous system: a review on serine deficiency disorders. Mol Genet Metab 2010; 99(3): 256–62. [PubMed: 19963421]
6. Byers HM, Bennett RL, Malouf EA, et al. Novel Report of Phosphoserine Phosphatase Deficiency in an Adult with Myeloneuropathy and Limb Contractures. JIMD Rep 2016; 30: 103–8. [PubMed: 26589312]
7. Gahl WA, Tifft CJ. The NIH Undiagnosed Diseases Program: lessons learned. JAMA 2011; 305(18): 1904–5. [PubMed: 21558523]
8. Gahl WA, Markello TC, Toro C, et al. The National Institutes of Health Undiagnosed Diseases Program: insights into rare diseases. Genet Med 2012; 14(1): 51–9. [PubMed: 22237431]
9. Gahl WA, Mulvihill JJ, Toro C, et al. The NIH Undiagnosed Diseases Program and Network: Applications to modern medicine. Mol Genet Metab 2016; 117(4): 393–400. [PubMed: 26846157]
10. Rashid S, Saleem S, Luat AF. Sjögren-Larsson Syndrome: A Neuro-Ichthyotic Disorder With Unique Magnetic Resonance Features. Pediatr Neurol 2016; 62: 73–4. [PubMed: 27212566]
11. Gantner ML, Eade K, Wallace M, et al. Serine and Lipid Metabolism in Macular Disease and Peripheral Neuropathy. N Engl J Med 2019; 381(15): 1422–33. [PubMed: 31509666]
12. Brassier A, Valayannopoulos V, Bahi-Buisson N, et al. Two new cases of serine deficiency disorders treated with l-serine. Eur J Paediatr Neurol 2016; 20(1): 53–60. [PubMed: 26610677]
13. Karczewski KJ, Francioli LC, Tiao G, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature 2020; 581(7809): 434–43. [PubMed: 32461654]
14. Kumar P, Henikoff S, Ng PC. Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. Nat Protoc 2009; 4(7): 1073–81. [PubMed: 19561590]

15. Adzhubei IA, Schmidt S, Peshkin L, et al. A method and server for predicting damaging missense mutations. Nat Methods 2010; 7(4): 248–9. [PubMed: 20354512]
16. Rentzsch P, Witten D, Cooper GM, Shendure J, Kircher M. CADD: predicting the deleteriousness of variants throughout the human genome. Nucleic Acids Res 2019; 47(D1): D886–D94. [PubMed: 30371827]
17. Sirr A, Lo RS, Cromie GA, et al. A yeast-based complementation assay elucidates the functional impact of 200 missense variants in human PSAT1. J Inherit Metab Dis 2020; 43(4): 758–69. [PubMed: 32077105]
18. Ferreira CR, Goorden SMI, Soldatos A, et al. Deoxysphingolipid precursors indicate abnormal sphingolipid metabolism in individuals with primary and secondary disturbances of serine availability. Mol Genet Metab 2018; 124(3): 204–9. [PubMed: 29789193]
19. Jaeken J, Detheux M, Fryns JP, Collet JF, Alliet P, Van Schaftingen E. Phosphoserine phosphatase deficiency in a patient with Williams syndrome. J Med Genet 1997; 34(7): 594–6. [PubMed: 9222972]
20. Méneret A, Wiame E, Marelli C, Lenglet T, Van Schaftingen E, Sedel F. A serine synthesis defect presenting with a Charcot-Marie-Tooth-like polyneuropathy. Arch Neurol 2012; 69(7): 908–11. [PubMed: 22393170]
21. de Koning TJ, Klomp LW, van Oppen AC, et al. Prenatal and early postnatal treatment in 3-phosphoglycerate-dehydrogenase deficiency. Lancet 2004; 364(9452): 2221–2. [PubMed: 15610810]
22. Auranen M, Toppila J, Suriyanarayanan S, et al. Clinical and metabolic consequences of L-serine supplementation in hereditary sensory and autonomic neuropathy type 1C. Cold Spring Harb Mol Case Stud 2017; 3(6).
23. Garofalo K, Penno A, Schmidt BP, et al. Oral L-serine supplementation reduces production of neurotoxic deoxysphingolipids in mice and humans with hereditary sensory autonomic neuropathy type 1. J Clin Invest 2011; 121(12): 4735–45. [PubMed: 22045570]
24. Fridman V, Suriyanarayanan S, Novak P, et al. Randomized trial of l-serine in patients with hereditary sensory and autonomic neuropathy type 1. Neurology 2019; 92(4): e359–e70. [PubMed: 30626650]
25. Nelson L Primary Ovarian Insufficiency. New England Journal of Medicine 2009; 360(6): 606–14.
26. Glinton KE, Benke PJ, Lines MA, et al. Disturbed phospholipid metabolism in serine biosynthesis defects revealed by metabolomic profiling. Mol Genet Metab 2018; 123(3): 309–16. [PubMed: 29269105]
27. Penno A, Reilly MM, Houlden H, et al. Hereditary sensory neuropathy type 1 is caused by the accumulation of two neurotoxic sphingolipids. J Biol Chem 2010; 285(15): 11178–87. [PubMed: 20097765]
28. Rizzo WB, Jenkens SM, Boucher P. Recognition and diagnosis of neuro-ichthyotic syndromes. Semin Neurol 2012; 32(1): 75–84. [PubMed: 22422210]
29. Martinelli D, Travaglini L, Drouin CA, et al. MEDNIK syndrome: a novel defect of copper metabolism treatable by zinc acetate therapy. Brain 2013; 136(Pt 3): 872–81. [PubMed: 23423674]

