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Review Article

The skeletal muscle phenotype of children with Neurofibromatosis Type 1 – A clinical perspective

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Abstract

Neurofibromatosis type 1 (NF1) can affect multiple systems in the body. An under recognised phenotype is one of muscle weakness. Clinical studies using dynamometry and jumping mechanography have demonstrated that children with NF1 are more likely to have reduced muscle force and power. Many children with NF1 are unable to undertake physical activities to the same level as their peers, and report leg pains on physical activity and aching hands on writing. Children and adolescents with NF1 reporting symptoms of muscle weakness should have a focused assessment to exclude alternative causes of muscle weakness. Assessments of muscle strength and fine motor skills by physiotherapists and occupational therapists can provide objective evidence of muscle function and deficits, allowing supporting systems in education and at home to be implemented. In the absence of an evidence base for management of NF1-related muscle weakness, we recommend muscle-strengthening exercises and generic strategies for pain and fatigue management. Currently, trials are underway involving whole-body vibration therapy and carnitine supplementation as potential future management options.

Keywords: NF1, Muscle, Fatigue, Motor Skills, Strength

Introduction

Neurofibromatosis type 1 (NF1) is one of the commonest multi-system autosomal dominant monogenic disorders, with an incidence of 1 in 2600 to 1 in 3000 births[1,2]. Approximately 50% of cases are due to *de novo* mutations[1]. NF1 occurs due to inactivating germline mutations in the NF1 gene, which encodes neurofibromin[3]. Neurofibromin is a negative regulator of the Ras-MAPK signal transduction pathway, with a role as a tumour suppressor.

The hallmark clinical features of NF1 are café au lait spots (6 or more, >5 mm in diameter in prepubertal individuals, >15 mm in diameter in post-pubertal individuals), at least 2 neurofibromas of any type or one plexiform neurofibroma, axillary and/or inguinal freckling, optic pathway glioma, 2 or more Lisch nodules in the iris, a distinctive osseous lesion (such as sphenoid wing dysplasia, congenital pseudoarthrosis or significant kyphoscoliosis), and an affected first degree relative[4]. Diagnosis is based on the presence of at least two of these features. Other non-diagnostic clinical features include an increased incidence of short stature, behavioural and cognitive difficulties, renal artery stenosis, phaeochromocytoma and epilepsy[5]. Children with NF1 have low bone mineral density[6-12] and increased risk of fracture across both sexes and throughout childhood and older adulthood, with 3-fold and 5-fold increase in risk respectively[13].

A less well-known phenotype of NF1 is one of muscle weakness. Here we have reviewed the current knowledge of

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muscle weakness in NF1 and its pathophysiology, as well as the clinical symptoms and signs in children and adolescents that may be suggestive of this. We also discuss our approach to assessment and management of NF1-related muscle weakness in children and adolescents and review potential future therapies.

Muscle weakness in NF1

In the 20th century, specific skeletal muscle abnormalities had not been identified as a recognised feature of NF1. It was in a small cohort of children and adults with NF1 (n=21), that Souza et al were the first to show that the maximal grip force was significantly reduced compared to controls matched for age, gender and physical activity, even after accounting for the reduced arm muscle cross-sectional area in individuals with NF1[14]. This reduced grip force has been observed in patients with other Ras-MAPK pathway disorders[15], suggesting that it is dysfunction of this pathway that may underlie muscle weakness. Furthermore, Stevenson et al have demonstrated using peripheral quantitative computed tomography (pQCT) that children with NF1 had significantly reduced muscle cross-sectional area in the tibia compared to controls, even after controlling for age, gender, height and pubertal staging[16].

Within the paediatric population, Cornett et al demonstrated that the magnitude of difference in muscle force measured using hand-held dynamometry between cases and controls ranged from 3-43% depending on muscle group, but without any pattern in types of muscles more severely affected[17]. On the other hand, another group showed only significant reductions in force production on hip extension, but not knee extension or ankle plantar flexion, in keeping with a proximal muscle weakness[18]. The differences in findings between the two studies may be due to differences in matching and relevant co-morbidities.