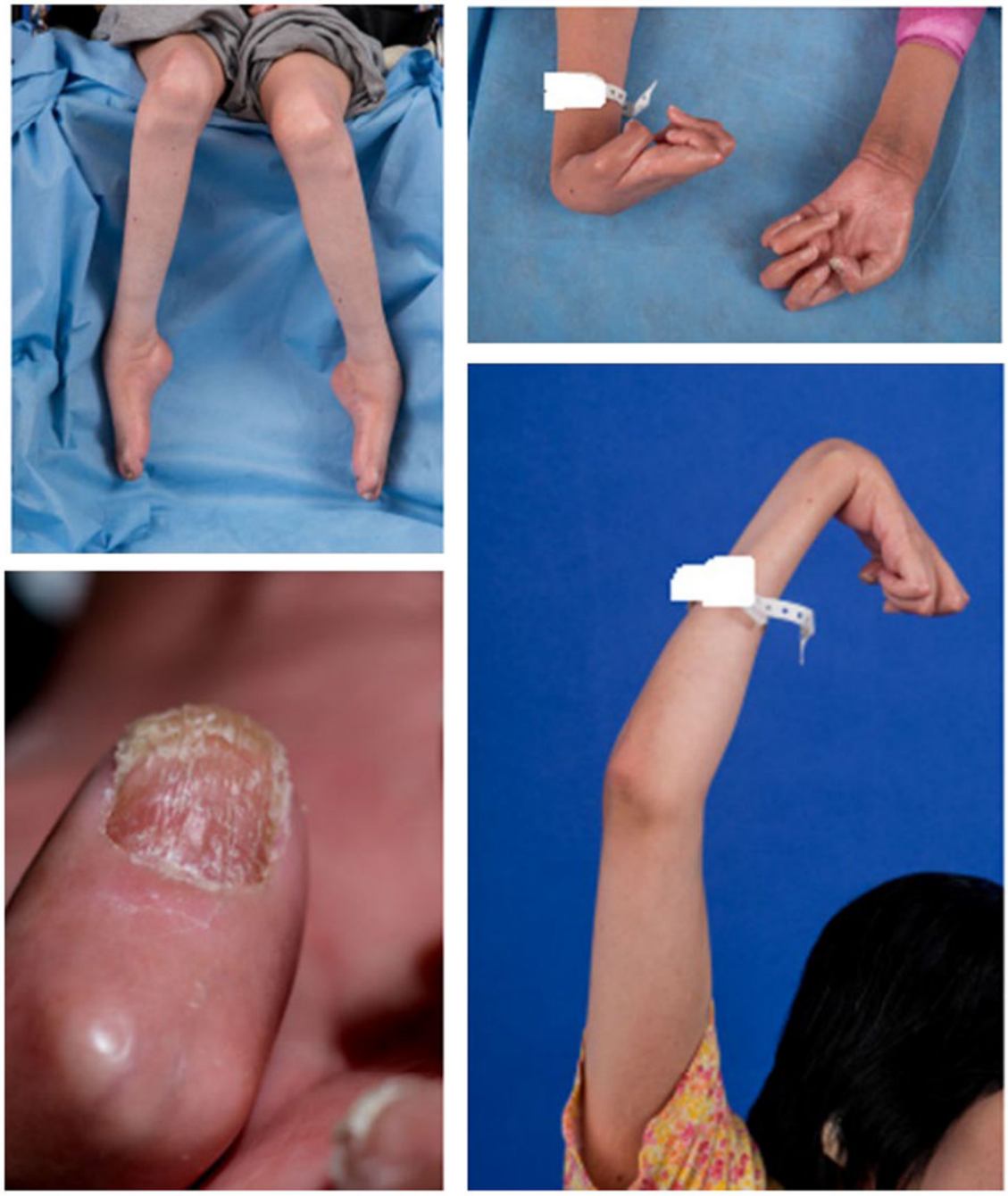

**Figure 1. Clinical features**

Top row, contractures of lower and upper extremities; bottom left panel, onychodystrophy; bottom right panel, preserved proximal