Dynamic muscle function, of greater clinical relevance, can be assessed using ground reaction force platforms. Using the single two-legged jump test, it was demonstrated that peak jumping power and force per kilogram of body weight were reduced in children with NF1 compared to siblings, following controlling for body mass, age and gender[19]. Of note, there were no differences between the cases and controls with regards physical activity, dietary calcium intake and serum 25-hydroxyvitamin D [25(OH)D] levels, which is a reliable measure of an individual's vitamin D stores. Severe vitamin D deficiency can result in muscle weakness[20,21]. However, other paediatric studies have also not demonstrated a significant difference in 25(OH)D levels between NF1 cases compared to controls[22-24].

Deficits in gross motor (tone, coordination, balance, gait) and fine motor (coordination, speed, steadiness) function have been noted in children with NF1 compared to controls, when investigating neurological, cognitive and developmental dysfunction[25-30]. Although there is an important cognitive element to these tasks, adequate muscle function is also required to execute these higher level instructions, suggesting some of this deficit may also be due to muscle weakness. A study by Johnson et al helps to understand the impact of muscle function on motor tasks in children with NF1[31]. They used the Bruininks-Osertsky Test of Motor Proficiency second edition (BOT2) in 26 children with NF1, and examined both cognition-dependent and relatively cognition-independent motor tasks. The 'Strength and agility' composite demonstrated the greatest deficit and accounted for the greatest variance in the total motor composite score. Given that the 'Strength and agility' domain is the least cognition-dependent, this suggests that impaired muscle strength and function may partly contribute to the low total motor composite scores.

Recently, muscle biopsies have been examined from six individuals with NF1 and compared to controls, demonstrating muscle fibrosis, as well as increased intramyocellular lipid and triglyceride content, which was negatively correlated with *NF1* expression[32]. This is in keeping with what has been demonstrated in mouse models[32-34].

Taken together, data from clinical studies suggests the muscle weakness is intrinsic to NF1, independent of confounding factors, such as vitamin D status, with muscle biopsies suggesting an underlying pathophysiology that involves defects in lipid metabolism. To date, all of these clinical studies have examined small cohorts, with the largest study evaluating 30 individuals with NF1. Larger studies need to be conducted to confirm this finding, as well as establish prevalence amongst individuals with NF1.

The potential impact of muscle weakness in children and adolescents with NF1

Trying to discern the impact that muscle weakness may have on some of the other recognized features of NF1 in children described below is challenging. Firstly, this is because there is very little literature that studies these potential associations, and therefore many of them are simply hypothesized. Secondly, many of the features are likely to be multi-factorial in their aetiologies due to a variety of comorbidities recognised in NF1. However, from our clinical experience, the following are some aspects that we have felt has been affected in individuals with NF1 who have muscle weakness.

As already mentioned, in addition to cognitive dysfunction, muscle weakness may also play a role in impaired gross and fine motor impairment in children with NF1. Deficits in gross motor skills, may affect their social interaction and participation, particularly in relation to physical activity[31]. In healthy children, there are some associations between muscle strength and physical activity[35,36]. Although these direct links have not been made in children with NF1, a study has demonstrated low physical activity and social participation in children with NF1[37]. This is likely to be multi-factorial, with comorbidities such as behavioural abnormalities and learning difficulties likely to be contributory also. Poorer hand-writing

Table 1. Summary recommendations for the clinical evaluation and management of children with NF1-related myopathy. This summary was achieved using a modified Delphi consensus. The initial phase involved review of the relevant literature by two members (AC, MZM) and formulation of a draft approach for evaluation and management of NF1-related muscle weakness. Round 1 involved a face-to-face meeting of all panel members, to discuss the 5 sections of the table that are important within a clinic setting: Important features in the history to consider; Important features in the examination to consider; Important investigations to consider; Other potential assessments to consider; Management options. Suggestions for each section were provided by panel members, along with rationale based on evidence and practical experience. Each suggestion was discussed individually amongst the panel members, with a final list agreed. Round 2 involved individual electronic voting by each panel member as to the 3 most important points within each section. This was then collated to produce the final table (the sections on Investigations and Management had 4 points rather than 3 due to equal point ratings). Round 3 involved email circulation of the final table for agreement. Panel members included 2 paediatric neurologists with a sub-specialty interest in NF1, 1 clinical professor in paediatric metabolic bone disorders with a major interest in NF1, 2 paediatric endocrinologists with an interest in NF1 musculoskeletal health, 1 academic clinical geneticist specialising in Ras-opathies, 2 NF1 clinical nurse specialists, 1 paediatric physiotherapist specialising in metabolic bone disorders and 1 occupational therapists specialising in metabolic bone disorders. CAMHS – Child and adolescent mental health services.

HISTORY
• Unable to do age-appropriate levels of physical activity[a]
• Aching legs, particularly following a day of greater than usual physical activity[b]
• Hands tire or ache when writing or drawing[c]
Features prompting consideration of alternative diagnosis: Focal pain, global or severe developmental delay, severe & progressive muscle weakness, family history of conditions other than NF1 that affect muscle function, concerns of psychological overlay
EXAMINATION
• Neurological examination[d]
• Focussed pGALS[e]
• Visual observation of foot position, including assessment for flat feet
Concerning features prompting consideration of alternative diagnosis: Altered neurology (especially if focal) other than subtle reduction in power
POSSIBLE INVESTIGATIONS (***only*** to be considered if suggestions in the history or examination of alternative aetiology to muscle weakness)
• Serum 25-hydroxyvitamin D
• Creatine kinase
• Thyroid function
• Brain imaging
OTHER POTENTIAL ASSESSMENTS[f]
• Upper limb: Point-of-care grip force measurement
• Lower limb: 6-minute walk test
• Perceived fatigue: PedsQL multi-dimensional fatigue scale
MANAGEMENT
• Information and education provided to parents and school to manage muscle weakness and associated physical features[g]
• Pacing advice - may need frequent periods of rest during physical activities[h]
• Education on pain management strategies – Relaxation, distraction, heat, occasional use of simple analgesia (paracetamol, ibuprofen) on days of particularly intense physical activity[i]
• Allied healthcare professional involvement - Physiotherapy: Muscle strengthening exercises - Occupational therapy: Adaptive pens, pencils, cutlery - Podiatry/orthotics: In-soles, orthosis, footwear advice and ankle support
Consider CAMHS/psychology/chronic pain team input if alternative needs identified, or management of pain/weakness out of proportion to degree of myopathy clinically

a. This subjective report would include requiring frequent rests during walking and school activity, not keeping up with their peers and friends, or requiring buggies/strollers for relatively short distances.
b. The pain from NF1 muscle weakness typically occurs in the evening and night following a day of physical activity, though be aware that pain can occur for a number of reasons in NF1. Therefore consider alternative diagnosis (particularly neurofibroma, plexiform or another tumour) if the pain is unilateral, focal or persistently disturbing sleep.
c. Although quality of hand-writing also deteriorates, this may be dependent on learning difficulties, dyspraxia and other central neurological issues.
d. This is primarily to exclude any central neurological deficits that may underlie muscle weakness. A mild reduction in power may be observed simply with NF1 muscle weakness. This may be evident on Gowers' manoeuvre – children with NF1 myopathy are usually able to perform the Gowers' manoeuvre, but slower and less efficiently.
e. This is primarily to quickly ascertain the functional impact on daily activities, as well as to ascertain any concurrent joint hypermobility. (If noted, hypermobility can be more formally assessed with the Beighton score.)
f. These assessments could be considered where available, to obtain a greater understanding of the degree of deficit in muscle weakness, and its impact, to guide the level of support needed.
g. This allows adjustments and allowances to be made (e.g. understanding that they may tire more easily than their peers, and provision for extra time for activities and schoolwork).
h. Advice to be given to remain as active as possible to allow muscle growth and strength to occur, but to allow frequent rest to prevent muscle ache and fatigue developing.
i. Consider alternative explanations if requiring analgesia regularly.

skills, in terms of tidiness and legibility, have been observed in children with NF1 compared to controls[27,30,38]. Although there is an important cognitive element to handwriting that affects fine motor skills, clearly muscle weakness will impact on letter formation also. Certainly, the deficits that have been demonstrated in grip force in children with NF1 will impact on writing performance. In clinical practice, we have also observed difficulties with other fine motor tasks, such as doing buttons and tying shoelaces. Johnson et al commented that the degree of motor dysfunction in 27% of their NF1 cohort would have qualified them for special educational services[31], highlighting the significant academic impact that this phenotype may have in children with NF1.