muscle strength in upper extremities.

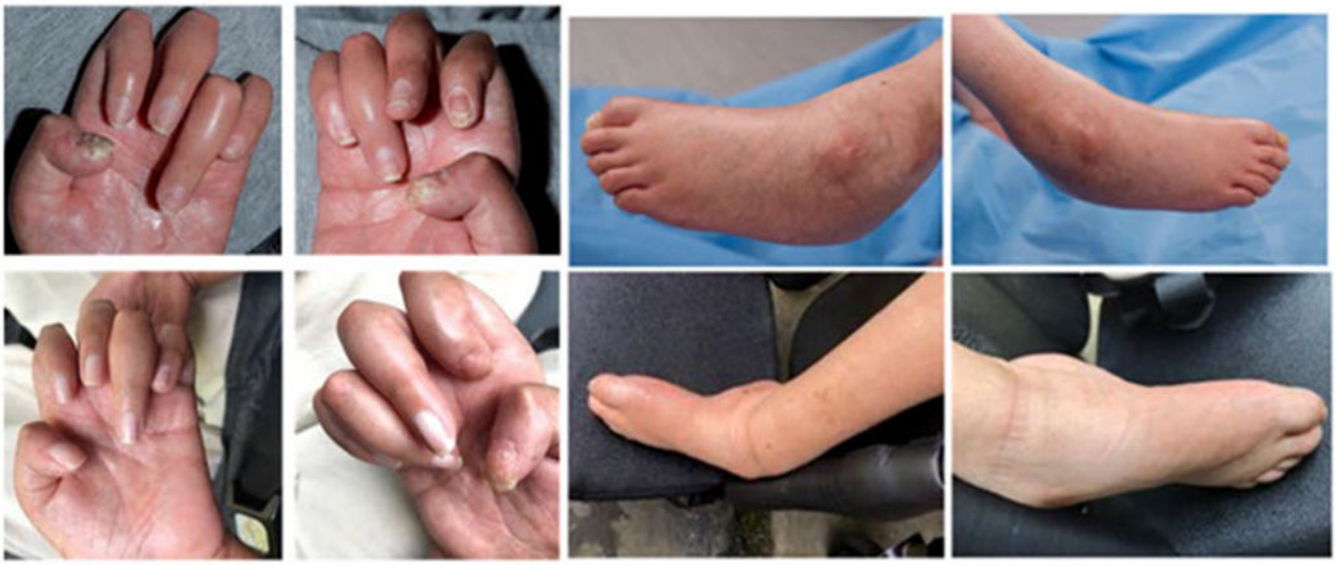

**Figure 2. Skin and nail improvement under serine treatment**

Top row: 2013 pre-treatment; bottom row: 2018 post-treatment