It is well recognised that muscle dysfunction can result in fatigue in a variety of other conditions associated with neuromuscular dysfunction, inflammation and disuse (reviewed in [39]). Fatigue is a common parental reported symptom in children and young adults with NF1 also[40-42]. Furthermore, using the PedsQL™ Multidimensional Fatigue Scale, children themselves with NF1 report significantly greater perceived fatigue compared to healthy controls[43]. It is accepted that fatigue is multifactorial in aetiology[39], although the contributory factors to fatigue in NF1 have yet to be explored. However, in our clinical practice, children and their families often relate the muscle aches and pains from their muscle weakness to their degree of fatigue, suggesting that muscle weakness is a substantial contributory component to perceived fatigue. Children with NF1 have been demonstrated to have a reduced quality of life[40,41,44-47]. It is quite possible that, much like muscle weakness could affect fatigue, physical activity and academic performance, that it could therefore indirectly affect quality of life also.

In summary, muscle weakness in NF1 has the potential to impact (to a variable extent) on many of the features observed in NF1. However, further research is required to establish whether such associations exist in clinical practice.

Clinical evaluation of muscle weakness in children and adolescents with NF1

Although not reported in the literature, clinicians had for many years observed clinical features suggestive of muscle weakness in some children and adolescents with NF1, including poor exercise tolerance, fatigue and lower limb pains. Currently there is no evidence base on the clinical assessment of NF1-related muscle weakness and management of its symptoms. Therefore, the following recommendations (Table 1) are based on modified Delphi consensus from practice within our multi-disciplinary highly-specialised National NF1 service, which includes paediatric neurologists, paediatric metabolic bone disorder specialists, geneticists, NF1 nurse specialists, as well as specialist paediatric metabolic bone disease physiotherapist and occupational therapist. This can thus serve as a guide to clinicians until a global consensus on the topic can be established, involving critical review of available trials and studies, as well as experience of international experts.

In the clinical history, NF1-related muscle weakness may manifest as fatigue, reported subjectively as not being able to do as much activity as their peers, insisting on use of buggies or strollers for even short walking distances and tiring hands when writing. Common symptoms include aches and pains due to relative muscle overuse and subsequent fatigue – in the lower limbs following a day of physical activity that is greater than normal, and in the hands when writing. The difficulty clinically is that these symptoms and descriptions are vague and non-specific, but would suggest the clinician to consider assessing for possible muscle weakness. However, it is important to bear in mind also that these symptoms can be multi-factorial in aetiology, particularly in children with NF1, with interplay between these factors complicating the clinical picture[48]. Therefore, other causes relevant to NF1 should also be considered in further examination and possibly investigated, particularly tumours if any pain is focal or intense or has neuropathic features. Additionally, joint hypermobility, central neurological deficits, cognitive difficulties and behavioural issues can also present with some of these symptoms in children with NF1, and need to be considered in the differentials and during clinical assessment. In younger children, muscle weakness may manifest as delayed gross and fine motor milestones, although severe or global developmental delay should prompt investigation for other aetiologies as suggested above.

Examination of a child or an adolescent with symptoms of NF1-related muscle weakness should include a neuromuscular examination to identify any neurological deficit that may be underlying any muscle weakness. A mild reduction in proximal muscle power may be observed when the Gowers' manoeuvre is performed in a child, although a more significant reduction in power should prompt assessment of other central neurological diagnoses[49]. The low muscle tone in children with NF1 is associated with joint hypermobility and pes planus (flat feet). Notably, some children with low muscle tone progress to develop tightness in their Achilles' tendons in adolescence, as may also be seen in other Ras-MAPK pathway disorders[50,51], as well as neuromuscular disorders such as Duchenne muscular dystrophy and other neuromuscular disease[52,53]. We would also encourage including a focused pGALS (Paediatric Gait Arms Legs Spine) examination[54] during clinical assessment, not only to identify any obvious issues in daily functioning that may be affected by muscle weakness, but also to point towards any joint hypermobility. If joint hypermobility is suggested, the Beighton score is a simple and validated measure to objectively assess for joint hypermobility[55].

Biochemical and radiological investigations to exclude other causes of muscle weakness are important to consider, but are rarely required and should only be carried out if there is a clinical concern about alternative or additional pathology (for example if there is a severe or focal muscle weakness reported in the history or noted on clinical assessment). Such investigations to consider at that time include thyroid function tests, serum 25-hydroxy-vitamin D (as severe

vitamin D deficiency can cause a myopathy in children[21] and vitamin D deficiency is very common[56-59]), creatine kinase (if a muscular dystrophy is suspected) and brain imaging (to exclude structural abnormalities, accepting that unidentified bright objects are commonly noted in individuals with NF1 and therefore the imaging should be reviewed by a neuroradiologist with experience in NF1).

Objective assessments of muscle strength and function are usually considered only after clinical review and guidance by physiotherapists and occupational therapists, and are usually carried out by these healthcare professionals. Many such assessments are available which evaluate upper limb muscle performance (e.g. grip force, speed of handwriting assessments, manual dexterity tasks) and lower limb performance (e.g. 6-minute walk test, jumping mechanography, sit-to-stand tests), as well as complete assessments of fine and gross motor function (e.g. Movement ABC). Although some of these assessments have been used within the research setting for children with NF1 (as described earlier in this article), as far as we are aware they are not used routinely in clinical practice for this cohort. However, point-of-care grip force measurement using a handheld-dynamometer is a simple, easy and validated tool that could be used where available, as it provides a clinically useful parameter of upper limb muscle performance, given that there is widely available normative data that allows for objective calculation of the degree of deficit[60,61]. Furthermore, this can provide valuable objective information for schools and occupational therapists to direct their resources for additional support. Similarly, the 6-minute walk test is a validated measure of lower limb function and endurance with normative data that allows calculation of the degree of deficit[62,63]. However, it is more time-consuming than grip force measurement and therefore is perhaps more appropriate for use outside of the clinic setting.

Objective measurement of the degree of perceived fatigue is useful, to consider the impact that muscle weakness (if present objectively) may be having on an individual's life. We have found the PedsQL™ Multidimensional Fatigue Scale, a clinically validated tool, to be informative with this regard[43].

Management options for muscle weakness in children and adolescents with NF1

Despite recent advances in the identification of muscle weakness in children with NF1 and its underlying histopathology, there is no evidence-based clinical management guideline for this. However, clinical experience suggests that the muscle weakness impacts these individuals significantly, with concerned families often seeking advice from healthcare professionals about how to manage it. We have found that enabling recognition and management of significant fatigue and the aches and pains following activity can in itself help to alleviate parental anxiety. Furthermore, enabling school services to understand the issue is also important, so that adequate provisions can be made that allow participation in activity whilst still permitting frequent rests.

Whilst current trials are awaited that may address the issues with muscle metabolism underlying the weakness, clinicians currently use generic approaches to manage the fatigue and pain resulting from muscle weakness, which allows the child or adolescent to cope with the deficit (Table 1). This includes advice about pacing for those that tire easily, such as incorporating frequent rests during physical activities before pain or fatigue is experienced, to encourage a pattern of greater activity and participation[64]. Education on management strategies for the muscle ache is crucial – we advise simple approaches such as relaxation, heat and distraction strategies. Pharmacological management of the muscle ache using simple analgesics (e.g. paracetamol, ibuprofen) can be a challenging area. Although occasional use of these analgesics following particularly active days can be a useful approach in our practice, regular use of analgesics is to be discouraged as it can result in an over-reliance on medication (rather than pacing or exercise strategies) to resolve the symptoms, complications from analgesic overuse and masking of alternative issues. Education of parents and school staff about the child's muscle weakness and associated physical limitations and fatigue is an essential component of managing the impact of the muscle weakness. This will enable the appropriate understanding and adjustments to be made in order to establish the child's daily routine, promoting optimal participation in activities of daily living and school life, whilst managing pain and fatigue. Occupational therapy can provide strategies and advice to manage hand muscle fatigue and activities of daily living. Concurrent pes planus and joint hypermobility can contribute to the muscle ache and fatigue, for which orthotics or podiatry services may be required to provide relevant advice, ankle support and in-soles.

Muscle-strengthening training programmes (usually implemented by physiotherapists) have been shown in systematic reviews to cause improvements in muscle strength and function both in healthy children and in children with other conditions that can cause muscle weakness (such as cerebral palsy and osteogenesis imperfecta)[65-68]. Therefore, this represents an attractive option for children with NF1 who have muscle weakness. Johnson et al implemented a 10-week plyometric training programme in 3 children with NF1 aged 5-10 years with evidence of poor motor skills[69]. Plyometric training involves repetitive high impact activities with the aim of improving strength and activity. All 3 participants demonstrated improvements in throwing distance, with 2 participants showing an improvement in jumping distance[69]. This was followed by a study which examined subjective questionnaire outcomes following the same 10-week programme in 18 children with NF1, versus 18 children with NF1 that did not receive the intervention[37]. At the end of this intervention period, participant-reported upper extremity activity improved in the intervention group, whereas participant-reported happiness declined; the converse being true in the control group. Unsurprisingly, there were no significant differences between the two groups

at one year (nine months after cessation of the intervention programme), indicating no lasting changes. Despite this lack of data specifically in children with NF1, muscle-strengthening training programmes remain the primary management option to target the muscle weakness itself, based on its efficacy in other conditions and lack of alternative options at present. These are usually implemented by physiotherapists.

Potential future treatments

Muscle- and limb-specific mouse models of NF1 have demonstrated intramyocellular accumulation of lipid droplets, with an almost 10-fold increase in muscle triglyceride content and reduced levels of mitochondrial lipid transporters[34]. Furthermore, lipidome analysis showed significant increase in sub-species of neutral lipids implicating impairment in long-chain fatty acid (LCFA) metabolism[32]. Therefore, Summers et al introduced an 8-week diet for limb-specific *NF1* knock-out mice that aimed to reduce the LCFA burden – enriched with medium chain fatty acids (MCFA), low in LCFA and with added L-carnitine (which assists LCFA transport)[32]. Compared to mice fed standard diet, there was a 45% increase in muscle strength, with 71% reduction in intramyocellular lipid accumulation[32]. The same group have further published recently the impact of diets offering various combinations of high MCFA and L-carnitine in the same mouse models[70]. This showed that both high MCFA diet and L-carnitine individually can both reduce intramyocellular lipid accumulation. This improvement disappeared once the diets were discontinued, suggesting that long-term therapy would be required. Interestingly, neither high MCFA diets or L-carnitine (alone or in combination) improved force or fatiguability of the tibialis anterior muscle studied. Nonetheless, since this treatment potentially addresses the underlying pathophysiology, and carnitine supplementation has been used safely for muscle dysfunction in metabolic myopathies[71,72], a proof-of-concept study using carnitine supplementation is currently underway by the same group in children with NF1 (trial registration number ACTRN12618002021257).

Within the clinical setting, implementation of a therapy programme that targets functional muscle strength is needed, not only to improve muscle function, but also the concomitant health issues such as deconditioning and sedentary lifestyles. To address some of these issues, the authors are currently undertaking a preliminary interventional study using side-alternating low-frequency high-amplitude whole-body vibration and muscle-strengthening exercises in children with NF1 with muscle weakness (trial registration number NCT03888248). Whole-body vibration causes repetitive muscle contraction by mechanical stimulation, resulting in increased muscle power[73]. Studies have already demonstrated improvements in muscle mass and strength, mobility and gross motor function using whole-body vibration in children with other neuromuscular disorders including cerebral palsy and Trisomy 21[74-76].

Conclusion

Over the past 20 years, there is strong evidence to support that individuals with NF1 suffer from a primary muscle weakness. Muscle weakness may impact on a number of complex parameters affected by NF1, including motor function, fatigue and physical activity, but further studies are required to establish whether clinically relevant effects are present, as well as the interplay between these. In a clinical setting, evaluation of muscle weakness should focus on key points within the history and examination that focus on the impact of the muscle weakness and exclusion of alternative aetiology. Management currently relies on simple measures along with physiotherapy and occupational therapy input to improve muscle strength and provide practical support with activities of daily living. However, in the future carnitine supplementation and focused exercise interventions may hold promise in improving muscle weakness in children with NF1.

Authors' contribution

AC: planned, researched, drafted and revised the main body of the manuscript. MZM: planned, drafted and revised the manuscript. GRV, EBW, JE, SW, EH, PG, AP, RP: revised the manuscript, and helped draft the clinical evaluation and management sections. All authors participated in the modified Delphi consensus

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